# Design for Biosecurity

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## Lecture 51

## Action Potential - Part 1

Welcome back to our lecture series on design for biosecurity! In our last session, we delved into the fascinating realm of whole-cell biosensors, exploring their foundational concepts. These biosensors exist in a unique space between the analysis we perform on bodily fluids, such as blood, urine, and sweat, and the in vivo measurements we obtain through a diverse array of techniques, including spectroscopic, optical, acoustic, and electrochemical methods. At the intersection of these two approaches lies the intriguing world of whole-cell biosensors.

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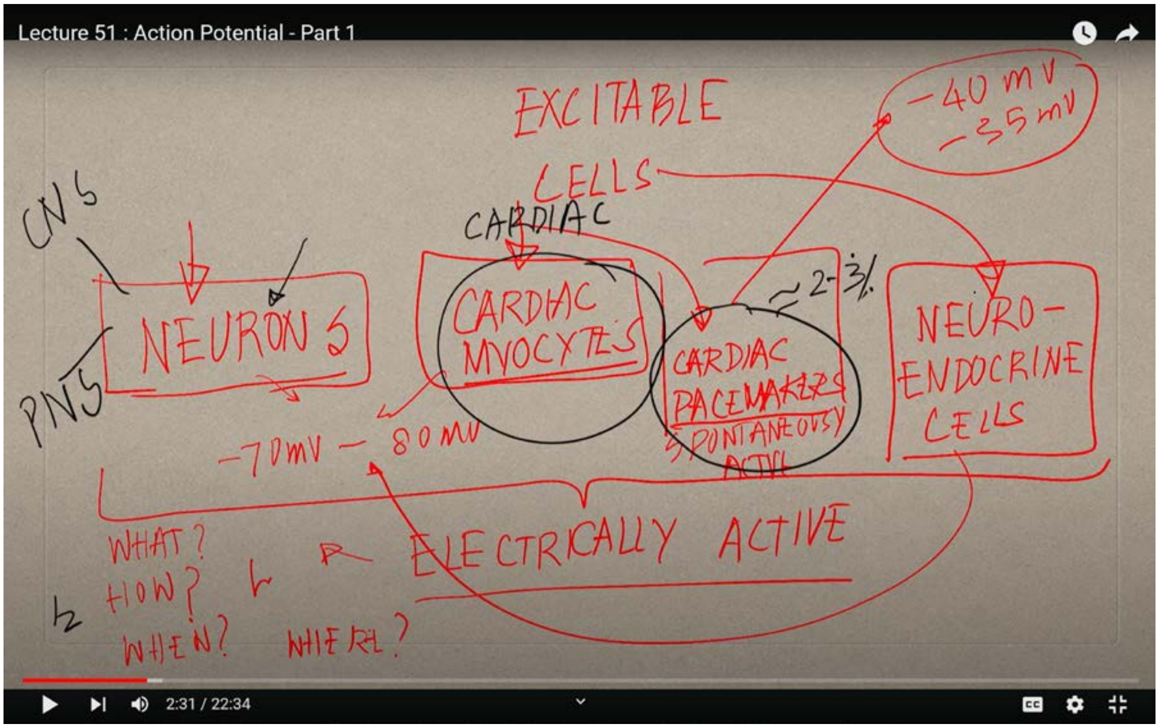

I previously introduced the concept of resting membrane potential, which is pivotal to understanding these biosensors. In my presentation, I classified the cells in our body into two primary categories: excitable cells and non-excitable cells. For our purposes, we are focusing solely on excitable cells, which earn their name due to their ability to generate electrical impulses.

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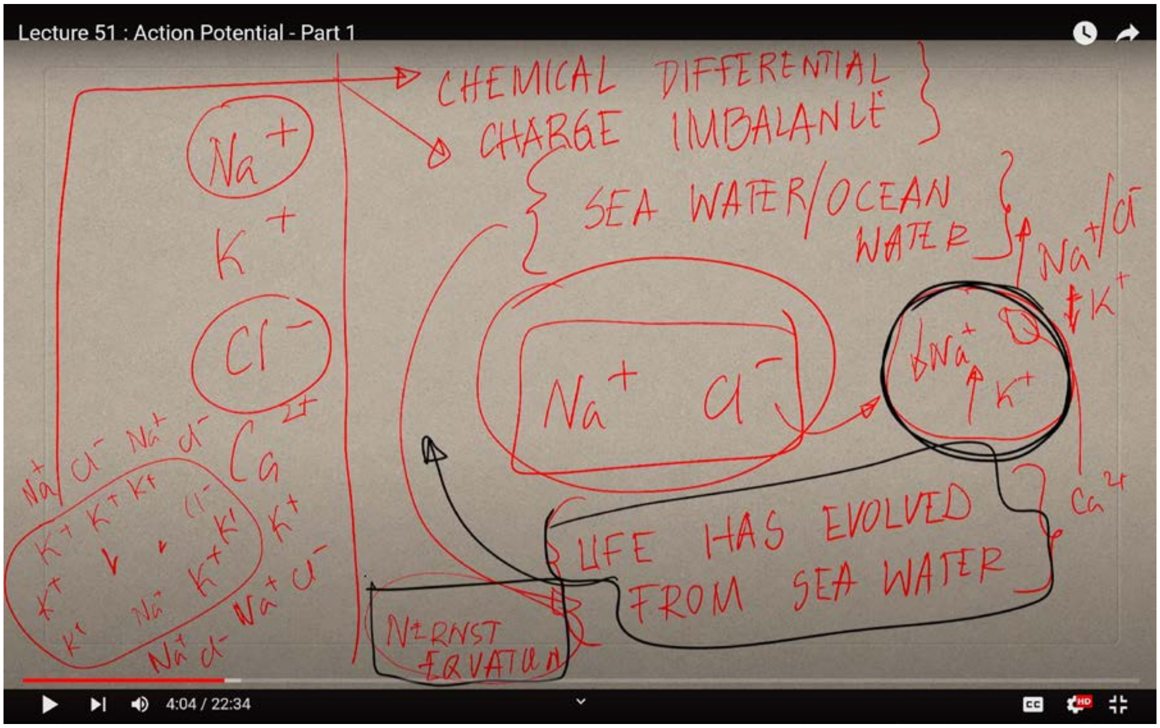

We discussed several types of excitable cells, primarily neurons, which include those from both the central and peripheral nervous systems. We also examined cardiac myocytes, the predominant cells of the heart. It's important to note that cardiac myocytes can be divided into two types of excitable cells, with only 2 to 3 percent of them functioning as cardiac pacemaker cells that regulate the heart's rhythm. The third key category we discussed consists of neuroendocrine cells. Together, these three families of electrically excitable cells form the backbone of our exploration.

We also covered how to measure resting membrane potential by placing an electrode inside the cell and another outside it, allowing us to quantify the potential difference between the two. Most cells typically exhibit a resting potential ranging from -70 to -80 millivolts, with some cells even reaching -90 millivolts. I illustrated this concept with a graph, showing how different cells can display spontaneous electrical activity, revealing their unique behaviors.

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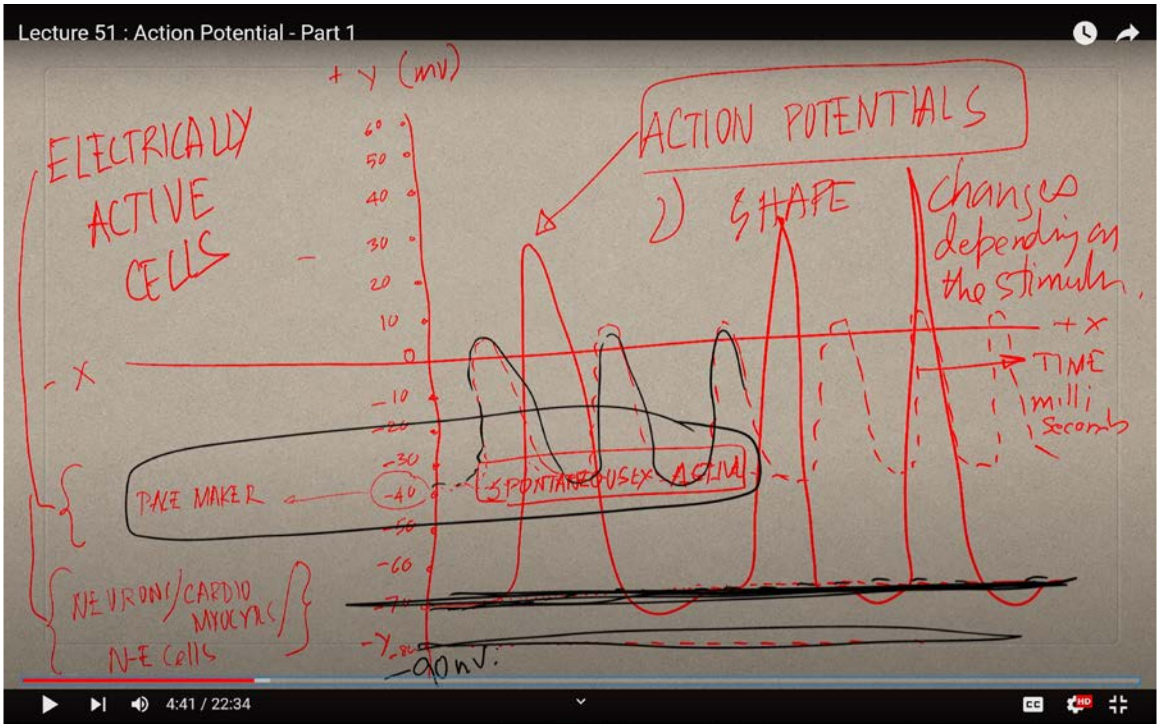

Now, as we concluded our last class, I posed an intriguing question: Why is there a lower concentration of certain ions inside the cell compared to the outside? This question prompts us to consider the origins of life itself, which many believe evolved from seawater. Naturally, this raises the question of why seawater is so saline. While there are various theories regarding this phenomenon, it is beyond the scope of our current discussion. However, it certainly highlights the remarkable aspects of nature, particularly the need for life forms to develop mechanisms that regulate sodium levels, leading to the evolution of the first cells. With that, let's embark on our exploration of these topics further in today’s class!

Let me share with you the fascinating concept of the Nernst equation! This equation provides a theoretical framework to explain why the membrane potential is at certain levels. For now, we won't delve into the unique case of spontaneous activity in pacemaker cells, but I promise we will revisit this intriguing topic in a few classes to explore why it occurs and what factors determine it.

Now, let's examine an experimental observation: many cells maintain a membrane potential of around -70, -80, or even -90 millivolts. The question arises: why is this the case? How can we theoretically elucidate this phenomenon? The answer lies in the celebrated work of Walther Nernst, a brilliant physicist and physical chemist, whose legacy continues to impact our understanding of cellular biology. Nernst's contributions emerged during a remarkable period in history when the scientific community was buzzing with excitement over the dawn of quantum mechanics.

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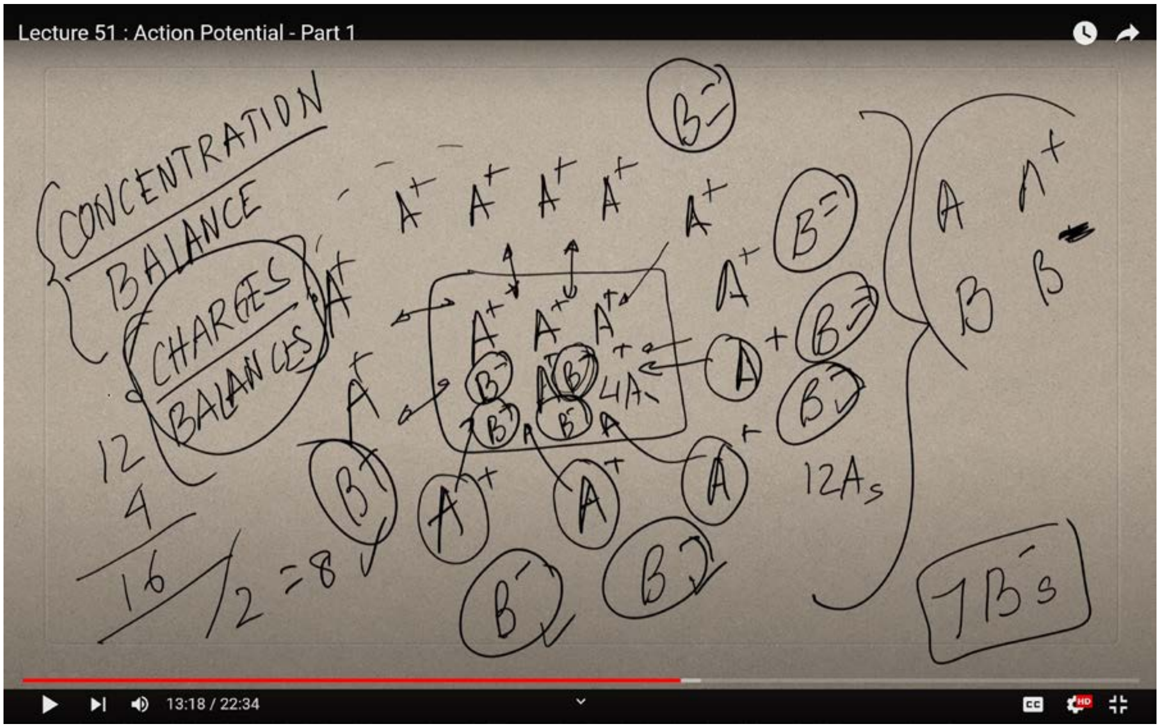

Imagine the era of the 1910s to 1930s, a time when luminaries like Schrödinger, de Broglie, Einstein, Max Planck, and Heisenberg were exploring the dual nature of light, discussing its particle-like and wave-like characteristics, and investigating the concept of quanta or packets of energy. Amidst this revolution in classical mechanics leading to breakthroughs in quantum mechanics, Nernst was pursuing a very different, yet equally significant, problem.

Now, let’s simplify this by picturing a generic scenario, one that transcends the specific context of cells. Imagine a confined space containing two types of particles, A and B. For our example, let's say we have particles of type A outside the confined area and some of them inside. If we visualize this, we could see that there are 12 particles of A outside and 4 inside. If we allow these particles to reach a state of chemical equilibrium, what do you think will happen?

Logically, since there are more particles outside, they will move into the confined space to achieve balance. This movement will continue until the concentrations equalize. With 12 particles outside and 4 inside, the total number of particles is 16. To find the equilibrium, we take the average: 16 divided by 2 gives us 8. Consequently, to achieve balance, 8 particles will move in, resulting in an equilibrium state where there are 8 particles on each side.

Of course, this scenario assumes that the particles of A can move freely without any restrictions. It’s a straightforward concept, but it’s crucial to keep in mind as we continue to explore the implications of these movements. Now, let's add another parameter to this situation and see how it further impacts our understanding.

Let’s introduce an additional parameter and explore the implications: let’s say that the particles, A, carry a positive charge. Now, we must consider not just the concentration balance, which we addressed earlier, but also the charge balance. When there are 8 particles of A inside and 8 outside, this means we have eight positive charges inside and eight positive charges outside. This scenario is straightforward, and we can certainly solve it without any issues.

Now, let’s increase the complexity of this situation a bit further. Imagine I introduce a new type of particle, which we’ll call B. This time, B carries a negative charge. Let’s count the particles: outside, we have 7 B particles, and inside, we have 4. So, we have a total of 11 B particles (7 outside + 4 inside). If we maintain the same conditions that allowed particles

A to balance, we can expect particles A and B to move accordingly to achieve equilibrium.

Given our numbers, if the situation allows for free movement, we could see something like this: particles A will balance themselves, and particles B will also find a way to reach equilibrium. However, if 1 B particle moves in, we end up with 5 inside and 6 outside. This indicates a still-existing imbalance, as the total count for B remains skewed.

Now, here’s where it gets more interesting. Suppose I impose a restriction that B particles can enter the cell but cannot exit. This changes everything! If 7 B particles can flow into the cell, and we already have 4 inside, we end up with a total of 11 B particles inside the cell. In this case, achieving charge and concentration balance becomes impossible.

At this point, you begin to see the complexity of the situation unfold. If both ions (A and B) could move freely, we would have no problem achieving charge and mass balances. However, with this new restriction on the flow of particles B, we’re confronted with a challenging dilemma.

Let’s visualize this by considering a semi-permeable membrane that separates two sides of our system. Imagine the left-hand side (LHS) and the right-hand side (RHS) of this membrane. The semi-permeable nature of the membrane creates a fascinating dynamic that we must now explore further.

Let’s visualize the scenario we have here. On one side, we have a significant number of particles A, while on the other side, there are only a few A particles. Now, since the membrane is semi-permeable and allows particles A to move freely in both directions, we can expect them to balance out. For instance, if we have 4 A particles on one side and 6 A particles on the other side, some A particles will naturally move from the more populated side to the less populated side until an equilibrium is reached.

So, if we denote 1 A particle moving over, we end up with 5 on one side and 7 on the other, demonstrating that the A particles can easily balance themselves. However, the situation becomes a bit more complex when we introduce particles B, which can only move from the right-hand side to the left-hand side. Given a higher concentration of B particles on the right, when 1 B moves to the left, we achieve a balance of 3 B particles on each side, which is acceptable up to this point.

Now, let’s introduce an additional layer of complexity: let’s say particles B carry a charge. To make things even more intricate, we add another type of particle, C, which also has a negative charge. Let’s count the charges on each side: on the left, we have 5 negative charges from particles C and 6 positive charges from particles A. Meanwhile, on the right side, there are 7 negative charges and only 4 positive charges remaining.

In this case, we have 7 negative charges on one side and 4 negative charges on the other. For charge balance, we should have a total of approximately 11. So, let’s say 5 particles are moving back and forth, attempting to achieve equilibrium. However, this only works if all the particles can move freely.

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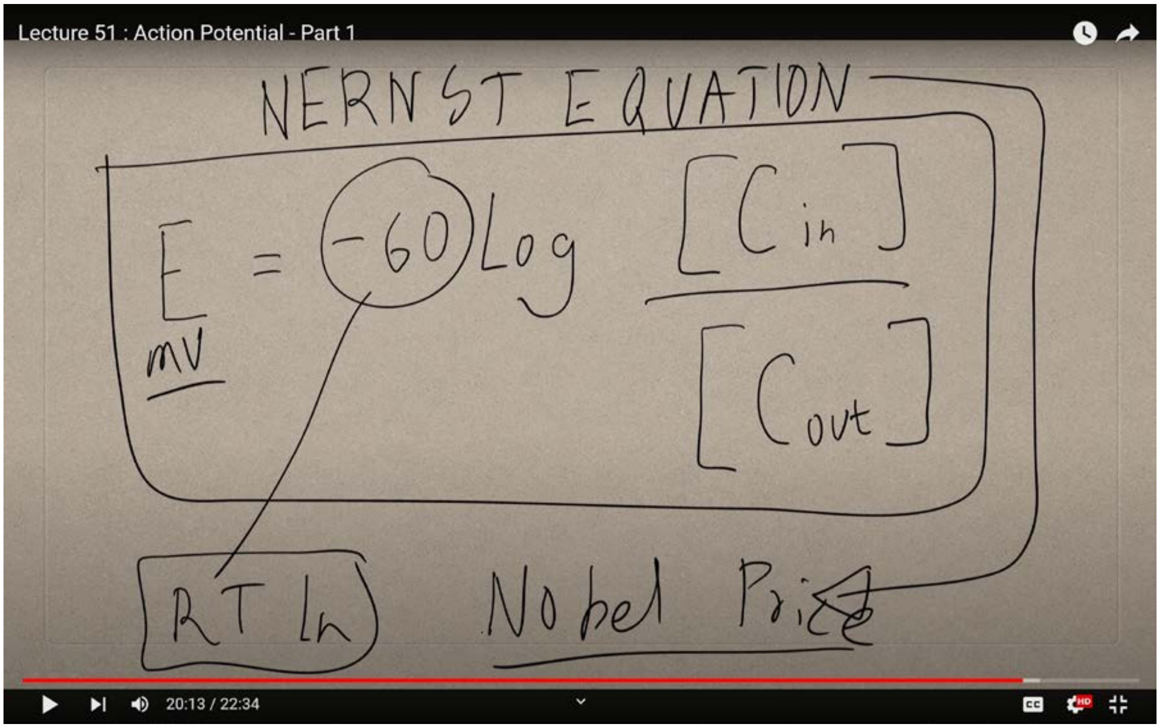

Now, let’s impose a crucial restriction: particles C cannot cross to the other side because of the semi-permeable nature of the membrane. Therefore, the 5 negative charges from particles C will remain confined to their side. Additionally, we have 2 B particles that cannot move in the opposite direction since they are restricted to travel only from left to right.

This means that there will always be 7 negative charges on the left side, with particles C effectively creating a situation where there are more negative charges than positive charges. How can we reconcile this imbalance? With the restrictions in place, we see that the negative charge predominates on one side, presenting a significant challenge for achieving overall balance.

Let’s dive deeper into the fascinating world of cell membrane potential. In our discussion, we realize that some negative charges ideally should move to the other side to achieve balance, yet they remain unable to do so. This brings us to a critical question: how do we determine the potential drop across the membrane? This is precisely the challenge presented by cells.

When we observe a typical cell sitting at approximately -80 millivolts, we need to explain the significance of this negative value. To understand this, we turn our attention to the voltage across the membrane, which leads us to the celebrated Nernst equation formulated by Walter Nernst. In its simplified form, the equation can be expressed as:

$$E = -60 \log \left(\frac{i_{in}}{i_{out}}\right)$$

This equation provides us with a profound insight into the relationship between ion concentration and membrane potential. The constant 60 originates from the natural logarithm of RT/F, where R represents the gas constant, T is the temperature in Kelvin, and F is Faraday's constant. It’s important to note that E is measured in millivolts.

This remarkable equation earned Walter Nernst a well-deserved Nobel Prize, and it serves as a cornerstone in our understanding of electrochemical gradients across membranes. Now, let’s visualize a typical cell structure: imagine a lipid bilayer embedded with protein structures. On one side, we have the extracellular environment, while the other side houses the intracellular contents, including a nucleus that contains DNA, mitochondria for energy production, the Golgi apparatus for protein processing, and, in plant cells, chloroplasts for photosynthesis.

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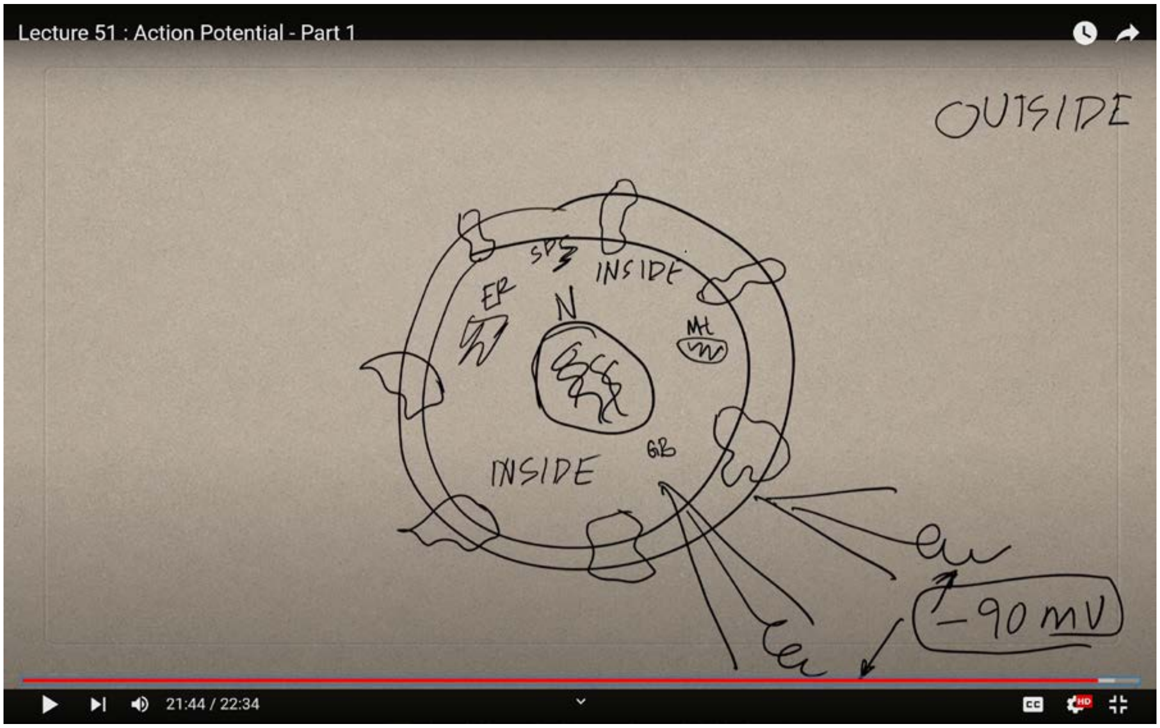

When we insert an electrode into the cell and another into the surrounding medium, we observe a voltage of about -90 millivolts. We’ve previously discussed this phenomenon, and now we’re delving into the underlying reasons for this negative potential.

In our upcoming class, we will explore intriguing features related to ion movement: specifically, which ions are capable of traversing the membrane and which are not. We will also discuss how these barriers can be breached. So, let’s conclude this session, and in the next class, we will continue our discussion on the Nernst equation before moving on to measurement techniques. Thank you for your attention!