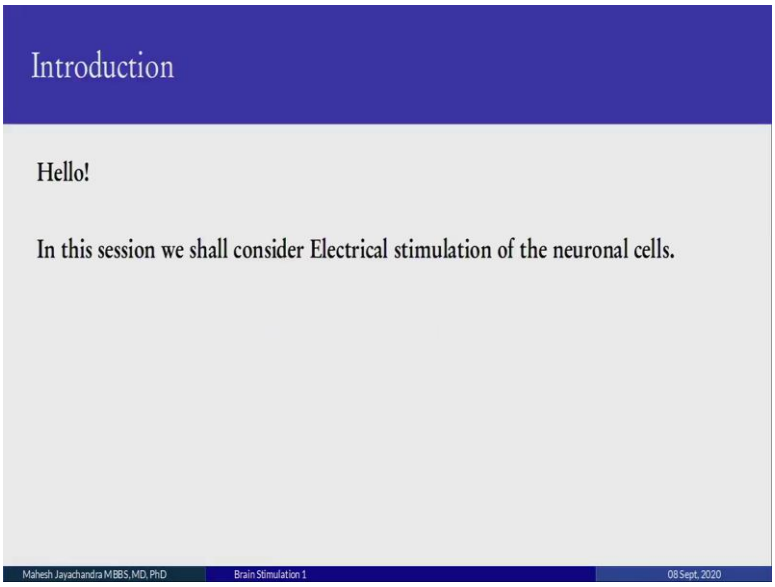
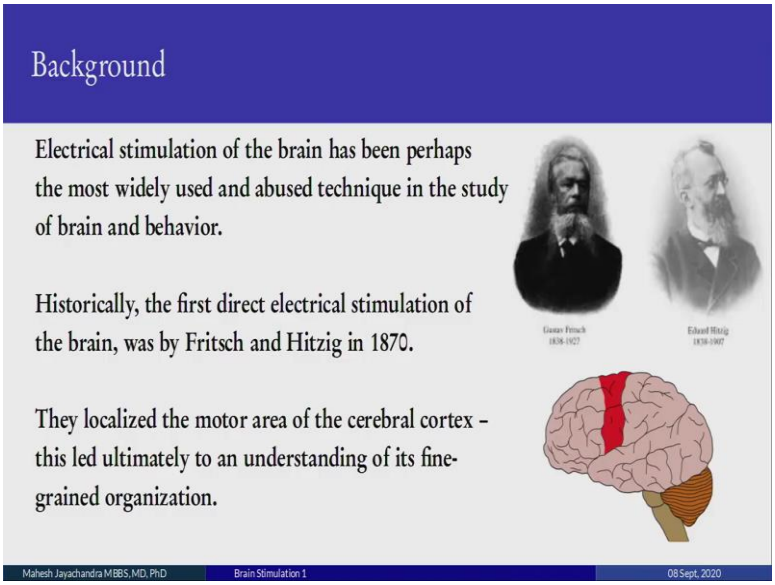
Introductory Neuroscience and Neuro-Instrumentation
Professor Mahesh Jayachandra
Center for Bio Systems Science and Engineering
Indian Institute of Science, Bengaluru
Lecture 01: Electromagnetic Stimulation of the Brain

(Refer Slide Time: 0:22)

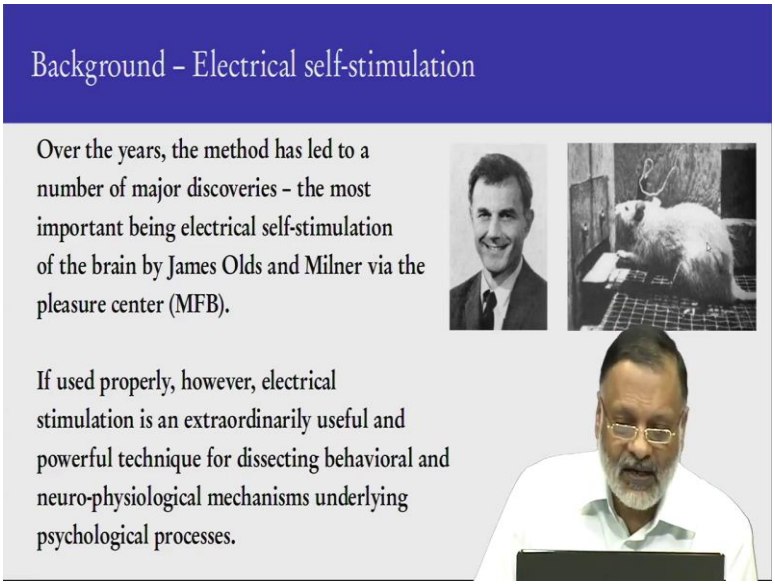




Introductory Neuroscience and Neuro-Instrumentation: Electromagnetic Stimulation of the Brain, lecture 1. Hello, in this session, we shall consider the electrical stimulation of neuronal cells. Some background first. Electrical stimulation of the brain has been the most widely used and sometimes abused technique in the study of brain and behavior.

Historically, the first direct electrical stimulation of the brain was demonstrated by Fritsch and Hitzig in the 19th century, 1870. They localized the motor area of the cerebral cortex, which you can see, below there are pictures. This is the central sulcus and this is the area in front of it. So it is the motor cortex. And this led ultimately to an understanding of how the motor cortex is organized.

(Refer Slide Time: 01:10)

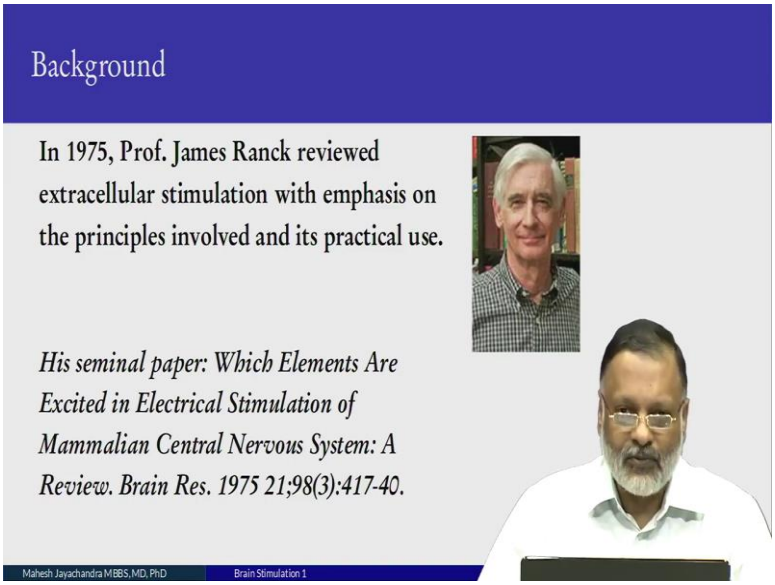


So, over the years electrical stimulation has led to important discoveries in brain function. The most important being that electrical self-stimulation which occurs when you have the electrodes stimulating the pleasure center. It is also called the Median Forebrain Bundle, or the Fasciculus Medialis Telencephali. So here you have a picture of James Olds, is a very famous Canadian neuroscientist.

And here next row, you have the rat. And a rat has electrodes implanted into his pleasure center. So they found, this is a sudden repetus discovery. They were not looking for it. They found that the rat would keep self-stimulating itself regardless of other stimuli. It would ignore food, it would ignore water, they even tried drugs like cocaine, it would ignore it. And it would keep self-stimulating itself literally to death. 7 hours, 24 hours and then it dies of exhaustion.

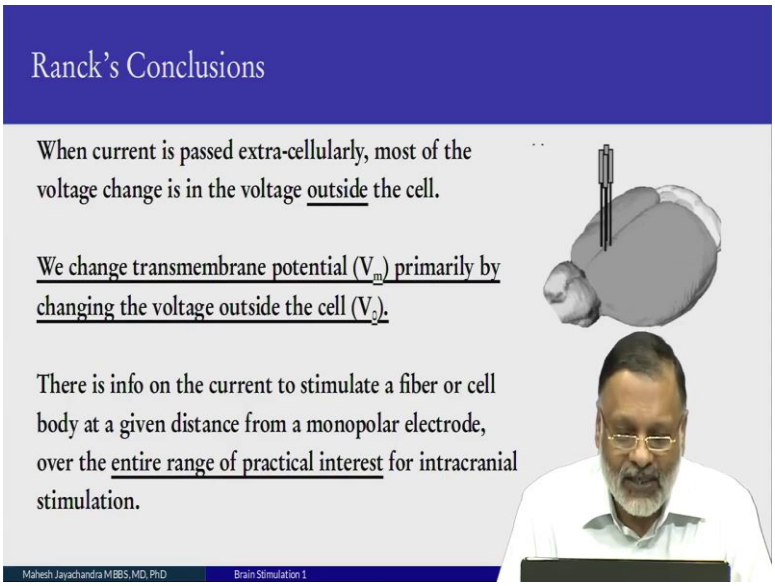
So this was a very interesting discovery that you have a pleasure center and stimulation of the pleasure center overrides all other stimuli. We will come back to it in the last slide. If used properly, electrical stimulation is an extraordinarily useful and powerful technique for dissecting behavioral and neurophysiological mechanisms underlying brain and behavior.

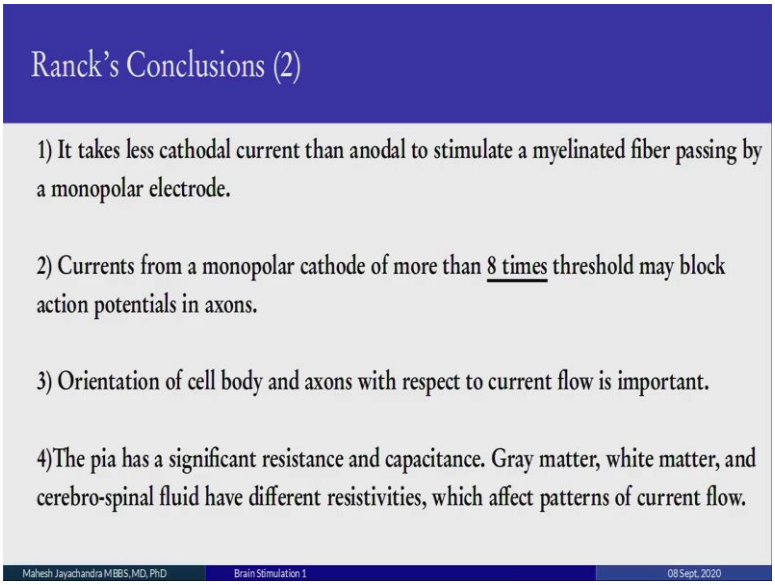
(Refer Slide Time: 02:42)



So, in 1975, Professor James Ranck reviewed extracellular stimulation with an emphasis on the principles involved and its practical use. This remains a seminal paper, which elements are excited in electrical stimulation of the mammalian central nervous system. And I strongly advise you to check it out if you want a more detailed understanding of electrical stimulation. Jim was also one of my mentors in grad school. The head of my program in Suni Brooklyn.

(Refer Slide Time: 03:14)



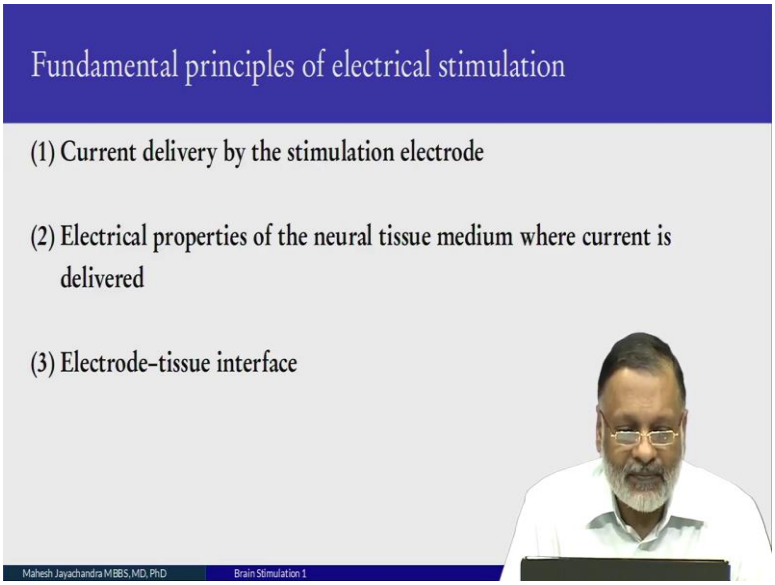


So his conclusions. So, when current is passed extracellularly, most of the change, the voltage change is in the voltage outside the cell. So we change the transmembrane potential, if you remember V subscript m, primarily by changing the voltage outside the cell, that is V naught. So there is a lot of information on the current needed to stimulate a fiber or a cell at a given distance from a monopolar, a single electrode over the entire practical interest, range of practical interest for intracranial stimulation.

So some of these conclusions, first of all, it takes less cathodal current than anodal to stimulate a myelinated fiber passing a neuro monopolar electrode. The currents from a monopolar cathode if it is more than 8 times the threshold, may block the action potentials in the axon. Another important point is what is the orientation of the cell body and axons for current flow.

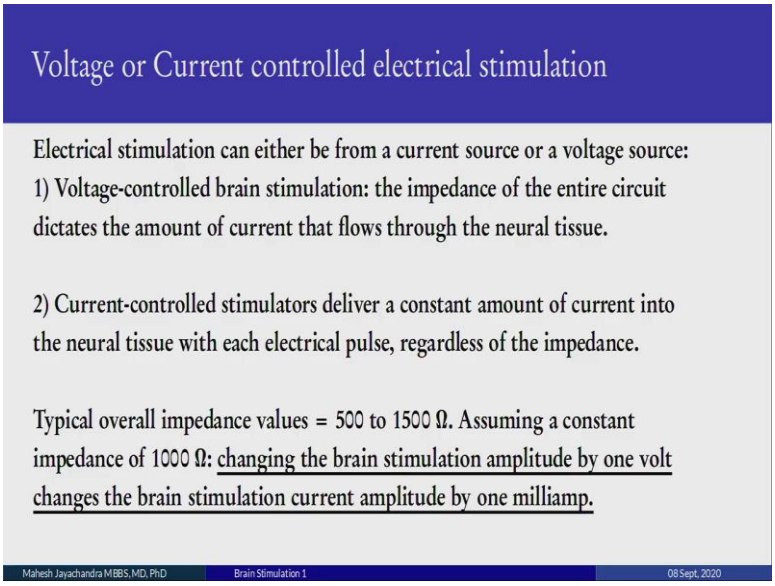
And the coverings of the brain, they call them NNGs, we have not dealt with them in detail. But one of the coverings, the pia motor and it has significant resistance and capacitance. These coverings are below the bone, the cranial. So gray matter, white matter, and cerebrospinal fluid, all have different resistances, resistivities if you will and these affect the patterns of current flow.

(Refer Slide Time: 04:45)



Fundamental principles of electrical stimulation. So current delivery is by the stimulation electrode. That is one point. The second point is the electrical properties of the neural tissue medium where the current is delivered. And finally, the electrode-tissue interface. All these parameters are important when we do electrical stimulation. And if you have a good idea of these parameters, then you have successful electrical stimulation.

(Refer Slide Time: 05:15)

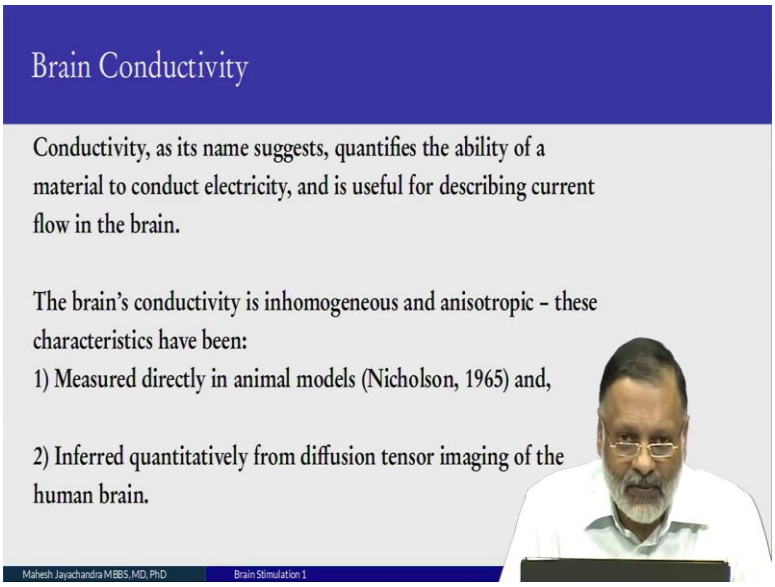


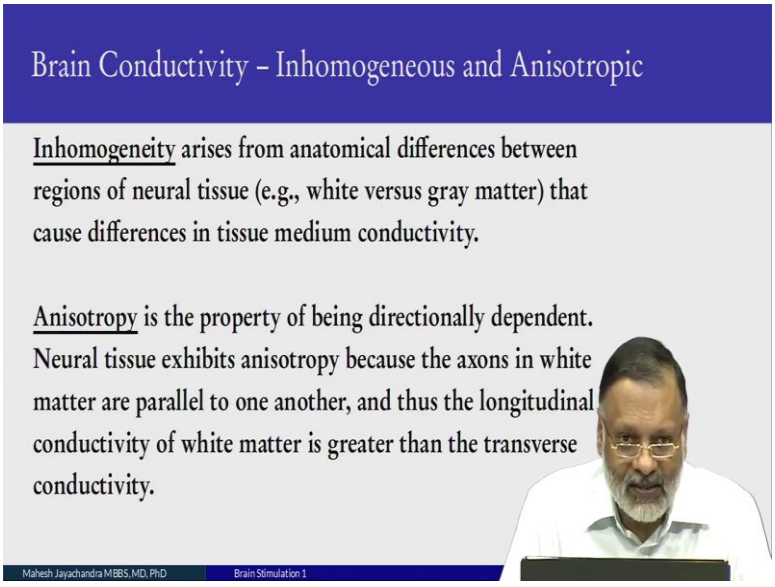
So, the electrical stimulation can either be of constant voltage or constant current. So, voltage-current brain stimulation, here the impedance of the entire circuit dictates the amount of current which flows through it. Ohm's law, V equals to IR, but here it would be V equals to IZ, where Z is the impedance. On the other hand, you have current constant, current

stimulators, or current control stimulators. These deliver a constant amount of current into the neural tissue with each pulse regardless of the impedance.

So, usually, we talk of impedance because some of the earliest, earlier work on electrical stimulation was done with AC stimulators. Typical overall impedance values range from 50, 500 to 1,500 Ohms. So assuming a constant impedance of 1K, changing the brain stimulation amplitude by 1 volt, changes the brain stimulation current by 1 milliamp straightforward.

(Refer Slide Time: 06:21)



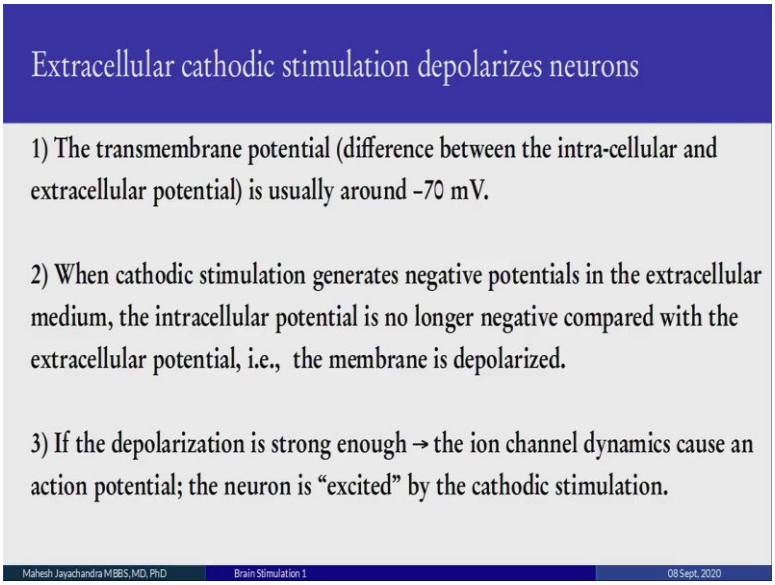


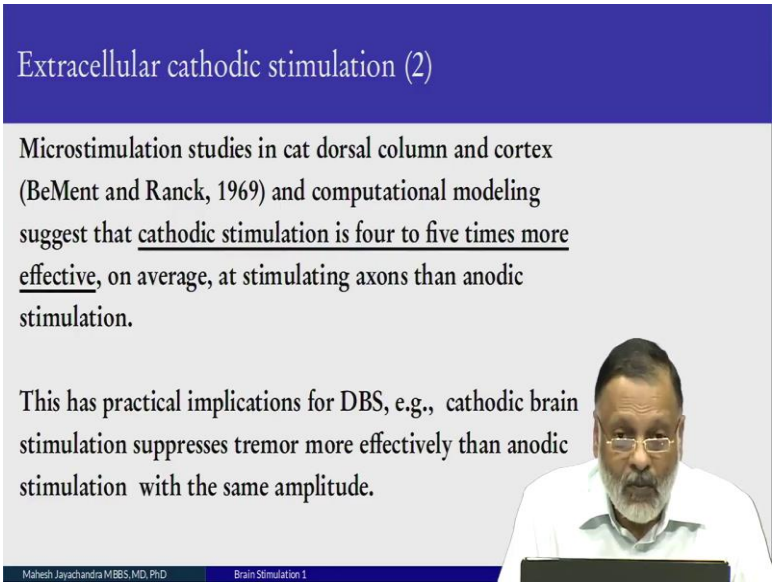
So, now let us come to conductivity. So, as its name suggests, this quantifies the ability of the material to conduct electricity and is useful for describing current flow in the brain. So the brain's conductivity is inhomogeneous and anisotropic. And these characteristics have been measured directly in animal models by Charles Nicholson and inferred quantitatively from

diffusion tensor imaging of the human brain. So, what is inhomogeneous and anisotropic? So, inhomogeneity arises from the anatomical differences between different regions. Like for example, from the white matter versus the gray matter.

And these cause differences in tissue medium conductivity. Anisotropy is the property of being directionally dependent like a vector. Neural tissue exhibits anisotropy because the axons in the white matter are parallel to one another. So, therefore, the longitudinal conductivity of white matter is greater than the transverse conductivity because of the membranes, so on and so forth. So, this is important. The conductivity of the brain is influenced both by the inhomogeneous structure of the brain and the anisotropy of the directional elements.

(Refer Slide Time: 07:45)



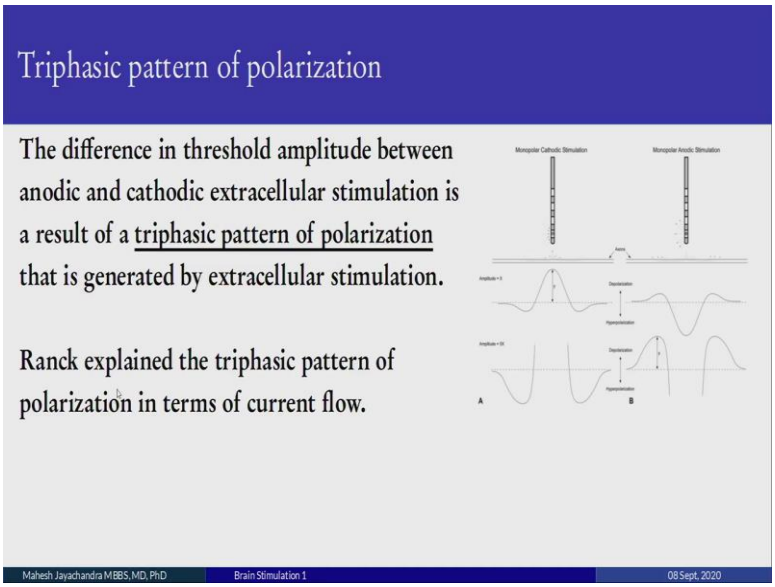


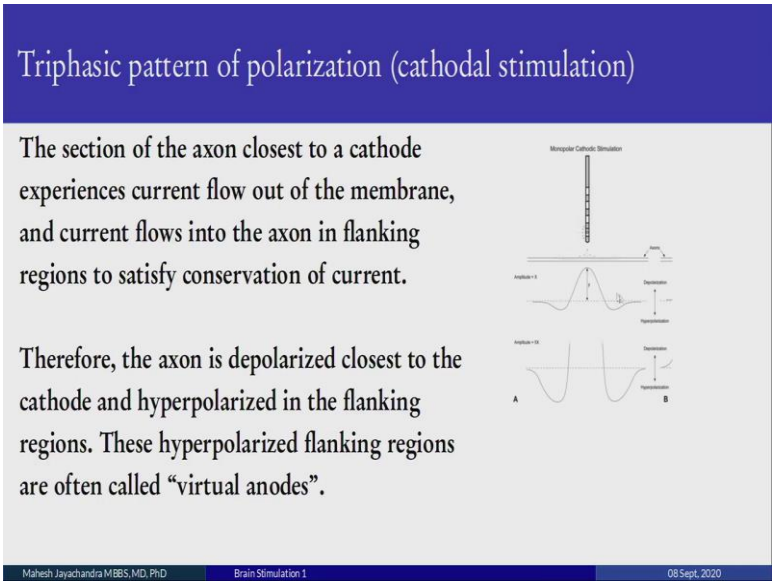
So, suppose you have a cathode in the extracellular space, and you stimulate with cathodic current, so if you remember, the transmembrane potential which is the difference between the intracellular and the extracellular potential is usually around minus 70 millivolts. When cathodic stimulation generates negative potentials in the extracellular medium, the intracellular medium is no longer negative, so negative compared to the extracellular medium.

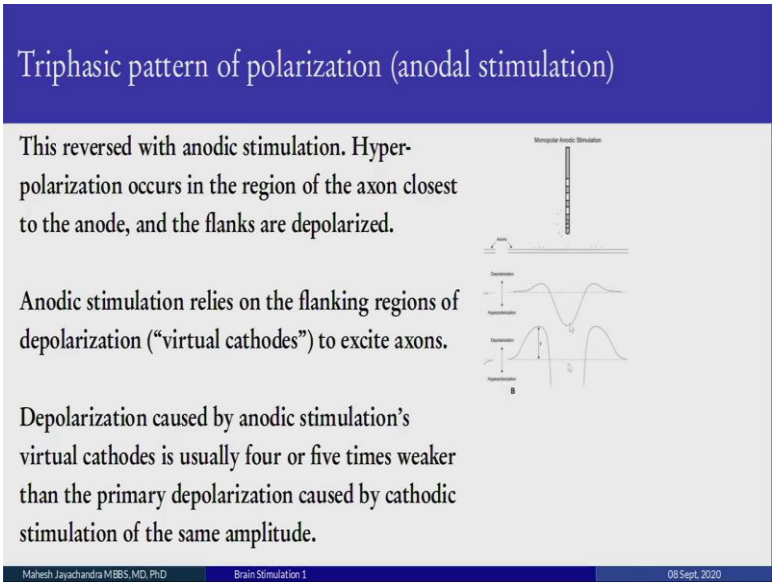
So the membrane is depolarized. If the depolarization is strong enough, then the ionic channel dynamics which we studied in the action potential lectures cause an action potential i.e. the neuron is excited by external cathodic stimulation. So, these studies were done in the cat dorsal column and cortex by James Ranck in 1969.

And computational modeling suggests that cathodic stimulation is 4 to 5 times more effective on average as stimulating axons than anodic stimulation. Now, why is this important? This has practical implications for deep brain stimulation. So cathode stimulation deep inside the brain, it suppresses tremor, for example, Parkinsonic tremor more effectively than anodic stimulation with the same amplitude.

(Refer Slide Time: 09:15)







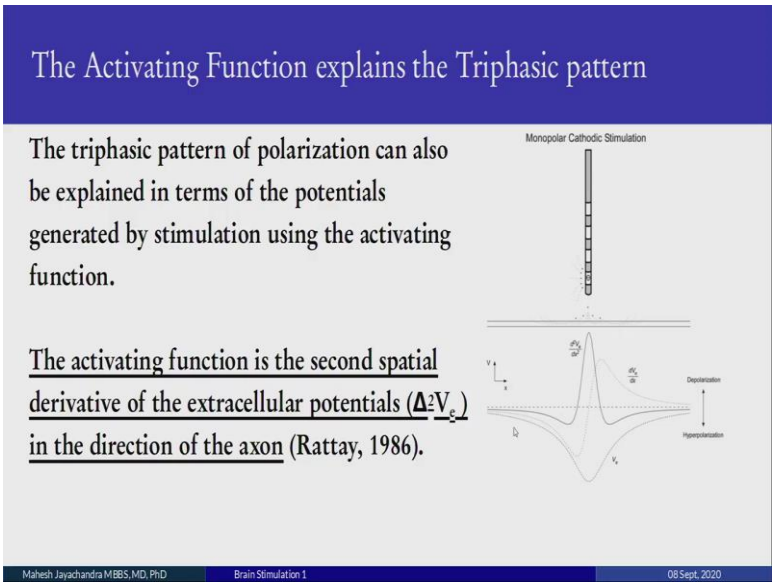
So, what is the current profile when you have a cathode or an anode stimulating an axon? So, on the right, you have a cathodic stimulation on the left and anodic stimulation. These are monopolar electrodes and there is some distant electrode that is not close by which allows for the current to return to the circuit. So, with both kinds of stimuli, you get a triphasic pattern of activation, like so. So, this is an amplitude X and then at amplitude 5X, it becomes much more. So Jim Ranck explained the triphasic pattern of polarization in terms of current flow.

So we shall deal with a cathode, a cathodic stimulation first. So, consider this, the monopolar cathode is next to an axon. And we, it draws current through the electrode. And this is the triphasic pattern profile of current in the axon. So, the section of the axon closes to the cathode, experiences current flow out of the membrane. And current flow occurs in the

flanking sections inside. And so you have this depolarization occurring here and next to it you have hypopolarization.

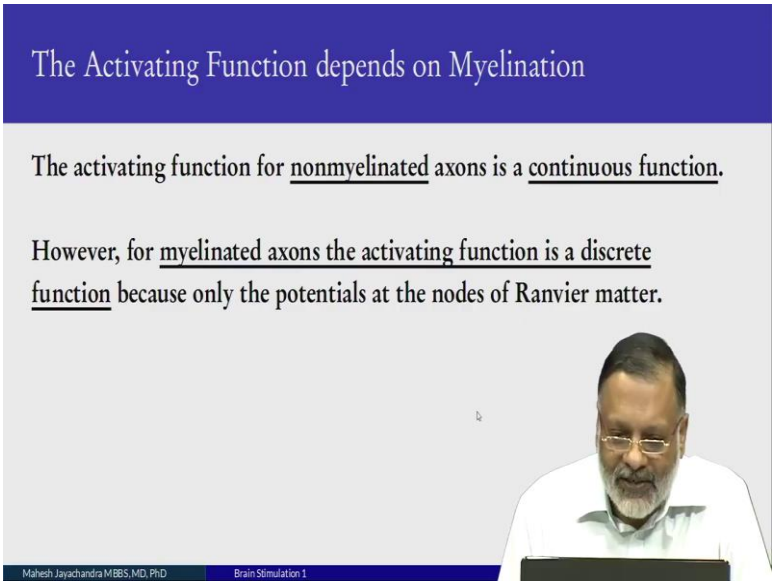
So these hypopolarized areas flanking the depolarized area are called virtual anodes because it behaves like a virtual anode. The situation is reversed with anodic stimulation. So, here you have current going into the axon, coming out from the flanking regions. And you have virtual cathodes on either side of the virtual anode. And in the middle, it gets hypo polarized. And again depolarization caused by anodes is usually 4 to 5 times weaker than the primary depolarization caused by cathodic stimuli of the same amplitude.

(Refer Slide Time: 11:24)



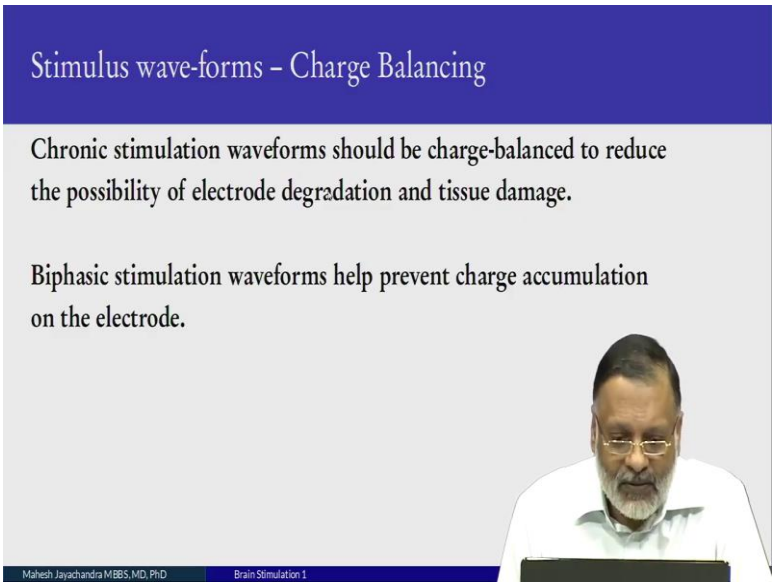
So, you have this concept of an activating function which is first shown by Rattay in 1986. So, the activating function is the second special derivative of the extracellular potentials in the direction of the axon. So, this is the voltage. This is the voltage being induced. This dotted line over here is the first spatial derivative and the solid line here is the second spatial derivative. This concept comes again in neurophysiology with current source density analysis, which shows the sources and syncs.

(Refer Slide Time: 12:10)



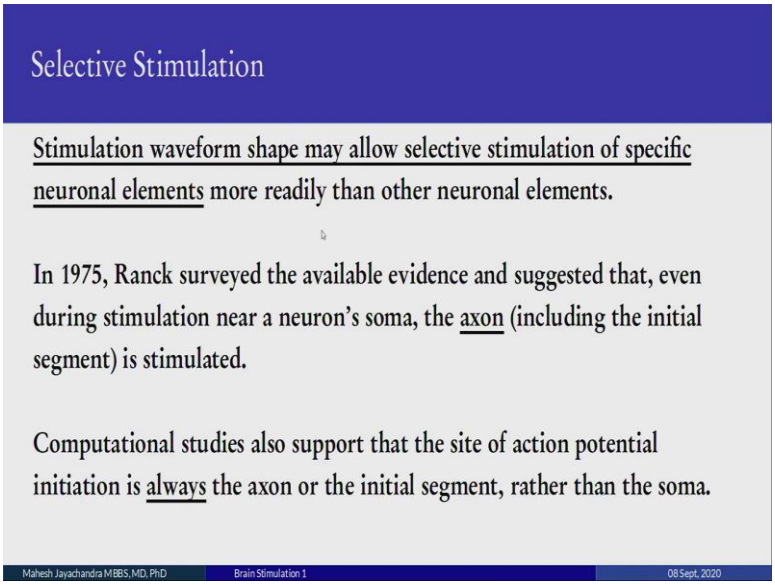
So, the activating function depends on myelination. So if there is no myelin, the activating function, is a continuous function. But if it is myelinated, remember you have the action potential occurring at the nodes of Ranvier because of salutatory function. So here it is a discrete function because the potentials only at the nodes of Ranvier matter. For nonmyelinated axons, there are no nodes of Ranvier, so it is a continuous function.

(Refer Slide Time: 12:40)



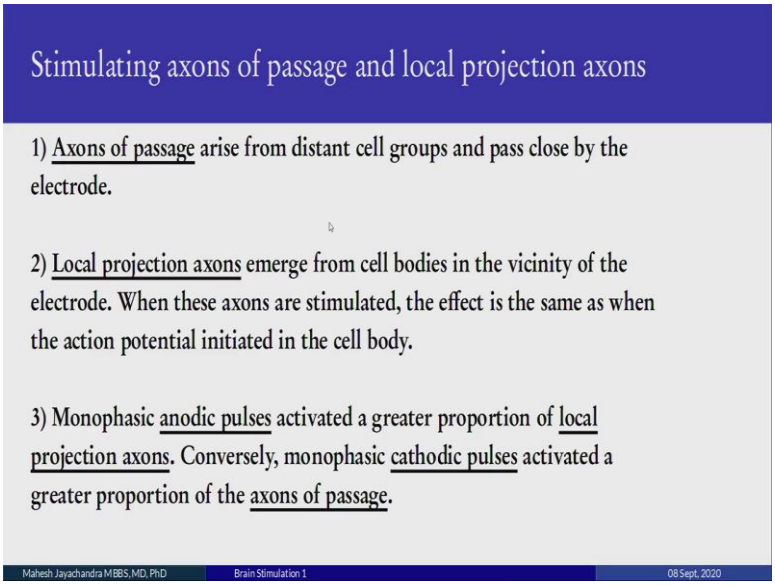
So, what are the, when you give a stimulus, when you use electrical stimulation of neurons, they have to be charge-balanced because if they not, there would be electrode degradation and tissue damage at the electrodes. And by physics stimulation waveforms help in preventing charge accumulation on the electrode.

(Refer Slide Time: 13:02)



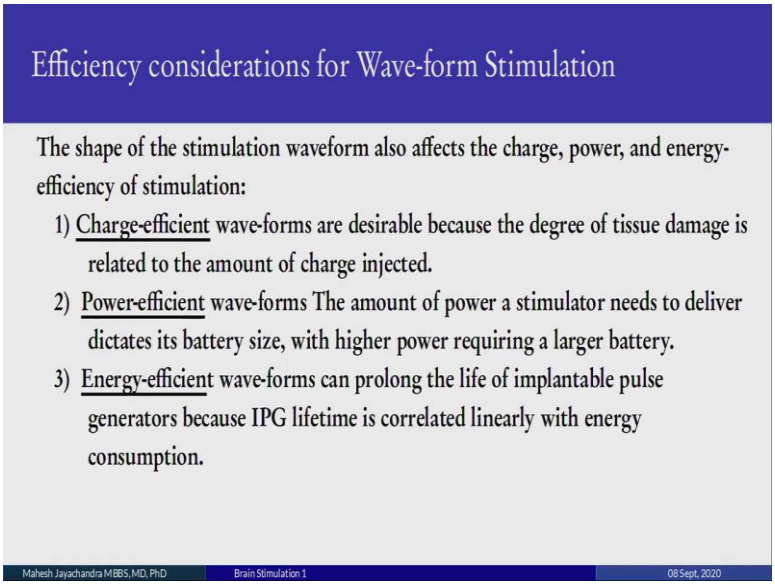
So, depending on the stimulus waveform shape, you can selectively stimulate specific neuronal elements more easily than other neuronal elements. In 1975, Jim Ranck surveyed the available evidence and suggested that even during stimulation near an axon soma, the axon including the initial segment which we considered previously is stimulated. And recently computational modeling studies also support the fact the site of the action potential initiation is always the axon or the initial segment rather than the cell body or soma. This because the initial segment is easier to excite because of the preponderance of voltage sodium channels in it.

(Refer Slide Time: 13:56)



So, there are, when you stimulate neural elements and axons, there are two definite populations that can be stimulated. So, one is axons of passage. They arise from distant cell groups. They just happen to be close to the stimulating electrode. Local projection axons, on the other hand, come from the cell bodies in the vicinity of the electrode. So when you, these axons are stimulated, the effect is the same as when the action potential is initiated in the cell body. So monophasic anodic pulses activate a greater proportion of local projection axons. Conversely, monophasic cathodal pulses activate a greater proportion of axons of passage.

(Refer Slide Time: 14:50)

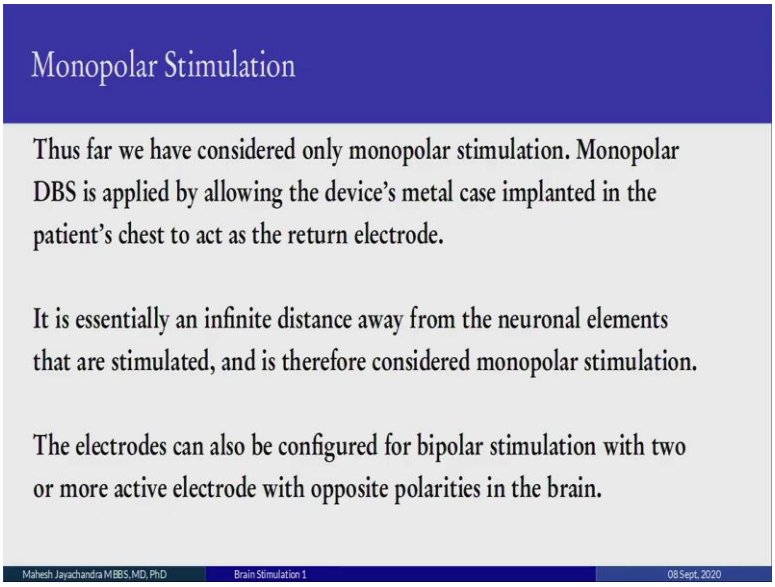


So what are the considerations, efficiency considerations for electrical stimulation? So the shape of the stimulation waveform affects the charge, power, and energy efficiency of

stimulation. So charge efficient waveforms are desirable because there is less tissue damage related to the amount of charge injected.

Power efficiency. The amount of power a stimulator needs to deliver dictates the battery size with higher power requiring a larger battery. Then energy efficiency. So the more energy efficient a waveform is it can prolong the life of an implantable pulse generator. These generators are implanted in the brain for deep brain stimulation, Parkinson's, and a few other diseases, and this IPG lifetime is correlated linearly with energy consumption. If it is inefficient, then you have to replace it every few months and if it is efficient, you can go on for years.

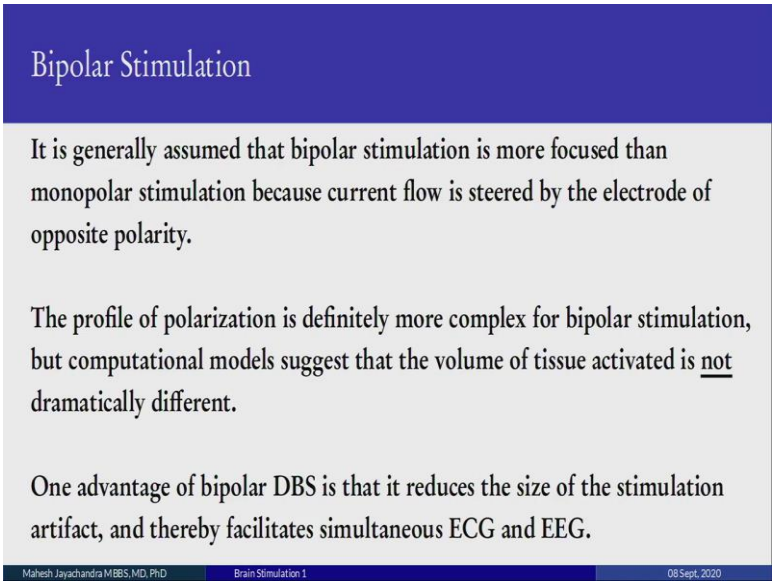
(Refer Slide Time: 15:50)



So monopolar stimulation. So far we have just considered monopolar stimulation. And that is a single electrode close to the neuronal elements. And monopolar deep brain stimulation is applied by allowing the device's metal case implanted in the chest to act as a return electrode. So you have the electrode in the brain and then you have a device which is implanted somewhere in your chest and the chassis of the device, that acts as a return electrode.

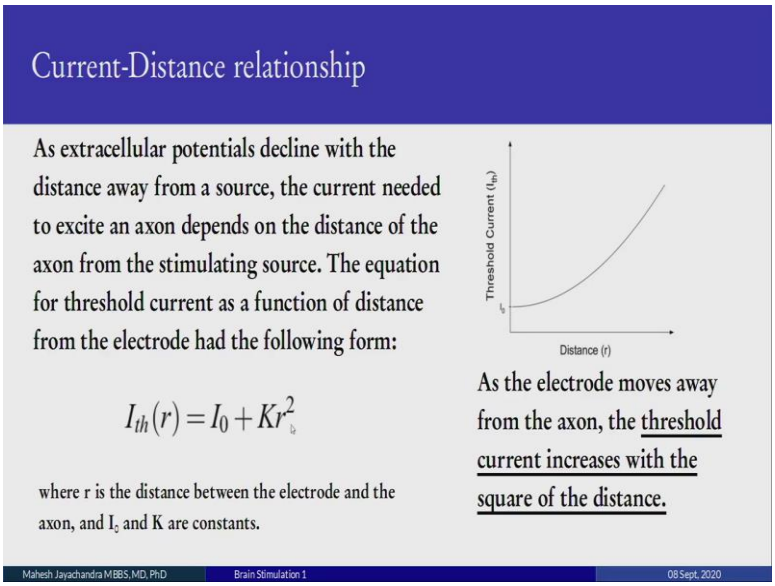
It is considered an infinite distance away from the neuronal element, here I suppose to here. And therefore, this electrode would be considered monopolar. The electrodes can also be configured for bipolar stimulation with two or more electrodes of opposite polarities in the brain or close to each other.

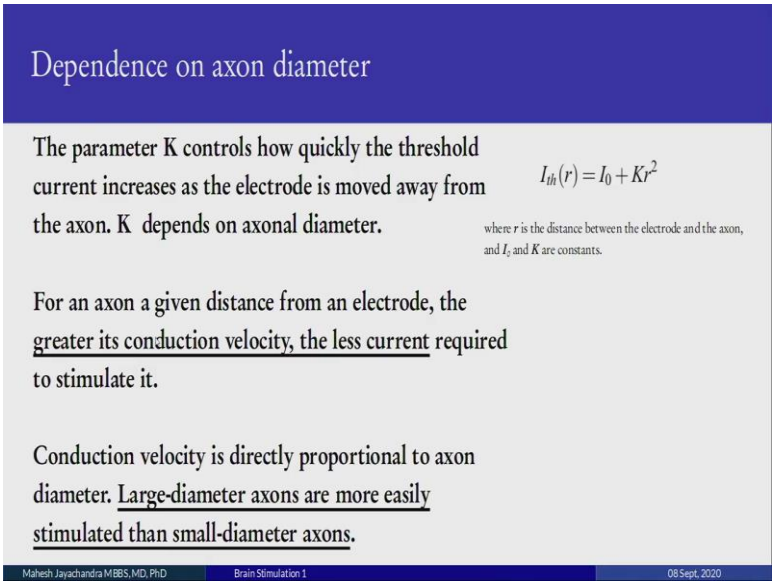
(Refer Slide Time: 16:42)



So, it is assumed, I mean just by intuition that bipolar stimulation is more focused than monopolar stimulation because the current flow is steered by the electrode of opposite polarity. So while the profile of polarization is more complex for bipolar stimulation, the computational model suggests that the volume of tissue activated is not that much different from monopolar stimulation. However, one major advantage of bipolar deep brain stimulation is that you decrease the stimulus artifact, and therefore you can simultaneously record ECG and EEG.

(Refer Slide Time: 17:27)





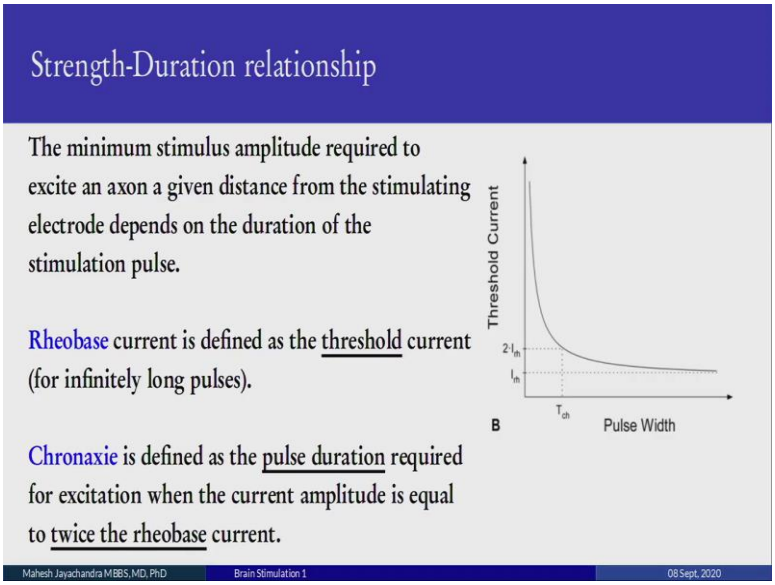
So what about, how far should the electrode be from the site of interest? So as extracellular potentials decline with distance from a source, the current needed to excite an electron depends on the distance of the axon from the stimulating source. So this equation for threshold current as a function of distance from the electrode is of the following form,

$I_{th}(r) = I_0 + Kr^2$

where r is the distance between the electrode and the axon, and I_0 and K are constants.

So if you look at the graph on the right, as the electrode moves away from the axon, the threshold current increases with the square of the distance. So non-linear. So the parameter K controls how quickly the threshold current increases as the electrode is moved away from the axon and K depends on the diameter, axonal diameter. So for an axon of a given distance from an electrode, the greater its conduction velocity the less the current needed to stimulate it. Now we know that conduction velocity is directly proportional to axon diameter. Therefore, large-diameter axons are more easily stimulated than small-diameter axons.

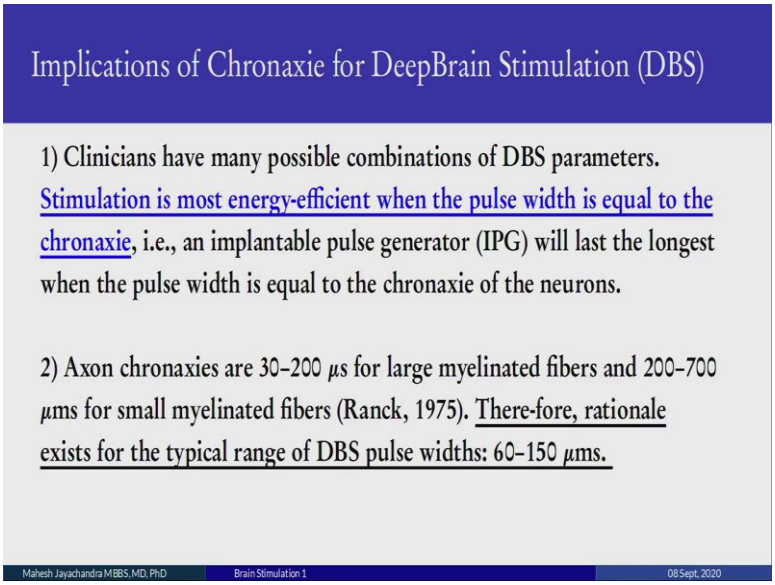
(Refer Slide Time: 18:45)



So now we get into strength-duration relationships. So the minimum stimulus amplitude required to excite an axon at a given distance from a stimulating electrode depends on the duration, also depends on the magnitude, but also on the duration of the stimulation pulse. So the threshold. So, this is, these concepts were first put on the table by Lapiq, a French neurophysiologist. So rheobase is the threshold.

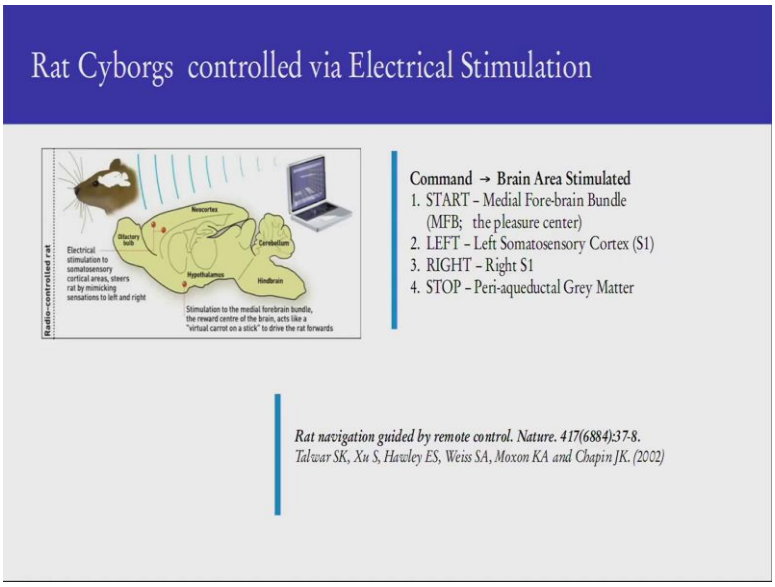
Rheobase current is defined as a threshold current for infinitely long pulses. So an infinitely long pulse and this is the threshold current, I_{rh} is the rheobase current. Chronaxie is defined as the pulse duration required for excitation when the amplitude of the current is equal to twice rheobase. So twice of this and this is the pulse width. These parameters were further amplified and studied in detail by W. A. H. Rushton FRS, physiological society.

(Refer Slide Time: 19:56)



And why is it important? So, clinicians, when we stimulate, when clinicians stimulate the brain with, for Parkinson's they use deep brain stimulus parameters. Stimulation is the most energy-efficient when the pulse width is equal to the chronaxie, i.e., an IPG, an implantable pulse generator will last the longest when the pulse width is equal to the chronaxie of the stimulated neurons. So, from Jim Ranck's data, axon chronaxies are 30 to 200 microseconds for large myelinated fibers. And 200 to 700 microseconds for small myelinated fibers. Therefore, a rationale exists for the typical range of deep brain stimulation pulse widths of 60 to 150.

(Refer Slide Time: 20:50)



So, finally, how is it important? One is it is important for deep brain stimulation, but also you can make rat cyborg. And this was first shown by Talwar Atal, from Suni Brooklyn and the group is headed by John Chapin and 2002, what they did was put different electrodes in the rat's brain. And the rat, moves its way through the environment using its whiskers. The whiskers sense obstacles. So, when it feels like an obstacle on this side, it moves to the other side.

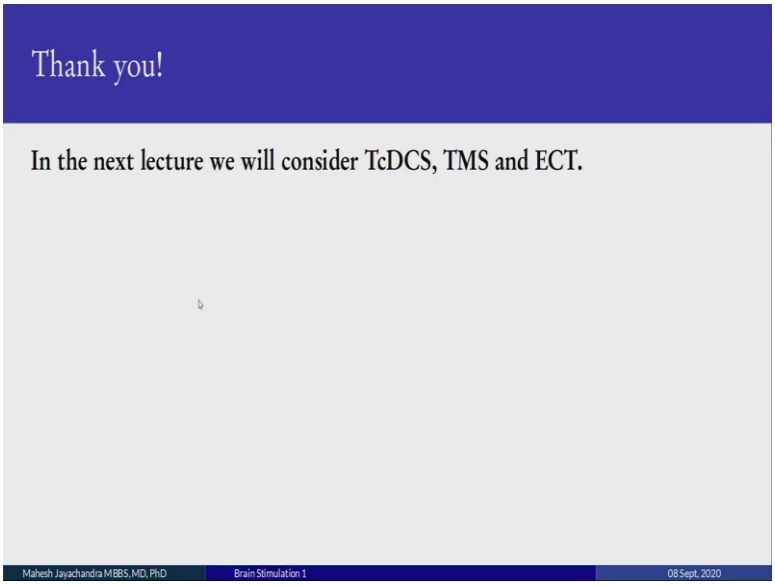
And when it feels an obstacle over here, it moves this side. So what we do is since the brain is contra-laterally represented, the whiskers over here are represented at this side on this hemisphere, so we put an electrode over here. And when we stimulate it over here, the rat feels an obstruction and moves this side and likewise over here. And we can make it move. Now, why should it move? Remember, Olds, James Olds earlier on in this lecture, so when you couple this to the pleasure center, and then you can control this movement.

So if it moves this side with stimulation, appropriate stimulation, and it moves correctly, you stimulate its pleasure center. Now the pleasure center is the ultimate pleasure a mammal can get. It overrides everything, better than food, better than sex, better than drugs, much much more. So it is compelled to do it. And what they did was they showed it. So, over here you have the two somatosensory cortical areas which steers rat by mimicking sensations left and right. And you get these pleasure centers over here, MFB, Medial Fore-brain Bundle.

And this is the reward, the central. So if the rat moves the way it is supposed to, then it gets a sort of pleasure. So these are the actual commands. So, for starting, we just stimulate the pleasure center and starts moving. For the left, we stimulate the left somatosensory cortex so it feels something on the right and moves away. And likewise for the right. And also there is an area called the peri-aqueductal grey matter, which is found by Chinese scientists.

And if you stimulate that area, the rat freezes and comes to a full stop. I might ask, what happens if you overstimulate the pleasure center, what does the rat do? Well, it starts circling, it goes round and round and round.

(Refer Slide Time: 23:27)



So, thank you. In the next lecture, we shall consider transcranial direct current stimulation, transcranial magnetic stimulation, and electroconvulsive therapy.