Design for Biosecurity

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Lecture 59

Cell Based Biosensors - Part 4

Welcome back! As I mentioned at the end of our last class, today we will translate the concepts we discussed into practical applications. Imagine you have an electrode that stimulates the muscles positioned on top of it. When the muscles contract, they generate vibrations in the microcantilever. These vibrations lead to motion, resulting in a change in the angle of reflection of a low-intensity laser beam.

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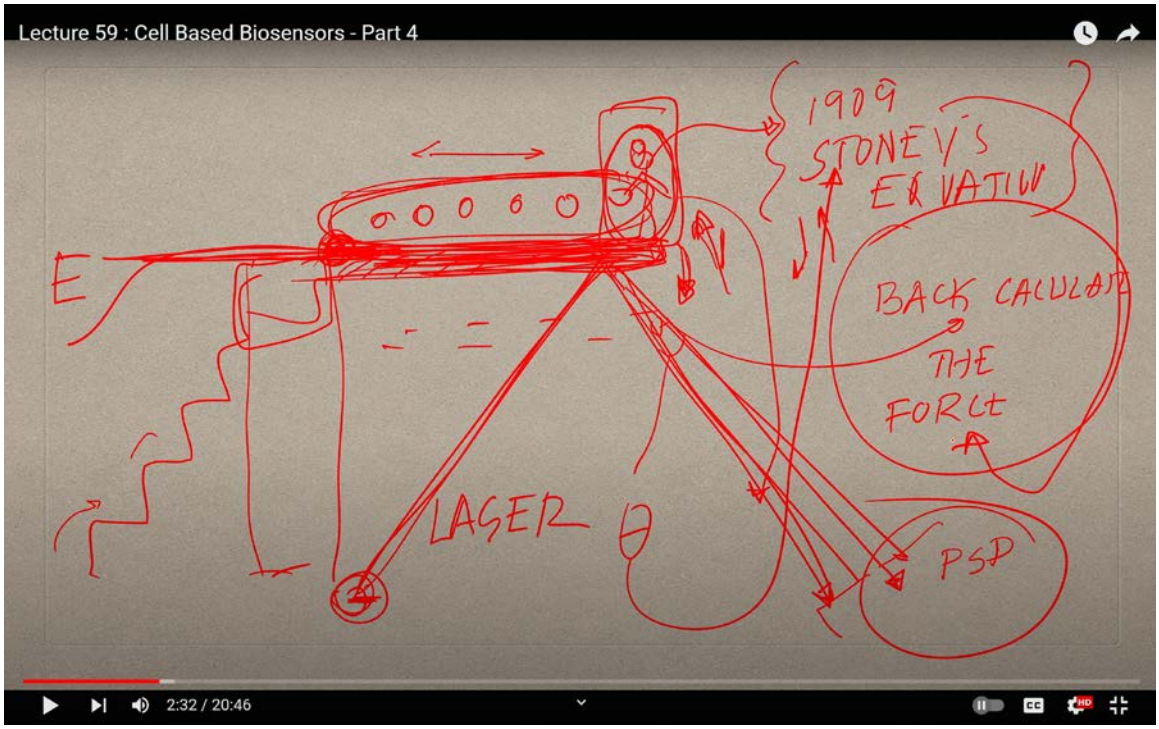

Let’s visualize this: picture the cantilever as a horizontal beam. Above it, we have the muscle, represented here by a blue pen. Below the cantilever, there's a black pen that emits

a laser beam directed upward. The light reflects off the cantilever and reaches a sensor positioned to detect this reflected light.

Now, due to the motion of the cantilever, the angle of reflection changes. We can denote this change in angle as θ. What's fascinating is that you can back-calculate the force exerted by the muscle based on this angle. I encourage you to look up Stoney's equation, published in 1909. Although it's not part of our course material, understanding this equation can be beneficial for your knowledge. By considering the muscle as a monolayer on top of the cantilever, you can plug the angle θ into Stoney's equation, make some modifications and assumptions, and ultimately calculate the force generated by the muscle.

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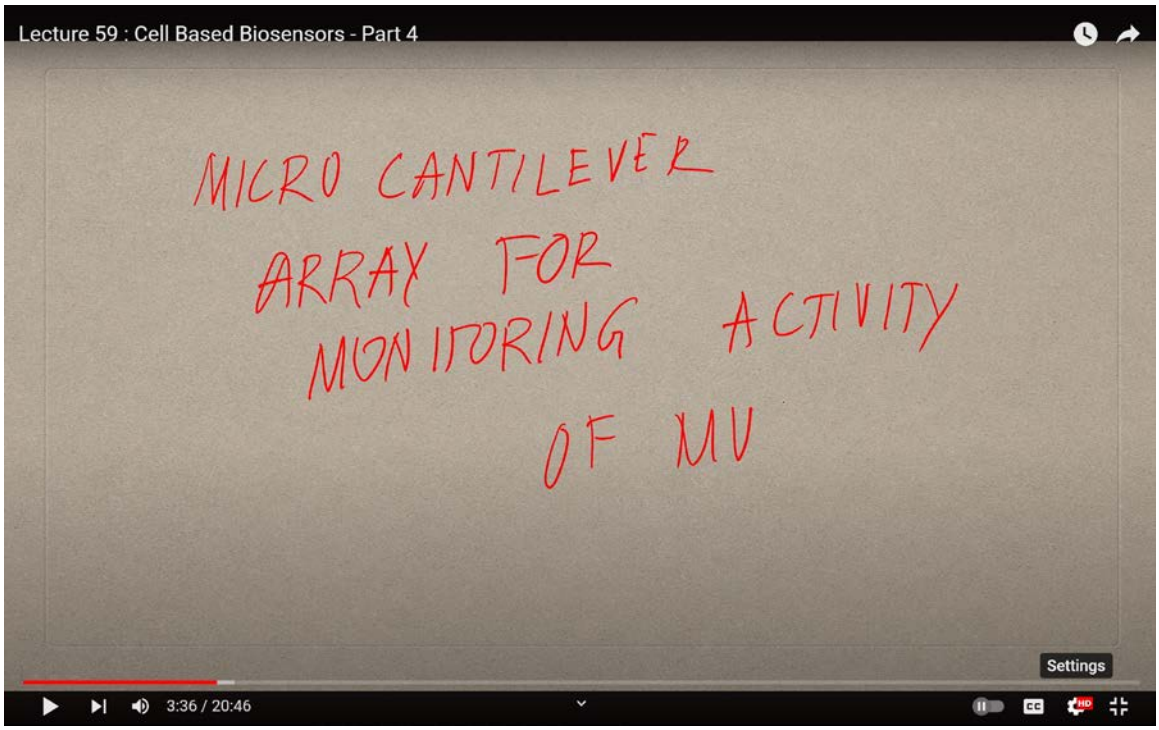

Now, let's delve a bit deeper. This same laser technology can be applied to multiple cantilevers. You can move the laser beam from one cantilever to another, capturing different angles θ with each movement. This is known as the microcantilever array technology, which is specifically designed for monitoring muscle activity.

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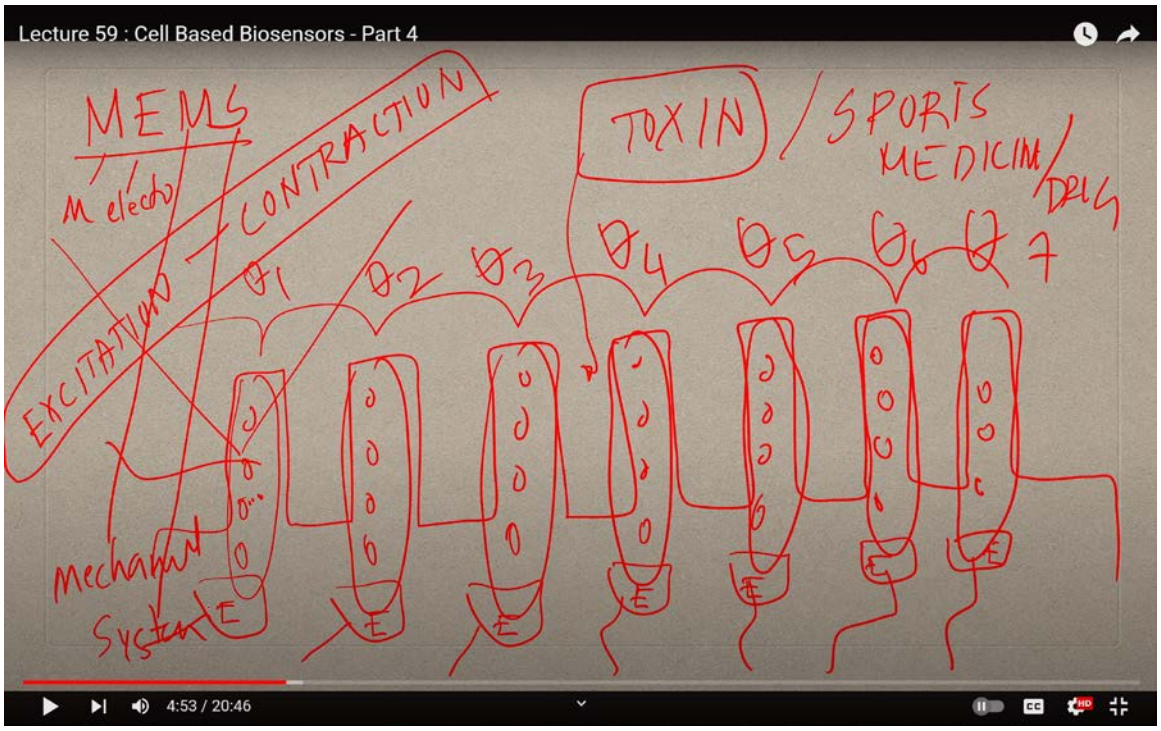

In this setup, you can explore numerous experimental options. For instance, you might introduce a toxin into the environment to see how it influences muscle activity. Alternatively, you could test the effects of performance-enhancing drugs, commonly used by athletes, on muscular contraction. The possibilities are vast, and this technology opens up exciting avenues for research and discovery.

Without causing harm to animals, a significant amount of microfabrication work can be accomplished, which falls under the broader category of MEMS, Micro Electro Mechanical Systems. To put it another way, if you examine your own body, you'll see that your muscles essentially function as cellular microelectromechanical systems. By integrating these biological systems with a synthetic microelectromechanical system, such as a cantilever, we can conduct precise measurements. This represents an exciting opportunity to combine microelectrode arrays with microcantilever arrays.

This particular technology is revolutionizing our understanding of how various toxins affect neuromuscular junctions, as it allows us to visually observe the effects in real time.

Now, let’s take this concept to the next level by discussing the integration of multiple organs. When I refer to "humans on a chip" or lab-on-a-chip technology, I am talking about the innovative structures being developed that contain neuronal chambers, muscle chambers, and even tissues like the liver and cardiac muscle. For instance, you can have brain neurons and skeletal muscle connected through an intricate network of microfluidic channels and microvalves, creating a functional multi-organ system that closely mimics the human body.

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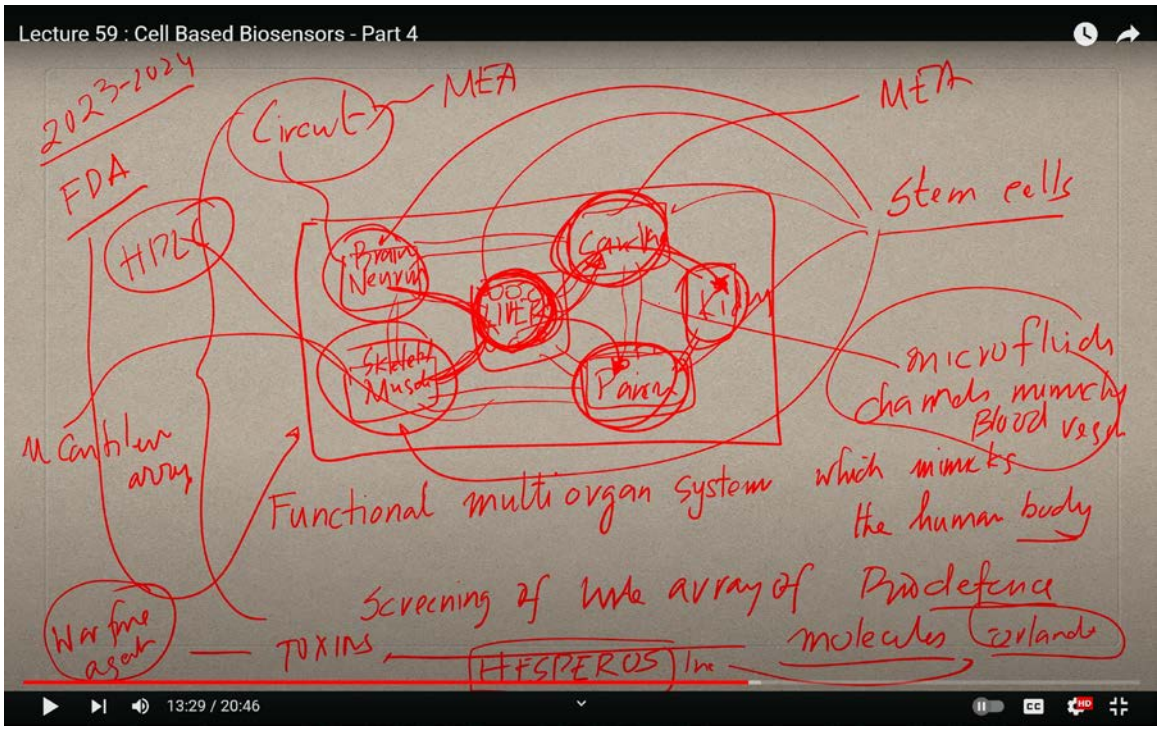

Most of these cells are derived from various sources of stem cells, making the process significantly more manageable. You may be surprised to learn that the United States FDA has recently approved the use of these systems, as of 2023-2024. This means that if a drug has been tested using this kind of multi-organ system, it can potentially bypass lengthy animal trials and proceed directly to human trials. This marks a monumental development in the drug discovery industry.

Moreover, this technology holds tremendous promise for screening a wide range of bio-defense molecules and toxic warfare agents, providing a more ethical and humane alternative to traditional animal testing, which is often painful and dangerous.

When we discuss this technology, we can visualize arranging brain tissue alongside skeletal muscle on a microcantilever array, while simultaneously organizing the circuits of a microelectrode array on a liver model. In this setup, we can create patterned substrates that closely mimic the liver's architecture. Similarly, cardiac tissue can be placed on microelectrode arrays, and the pancreas can be patterned as well. All these components are interconnected through microfluidic channels that effectively simulate blood vessels.

This cutting-edge technology is at the forefront of development, and those of you interested in this field may want to explore Hesperos, Inc., a U.S.-based company located in Orlando. They are the first organization in the world to develop a multi-organ human-on-a-chip system and are recognized as leaders in this niche market. Although it's a small company, visiting their website will provide you with fascinating insights into their work and the significant advancements they are making in this area. You will discover numerous aspects to consider as you delve into this innovative frontier.

What I'm sharing with you is based on extensive research conducted over the past 24 years, and even earlier, since the 1980s and 1990s, making it nearly 35 to 40 years of dedicated work in this field. Today, they stand as one of the foremost companies globally in this domain. The potential for integrating other organs, such as kidneys, is immense; the sky is truly the limit.

However, whenever we undertake this kind of integration, there are additional techniques that you have already learned about. For instance, we can extract fluid from these systems and analyze it using High-Performance Liquid Chromatography (HPLC) to identify the metabolites produced and to observe how toxins affect them. Imagine a scenario where a toxin impacts the liver, leading to the secretion of specific metabolites that influence skeletal muscle or neuronal function. Understanding these intricate interactions can be incredibly challenging, but with a system like this, we can study them more effectively.

Consider the liver releasing metabolites that might be detrimental to the cardiac system. How can we determine whether what we are observing is a cardiac arrest, or how those metabolites affect the pancreatic islets of Langerhans cells? Additionally, how do we discern whether they indirectly influence the kidneys in the purification process? The possibilities this technology opens up are vast.

However, to successfully leverage this technology, one must have a clear understanding of several key techniques that I previously highlighted. Firstly, a solid grasp of basic photolithography tools is essential. Understanding electrochemistry is crucial, particularly in handling and implanting electrodes to ensure accurate recordings. You will also need to possess a robust microsystem fabrication system; this means fabricating components at the microscale with exceptionally high precision. The required resolution is in micrometers, and achieving that level of detail is paramount.

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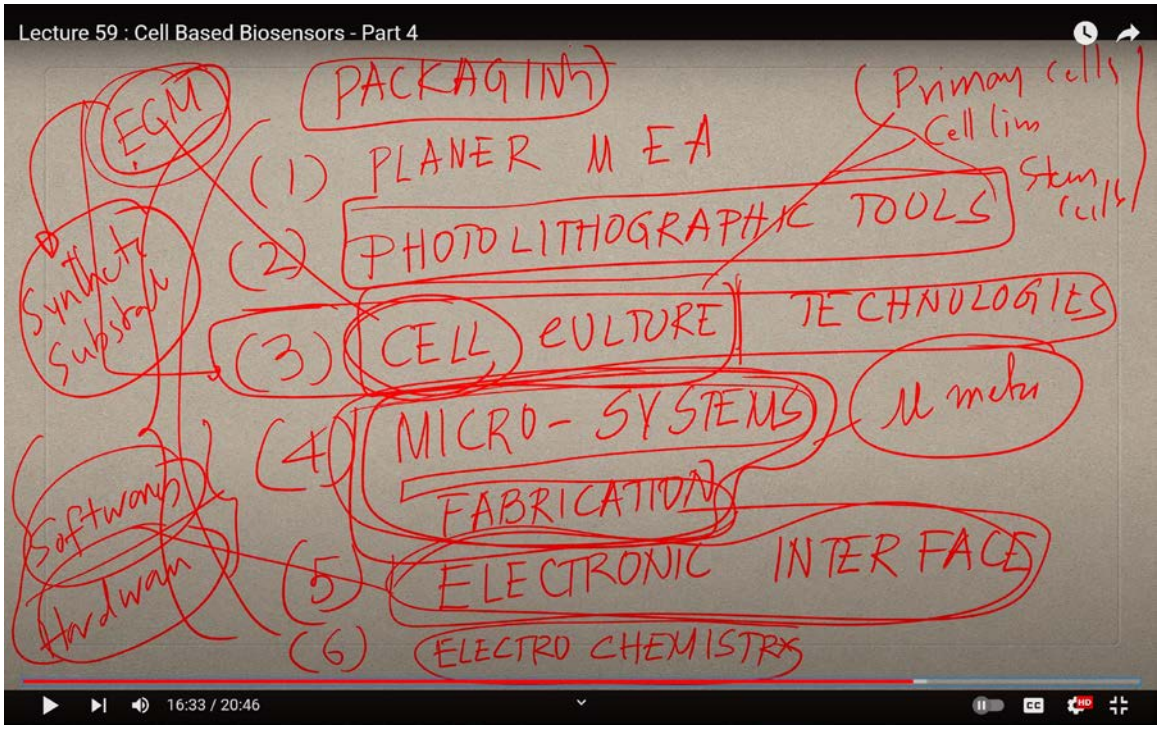

Next comes the need for channels and connectors, along with the electronic interface. For a system of this complexity, you will need a dedicated set of software and hardware to

facilitate its operation. The integration phase is critical; you must have a comprehensive understanding of cell culture technologies. Whether you are working with primary cells, established cell lines, or stem cells, you need to know your source and how to handle and cultivate those cells.

When discussing cell culture, a thorough understanding of the extracellular matrix (ECM) is vital, especially since you are integrating biological systems onto a synthetic interface. Without a clear comprehension of how to interface these cells with the ECM, particularly on top of a synthetic substrate, you may encounter significant challenges. This entire process of interfacing is of immense importance when we talk about the successful integration of cells into these advanced systems.

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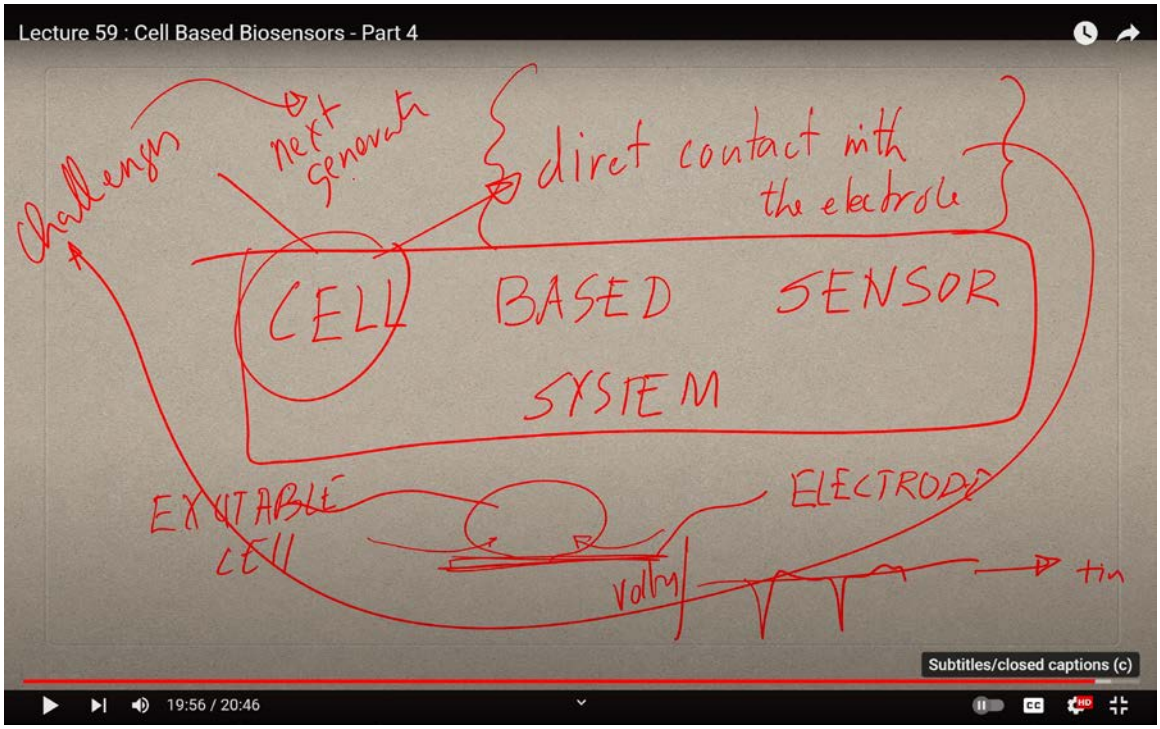

Next, let’s discuss the development of the device and the crucial aspect of packaging it. Once all the components are in place, you must ensure proper packaging because we will be conducting real-time monitoring. When we talk about chips like these, it is essential that they are packed thoroughly. Moreover, you must implement aseptic practices, especially

when handling biological cells, as there is a significant risk of contamination. This necessitates working within cleanroom environments to prevent microbial contamination.

It is important to recognize that sensor technology is increasingly shifting toward cell-based sensors. This is where the future of biosensing lies. The entire biosensor and biodefense mechanism revolves around these advanced cell-based sensor systems. When we discuss cell-based sensor systems, as I mentioned earlier, you need to have a comprehensive understanding of how to interact with various types of electrodes. You must consider the information you wish to gather from these electrodes, the materials that will constitute the electrodes, and how to source these materials in a cost-effective and readily available manner.

Without a thorough understanding of these technologies, you will inevitably face numerous challenges. However, these challenges also present a wealth of opportunities. As I emphasized at the beginning, the field of biosensors is extraordinarily complex, requiring expertise from multiple disciplines.

I want to highlight an interesting challenge related to our discussion. Imagine you have an electrode and an excitable cell placed on it. This is your electrode, and this represents your excitable cell. As I previously mentioned, you can observe a change whenever there is an influx of ions. If you recall the graph I showed you, it illustrates that electrical activity occurs, where the x-axis represents time and the y-axis represents voltage.

In these scenarios, we are dealing with a cell that is in direct contact with the electrode, similar to other biosensors where molecules are also in direct contact with the electrode. But what are the challenges that arise from this setup? In our next class, we will delve into these challenges and explore how to transition to the next generation of technologies. So, thank you. In the next class, we will talk about the challenges and next-generation technologies.