Design for Biosecurity

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Lecture 53

Action Potential - Part 3

Let us resume our class. This is our third session, and we concluded the previous class with a brief introduction to Hodgkin-Huxley formalism. I won't delve into its mathematical derivation, as that lies beyond the scope of our current study. However, it is important to note that there were two, possibly four, classic papers published in the Journal of Physiology during the 1940s and 50s, which were quite substantial, about 35 pages long. These papers laid the groundwork for what we now understand as the Hodgkin-Huxley formalism, elucidating the processes behind the generation of action potentials in excitable cells.

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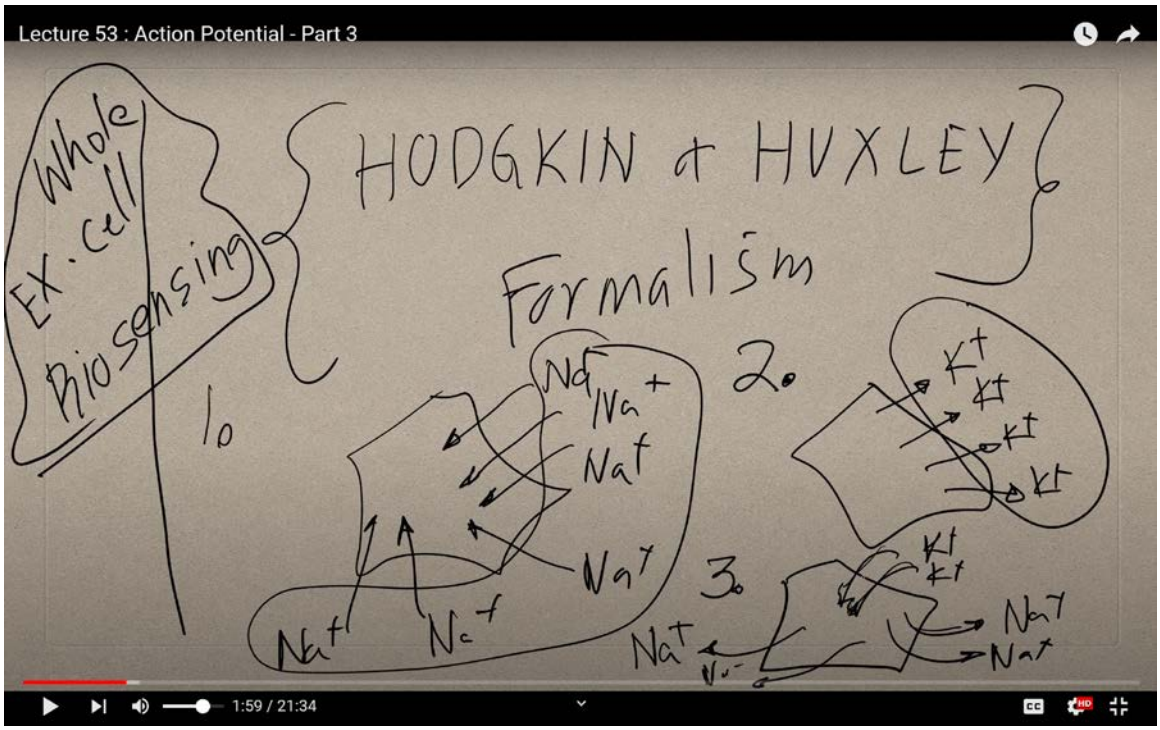

To reiterate, there are three fundamental events involved in this process. First, there is the influx of sodium ions, which they were confident about. While they were not entirely certain about the mechanisms of entry, they proposed the existence of unidirectional pores. Second, there is the efflux of potassium ions, leading to a notable increase in positivity outside the cell. Finally, the balance is restored through some mechanism, likely a pump, where sodium is expelled from the cell while potassium is reabsorbed.

With our modern understanding, we can clarify that sodium enters through very specific pathways. If we visualize the cell, it resembles a spherical structure surrounded by a lipid bilayer. Embedded within this bilayer are channels that allow sodium to flow into the cell through specialized sodium channels.

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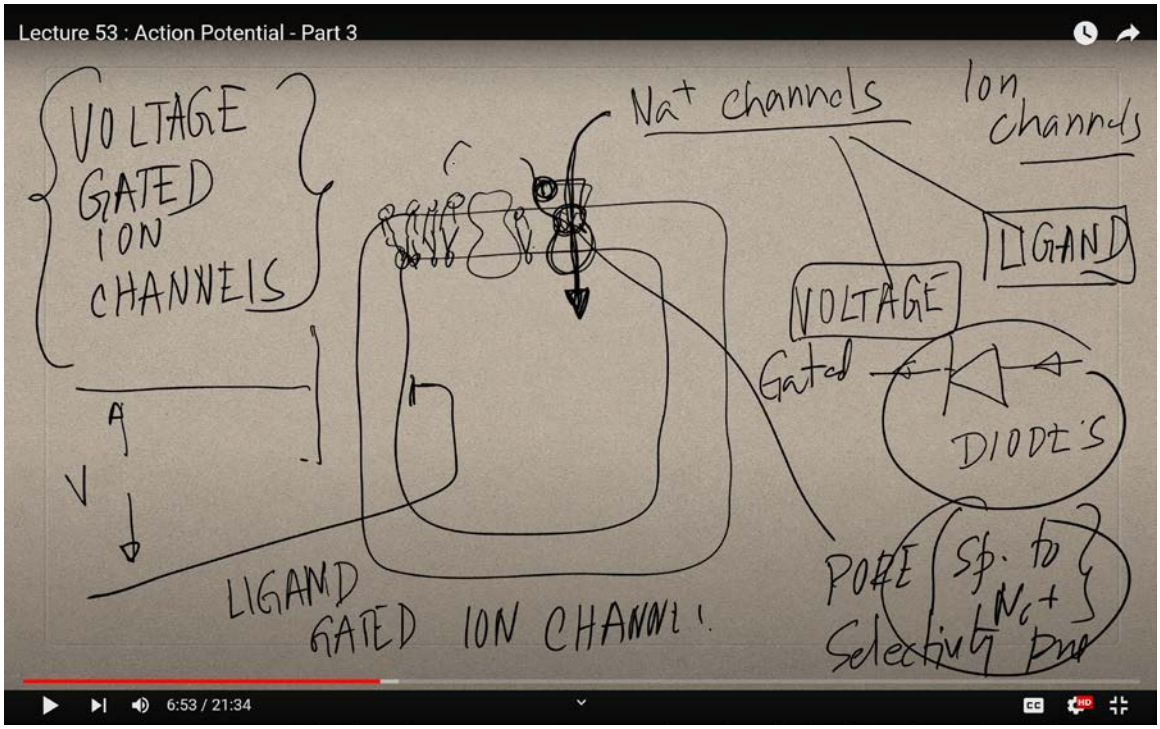

During the 1940s and 50s, the concept of ion channels was not yet established. Today, we know that sodium channels come in two varieties and are designed to open only in one direction, much like electronic diodes. These diodes allow current to flow in a single direction, and similarly, sodium channels facilitate the entry of sodium ions into the cell.

The opening and closing of these sodium channels are influenced by the voltage across the membrane or by the binding of ligands, both of which are crucial for biosensor research. When we talk about voltage, we mean the positive charge outside the cell compared to the negative charge inside. If we artificially manipulate this voltage, we can prompt these channels to open, allowing sodium to rush in.

This means that voltage-gated ion channels open their gates to allow sodium to pass through when a specific voltage is applied across the channel. These channels are referred to as voltage-gated ion channels. However, at the time Hodgkin and Huxley formulated their ideas, the understanding of membrane structure was quite limited. In fact, no one truly understood what a membrane was, and various theories were circulating. Microscopy had not yet advanced to the levels of electron microscopy, both scanning and transmission varieties were still in their infancy. Crystallography was also not well developed; the first crystal structure to be resolved was that of hemoglobin by Max Perutz in the 1960s. Despite this lack of knowledge, Hodgkin and Huxley hinted at the possibility of a specific type of force or passage allowing ions to traverse the membrane.

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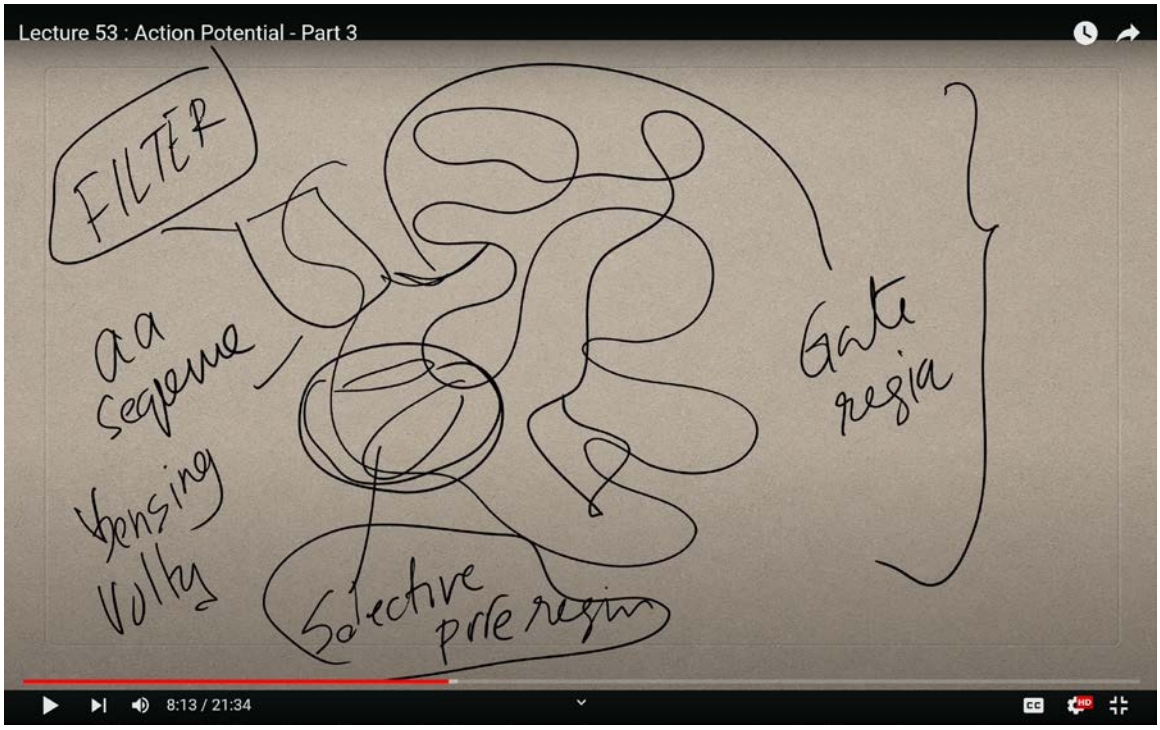

Their formalism was recognized with the Nobel Prize, an honor that Hodgkin and Huxley received for their groundbreaking work. Other researchers at the time shared the Nobel Prize with them, contributing to the same field, but I want to highlight the key contributions that led to our understanding of voltage-gated channels. It is important to note that ion channels can also be ligand-gated. When we talk about ligand-gated ion channels, we refer to those that open their gates in response to something binding to them.

Another fascinating aspect of these channels is that the pore through which sodium ions pass is highly specific to sodium itself. This creates a selectivity filter, allowing for unidirectional movement, and the opening and closing of these channels are regulated by voltage. If we were to illustrate this protein structure, we would see that it is incredibly complex. This protein has what is known as a voltage sensor, meaning that certain amino acid sequences can detect voltage changes. It possesses a pore region that opens up, a selective pore, and a gate region.

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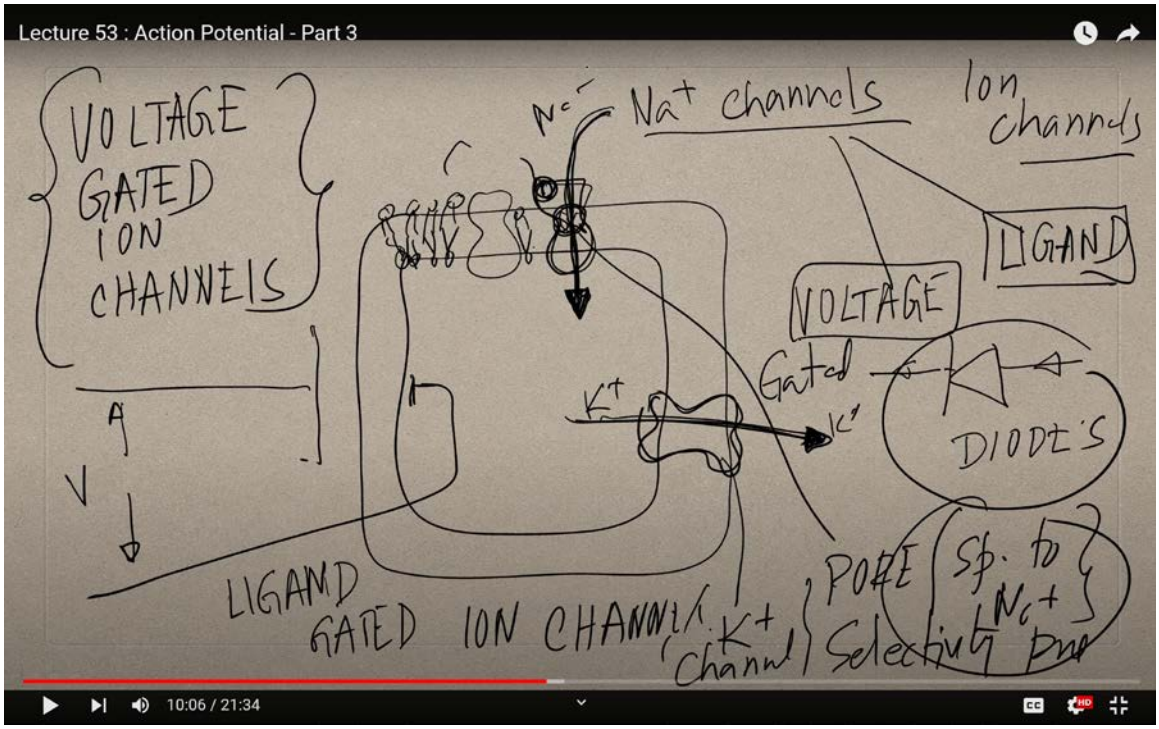

These are some of the most extraordinary evolutionary developments, arguably, the most

magical sodium filter ever created. These relatively simple proteins are embedded in the membrane, performing these remarkable functions. Just imagine: when voltage is applied across them, they can sense that voltage and open up, but they can only do so while integrated into the membrane.

The first event that occurs is the unidirectional movement of sodium ions into the cell. The second key event involves another set of channels known as potassium channels. In 1999, the Nobel Prize was awarded to Roderick MacKinnon from Rockefeller University, a pioneer who elucidated the structures of potassium pores. Initially thought to be mere channels, it was later discovered that they function as pores, and the credit for this understanding primarily goes to him. Interestingly, the structure of the sodium channel remains unclear, and to date, no one has received a Nobel Prize for elucidating that structure. However, the potassium channels allow potassium ions to flow exclusively from the inside of the cell to the outside.

These two types of channels operate within a specific voltage range, indicating that our excitable cells are equipped with numerous voltage sensors. Remarkably, they function almost like voltmeters, capable of detecting various voltages through specific amino acid sequences. Each sequence can sense a different type of voltage, showcasing the intricate electrical elements present in nature. This diverse ability allows potassium ions to exit the cell through channels known as voltage-gated potassium channels, which are sometimes referred to as delayed rectifier channels.

Now, let’s return to the action potential image for a moment. When sodium channels open within a certain voltage range, they reach full activation. However, it's crucial to note that the potassium channels only begin to open within a different range. This specificity means that while significant sodium influx occurs, bringing a wave of positive charge into the cell, the directionality of ion movement is pivotal to the action potential's progression. Understanding this gating mechanism is essential, as these channels open and close at distinctly different voltages.

For example, if we consider a resting potential of around -90 mV, the voltage-gated potassium channels start opening below -50 mV. By the time the membrane potential

reaches a certain threshold, they begin to close, typically around -30 mV to -10 mV. This narrow voltage window, where the gate opens and then promptly closes, illustrates the beauty of this system. Once the membrane potential increases, another set of voltage-gated channels activates, facilitating the movement of cations. We are specifically discussing two cations: sodium and potassium. In this context, potassium ions move from the inside to the outside of the cell, helping to restore balance.

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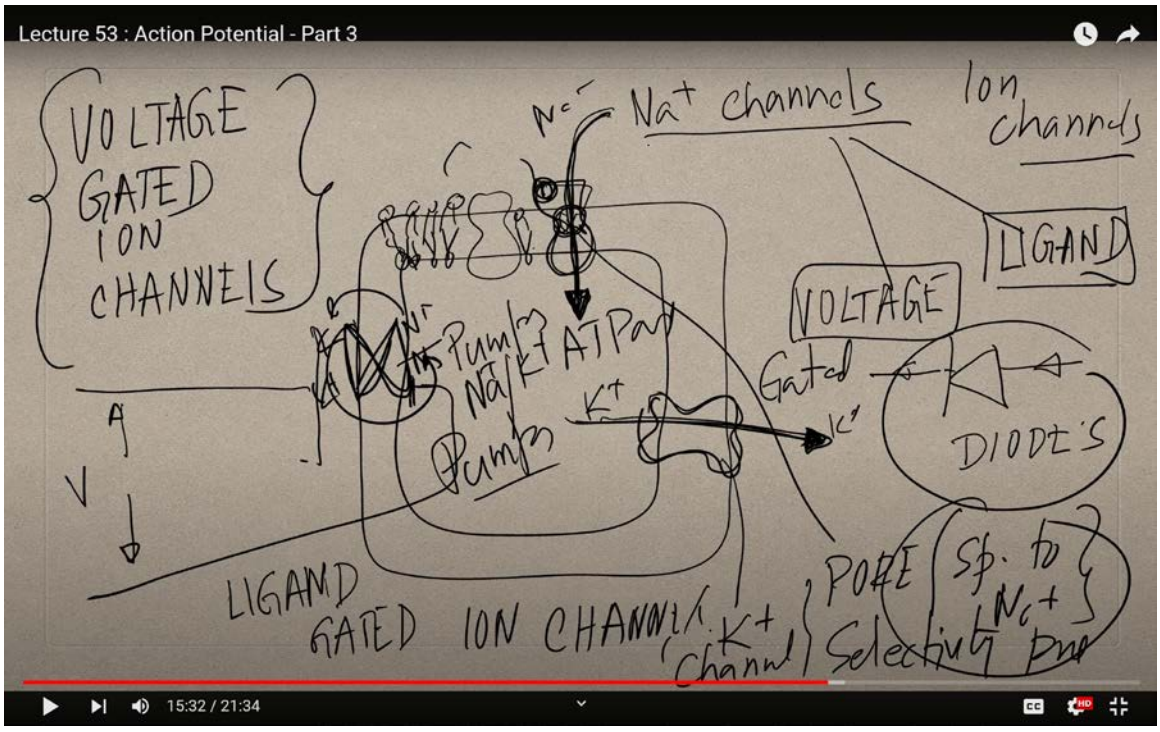

Now, this leads us to an intriguing phenomenon. If we consider the functioning of these channels, they effectively contribute to pulling the membrane potential back to its resting state. However, even Hodgkin and Huxley, during their groundbreaking work, were unaware of the intricate details surrounding these sodium and potassium channels. They simply referred to them as potassium pores and sodium pores, without a clear understanding of their mechanisms.

This brings us to the third crucial component in this process: the pumps. Specifically, we are talking about the sodium-potassium ATPase pumps. What do these pumps do? They

bind sodium ions from inside the cell and potassium ions from outside at a specific stoichiometry, then they twist back using ATP, hence the name ATPase. This process is vital for restoring the ionic balance within the cell. So, as illustrated here, these pumps play a fundamental role in maintaining homeostasis, ensuring that the concentrations of sodium and potassium ions are carefully regulated, allowing the cell to function optimally.

Here's where the pump takes action. This pump binds sodium ions from inside the cell and then twists back to bring potassium ions in, effectively restoring harmony to the normal state of the cell. As you can see, there are three critical molecular events at play: first, the opening of voltage-gated sodium channels, which allow sodium to flow into the cells; second, the exit of potassium ions through voltage-gated potassium channels, which prevents the cell from becoming excessively positive; and finally, the activity of the sodium-potassium ATPase pump, which helps maintain homeostasis by balancing the concentrations of these ions.

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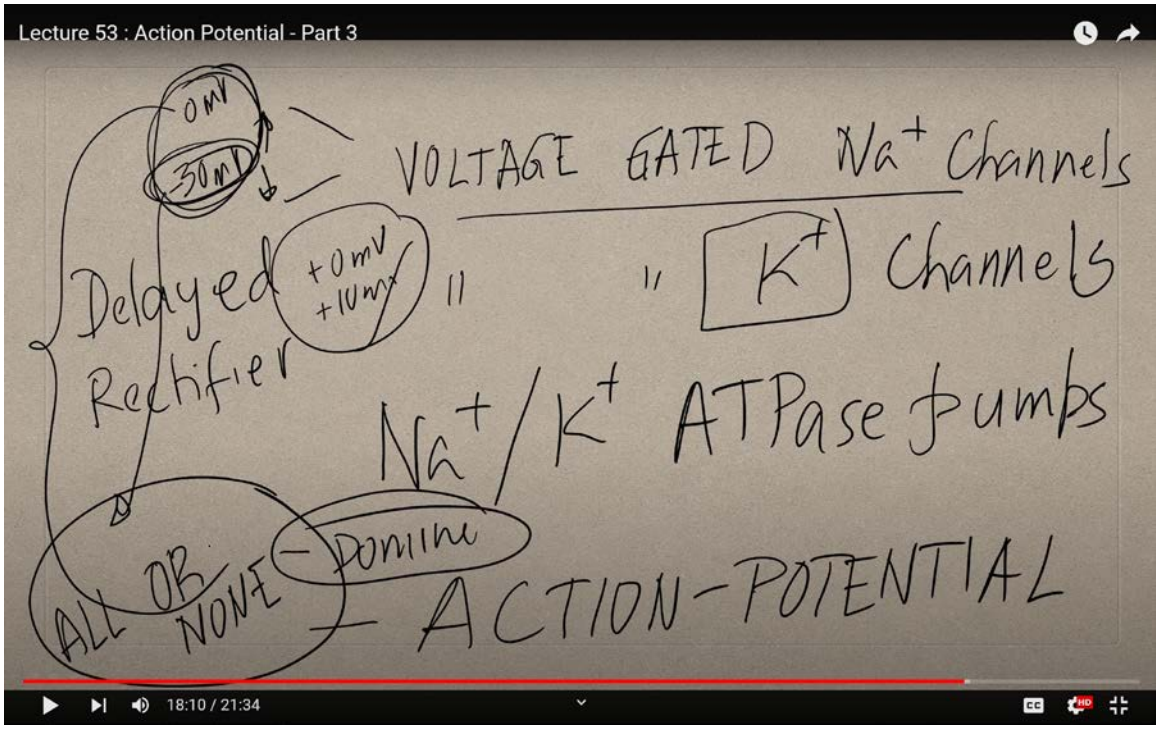

These three pivotal events have laid the foundation for the next century of

electrophysiology, driving our understanding of biosensors, molecular structures, and architectural designs at the molecular level. Across the globe, extensive research is underway, with esteemed organizations like the NIH and EMBL investing enormous resources, trillions, even zillions of dollars, to explore the intricate structures of these molecular machines. These machines perform incredible functions within our bodies.

To summarize, we have the following critical players: first, the activation of voltage-gated sodium channels; second, the voltage-gated potassium channels, which are also known as delayed rectifier channels; and third, the sodium-potassium ATPase pump. Together, these elements are essential for generating action potentials.

Now, this leads us to a fascinating concept. Given that all these channels are voltage-gated, let's consider an important detail. I've previously mentioned that these voltage-gated sodium channels operate within a narrow voltage window. They begin to activate around -30 millivolts and remain active until approximately 0 millivolts. It’s crucial to verify this precise window, especially since many potassium channels open around +10 millivolts.

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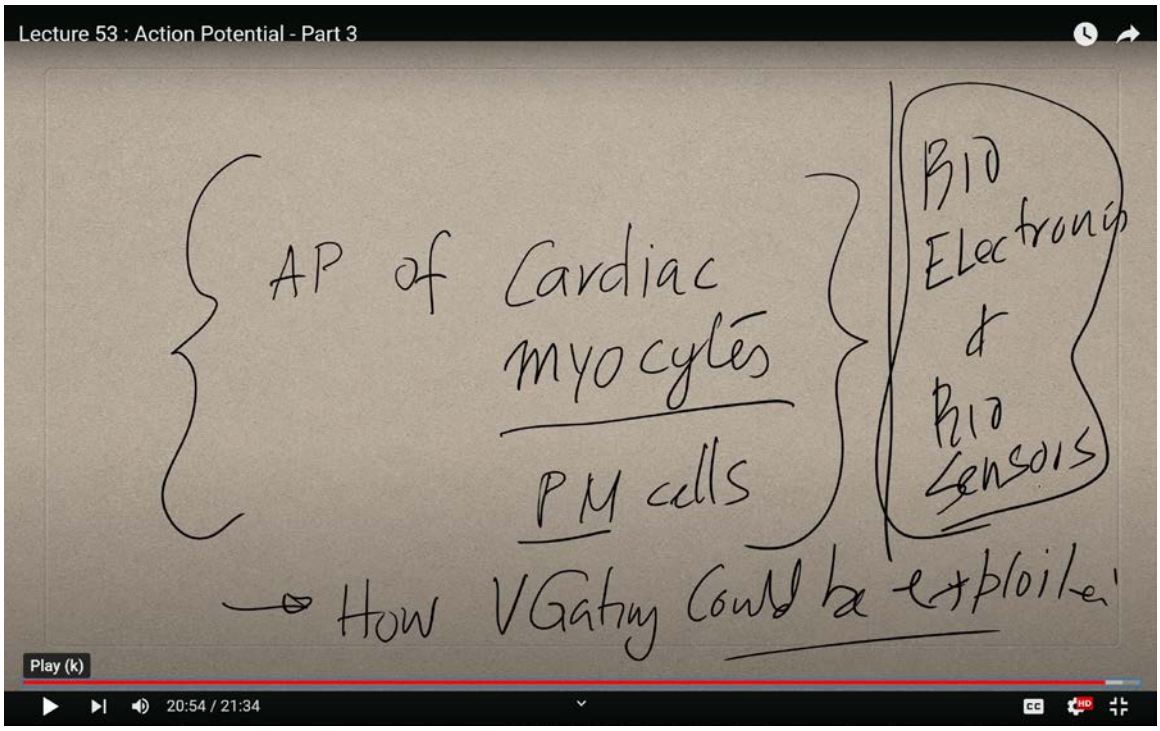

When a cell reaches this critical point, a cascading effect occurs, causing all the sodium channels to open in a domino-like fashion. This phenomenon characterizes action potentials, which are often referred to as "all or none." Essentially, if the membrane voltage decreases to -30 millivolts or lower, you will witness this domino effect, with all sodium channels opening simultaneously. At this moment, the cell undergoes a rapid depolarization, effectively reaching the zero-millivolt threshold and becoming positively charged. This is precisely why action potentials are termed “all or none”: they either occur fully or not at all, and if they do occur, everything shifts dramatically.

This brings us to a particularly intriguing point. Before I delve into further explanations, I want to clarify something about cells that exhibit spontaneous activity. Within our systems, certain cells are positioned within this voltage zone and can behave spontaneously. These spontaneously active cells are known as pacemakers, as they set the rhythm of electrical activity in the circuit. Such pacemaker cells are truly a marvel of nature; they do not conform to the typical action potentials we've been discussing here.

These pacemaker cells exhibit a distinctly different pattern of action potential compared to other excitable cells. Before delving deeper, I will outline another set of action potentials. This will lead us to a discussion on how voltage-gated channels can be utilized and how these cells may be harnessed for biosensor development.

In addition to that, I will touch on a couple of other important concepts and then present a slide about the action potentials of the next type of excitable cells: the cardiac myocytes. Naturally, this discussion will also include the pacemaker cells, which play a critical role in this context. Understanding these two types of cells is essential before we explore the potential applications of voltage gating in bioelectronics and biosensor technology.

With that said, I will conclude here. In our next class, we will examine the action potentials of cardiomyocytes, delving into their unique characteristics and significance. Thank you!