

# Synapses, Neurons and Brain Lecture 1-6

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## Synapses, Neurons and Brain Lecture 1-6

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Great Thinks

The Connectomics-Complete 3D road-map for the brain

Brainbow technology-Colorful, genetically-designed, brains

Brain-machine/computer interface (BMI)

Optogenetics-Light-activated brain circuits

Computer simulation of the brain-"Blue Brain Project"

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The Voltage Clapm & The Space Clamp

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QUIZ

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Neurogenesis and Learning

QUIZ

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- The Brain Computes
- Computation at the Level of Single Neuron
- Fundamentals of Dendritic Cable Theory
- Rall Cable Theory for Dendrites
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  - Input classification with dendritic neurons (Barlett Mel)
  - Neuron as directional selective computational device

Recent Breakthrough

QUIZ

## WEEK 1: Lesson 1-New Frontiers

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Understand brain, the machine, in physical terms.

### Great Thinks

The age of the modern Human (*Homo sapiens Sapiens*) is 200,000 years.

What happened to Homo Sapien's brain in 20000 years?

Why did the size of Homo Sapien's brain shrink in 10000 years ago? Even though we realize that less weight does not mean less intelligence, still, there must be a reason for the needs of smaller brain.

### The Connectomics-Complete 3D road-map for the brain

At the very beginning of modern neuroscience: Camillo Golgi (Italy) and S. Ramon Y Cajal (Spain)

using Golgi Staining method was very sparse. Very small percents of cells stained so the connection of synapses were not seen.

Harmonia Hall thought there should be **Units of Brain** - should be built from little units like other tissues

And he was right. These elements are not really physically a continuum. They are separated elements. There is a gap between them.

So here comes **Connectomics**.

The idea of **Connectomics** is to cut very thin slices of the brain, slice after slice after slice, at the nanometer scale. Then you detect the structure within each slice separately, and put the slices back, or align them back, one on a top of each other, one after the other at a very fine resolution and then **reconstruct a piece of the brain**. In this small piece of brain you can really see **whether they touch each other or not**. This is called **the electron microscope system**. And eventually you can see **whether neurons are making synaptic contact with each other or not**. That's how we map the whole brain in 3D anatomy, which is called the **Connectomics**.

### **What are the prospect and future of the Connectomics?**

1. being capable of building the "**blue print**", the anatomical foundation of the whole (healthy and sick) brain
2. Starting to bridge the "**structure-to-function**" problem and enable **realistic computer simulation** (simulation-based research) of the respected (healthy or sick) network

Even though the usefulness of connectomics is somewhat debated. Among popular arguments against it is that connectomics typically provides a static image. It can show which neurons have the possibility of interacting, but it does not show if they do, how much they do, and what the effect of that interaction is.

we have already built the complete road-map of *C.elegans* connectome. But to build human connectome is not realistic.

The completed connectome of *C. elegans* maps its 300 neurons and roughly seven thousand synaptic connections. This does not include synaptome or epigenome maps, but still took twelve years of manually recognizing and cataloging the neurons.

The human brain, in contrast, is eleven orders of magnitude more complex than *C. elegans* with around 100 billion neurons and 700 trillion synaptic connections. Therefore, creating a connectome using the same method as *C. elegans* is not realistic.

Basically, Macroscale connectomes are commonly collected using diffusion magnetic resonance imaging (dMRI); on the other hand, microscale connectors focus on a much smaller area of the nervous system with much higher resolution. So these datasets are commonly collected using electron microscopy imaging and offer single synapse resolution of entire local circuit.

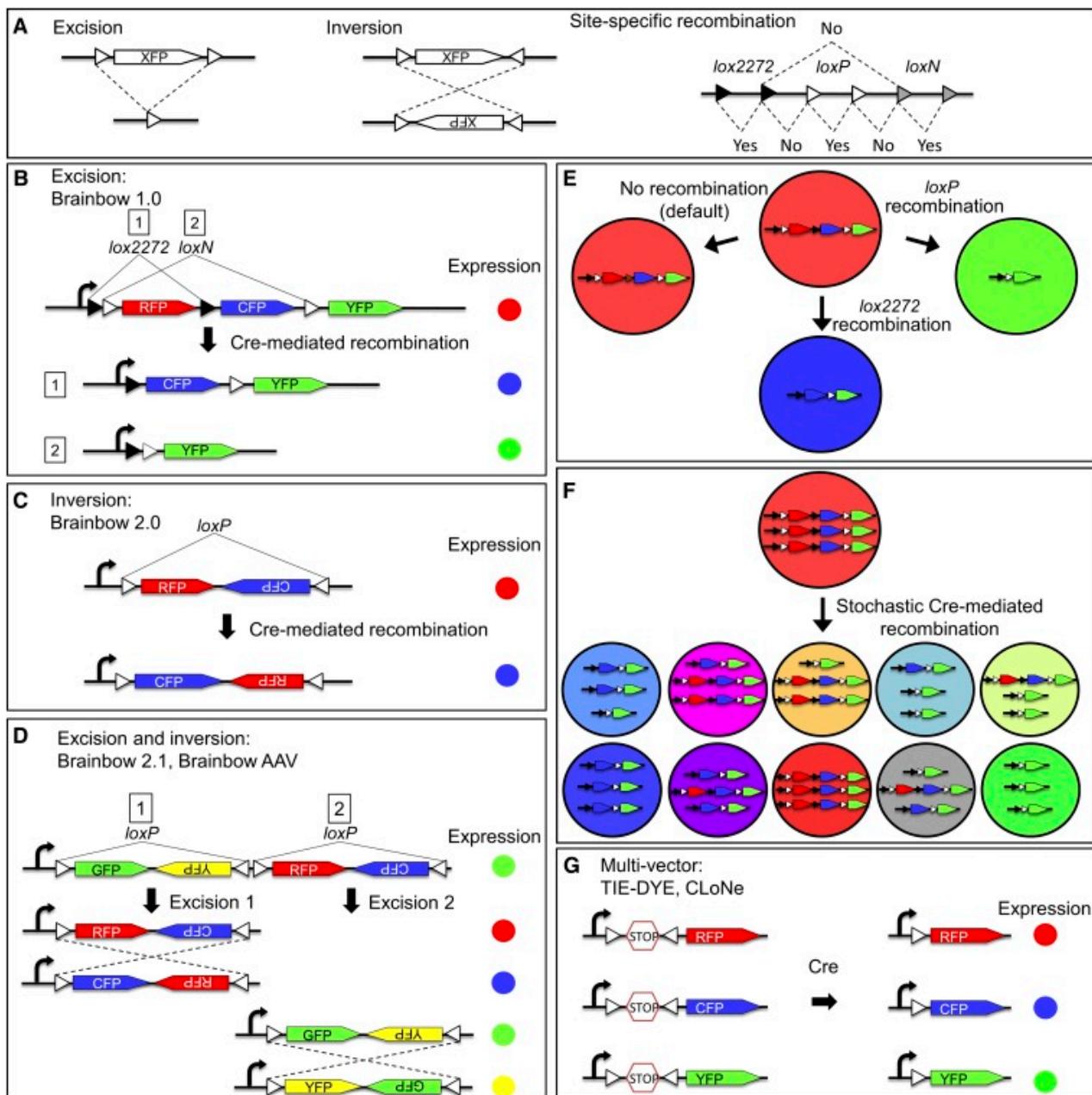
## **Brainbow technology-Colorful, genetically-designed, brains**

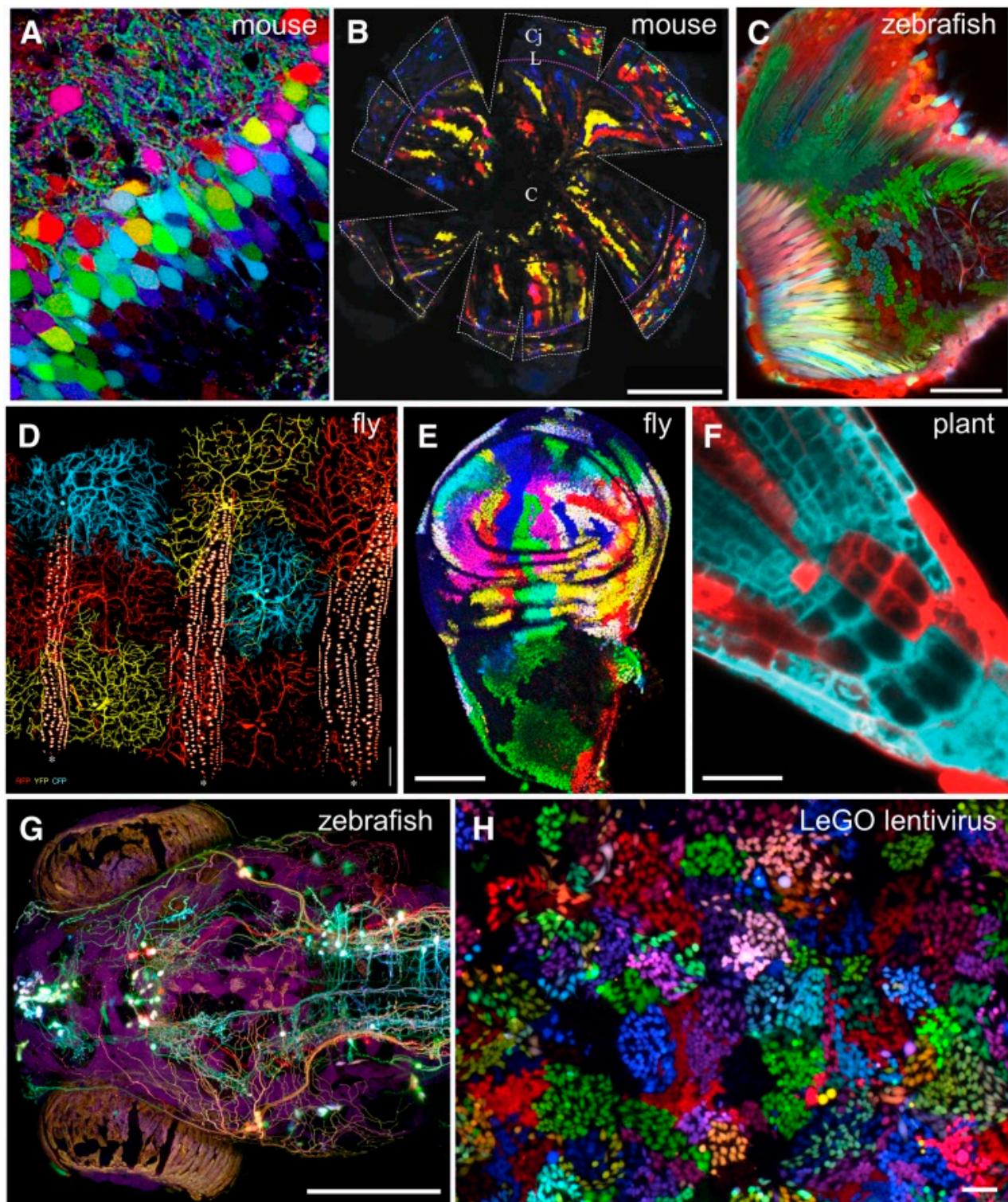
### **What is Brainbow?**

Brainbow is a genetic cell-labeling technique where hundreds of different hues can be generated by stochastic and combinatorial expression of a few spectrally distinct fluorescent proteins.

## Basically, this technology makes brain be seen with fluorescent colors.

Weissman, Tammy A., and Y. Albert Pan. "Brainbow: new resources and emerging biological applications for multicolor genetic labeling and analysis." *Genetics* 199.2 (2015): 293-306.





Brainbow makes neurons can be seen under the level of light microscope. Notably, even though the approximate "contact" can be seen between neurons, it can not be zoomed in and determined that what we saw is "the synapse". Because the resolution of light microscope is just not good enough to speak about synapses, which is smaller, in fact it is too small to see in the light microscope. But the brainbow is still important for modern anatomy.

Now let's talk about what we can do about the Brainbow.

1. looking at the structure basis for learning **in the brain in real time** to find out **anatomical changes**
2. tagging and generic-characterization of the **different cell-types** (the building blocks) in a given system (eg., retina)

### 3. Tracing **short-and-long range connections in brain circuits**

Brainbow is a process by which individual neurons in the brain can be distinguished from neighboring neurons using fluorescent proteins. By randomly expressing different ratios of red, green, and blue derivatives of green fluorescent protein in individual neurons, it is possible to flag each neuron with a distinctive color. This process has been a major contribution to the field of neural connectomics.

## Brain-machine/computer interface (BMI)

In a particular circuit, electrical signals are always running through and convey information. A brain-machine/computer interface need to process information as an input to understand the events happened in the region of the brain.

**Spikes in a cell-bar code of brain**, the selectivity generated by brain

Interestingly, these **pattern of code of the brain** can be used in diagnostication of disease. E.g., Parkinson disease.

Now BMI are used to treat patients.

### Future challenges for BMI

1. interaction between BMI and brain in a telemetric way by **developing chronic brain nano-probe** and **telemetric communication with the brain**

like putting some kind of chronic recorder or chronic probe **instead of wires** that will listen and record the electrical activity of many cells. (nanotechnology)

Besides, in order to put chronically a little piece of machine into the brain that will telemetrically send signals outside of the skull. So this telemetric communication with a brain both from the brain **outside** but also maybe to **stimulate the brain telemetrically**.

2. Developing **real time multi (millions) signal processing methods**
3. Developing **robotic sophistaced arm**
4. getting signals feed back from *sensors*

## Optogenetics-Light-activated brain circuits

The general idea of optogenetics-light-activated brain circuits is to develop again molecular genetic tools to be able to stain the cells. So that you would shine light in a particular wavelength onto the particular cell that was manipulated to become sensitive to light then the cell will respond electrically.

For example, cells in retina can transform light signal into electrical activity.

Interestingly, scientists found the gene or the molecule that can be embedded into the cells that usually are not sensitive to light in the brain. And then, when you shine light on this brain, this group of cells respond to the light electrically. Basically, you can make these cells sensitive to light by embedding specific protein/gene.

For example, you can embed **ion channels** into cells. When you shine blue light and the ion channels open and there is current flow and cells start to fire. (Blue light-spike)

The opposite thing happens when you put another kind of ion channels into the cell. The spike of cell will be restrained when the yellow light shines.

This will give scientists ability to manipulate brain cells by shining lights.

## Computer simulation of the brain—"Blue Brain Project"

Making a **replica** (a computer model) to computationally stimulate the real activity of brain or disease state of brain.

## WEEK 2: Lesson 2-Ingredients of Brain-Neurons

### The Neuron

#### History

1665-Robert Hooke first used a simple microscope to view living cells

1839-Theodor Schwann first built the "Cell Theory"

1870-Camillo Golgi developed a silver-based method to stain nerve cells

it is a random staining method and it only stained limited number of cells

**Axonal boutons, Axon nerve ends about one percent or less of the neurons in the system can be stained**

1887-S.Ramon Y.Cajal used Golgi technique to propose the "Neuron doctrine"

He believed that the nervous system is built from individual separate elements called "neuron doctrine".

**Camillo Golgi, who I just mentioned developing the technique to stain cells. Santiago Ramon y Cajal who used this technique.**

1891-Henrich Waldeyer coined the word "Neuron"

Also Sigmund Freud involved in the neuroscience. He is the part of this development of concept about the neurons as an individual.

1897-Charles Sherrington coined the word "synapse"

# The Neuron Doctrine

S.Ramon Y.Cajal thought:

1. Information flows through along the axon.

He could not see any communication. But he thought that information must flow this direction. And then it means that they must be somehow connected to each other through this link. And from this dendrite, receiving the input from the axon, information flows this direction from the dendrite to the cell body of this post neuron. And then from the cell body to the axon of this neuron, and then from the axon of this neuron to the dendrite of the next neuron.

2. From an axon to another dentritie there is a communication.

**Summarization:** The neuron doctrine based on the work of Ramon y Cajal is a theory suggesting The nervous system is constructed from discrete individual cells – neurons.

This was the beginning of his concept that one neuron and the second neuron are separated somehow. And so he can call each one of them a cell, a **nerve cell**, later on a **neuron**.

## The theory of dynamic polarization

he says the receiving cell, **the receiving dendrites are first polarized**, somehow polarized, **electrically** probably, ret polarized in this region, because the input comes to the dendrite. It polarizes here and **then the polarization flows from the dendrite** to the soma and **then to the axon and so forth**. So this is called the theory of dynamic or dynamical polarization, by Ramon Y Cajal.

## Summarization

Dendrites are **receptive (input)** devices

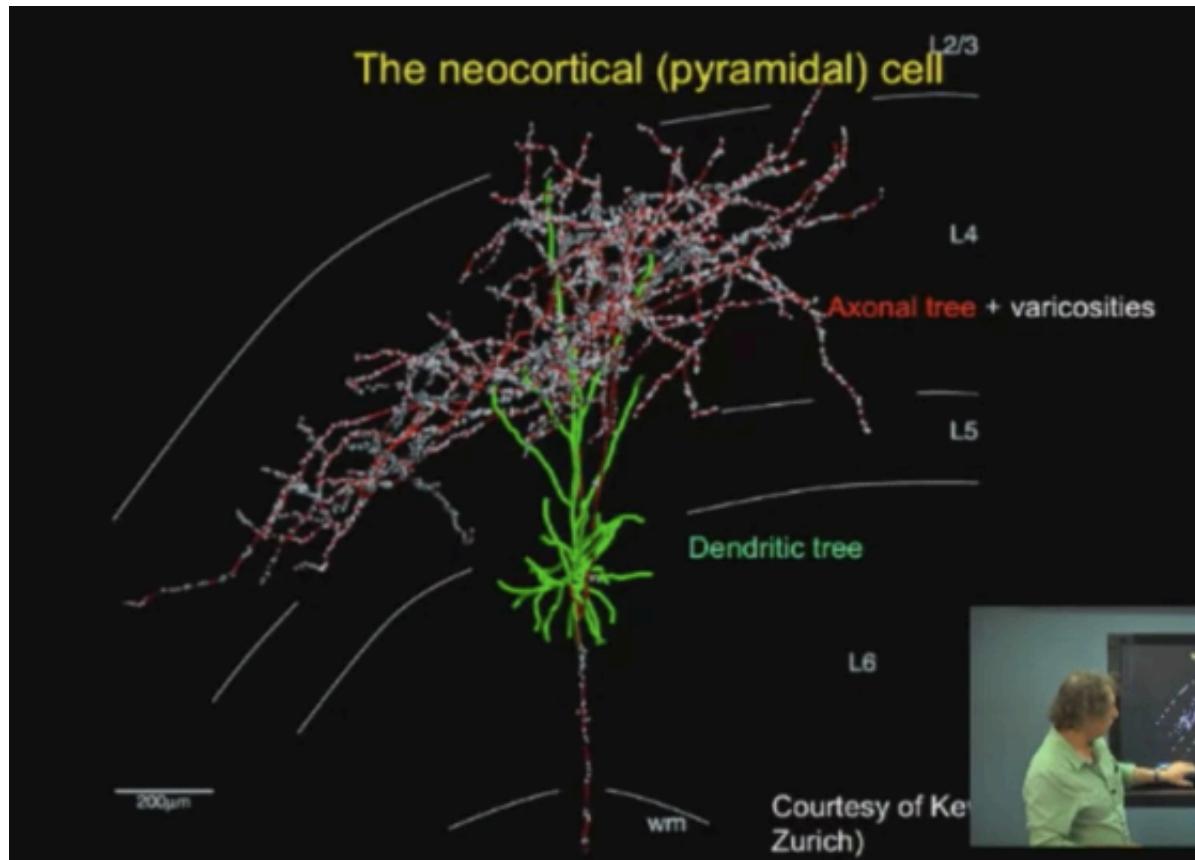
Axon are the **sending (output)** devices

But Golgi did not agree with Ramon Y Cajal. He did not feel that there is a distinction or separation between one neuron to the other. Golgi thought that they are all connected physically, they touch each other, which contributed to one big connected network.

**Golgi did not agree to the concept of neurons.**

Now we agree with Cajal that **the nervous system is built essentially from separated elements connected to each other via synapses.**

A modern view of neuron (in this case it belongs to a cat):

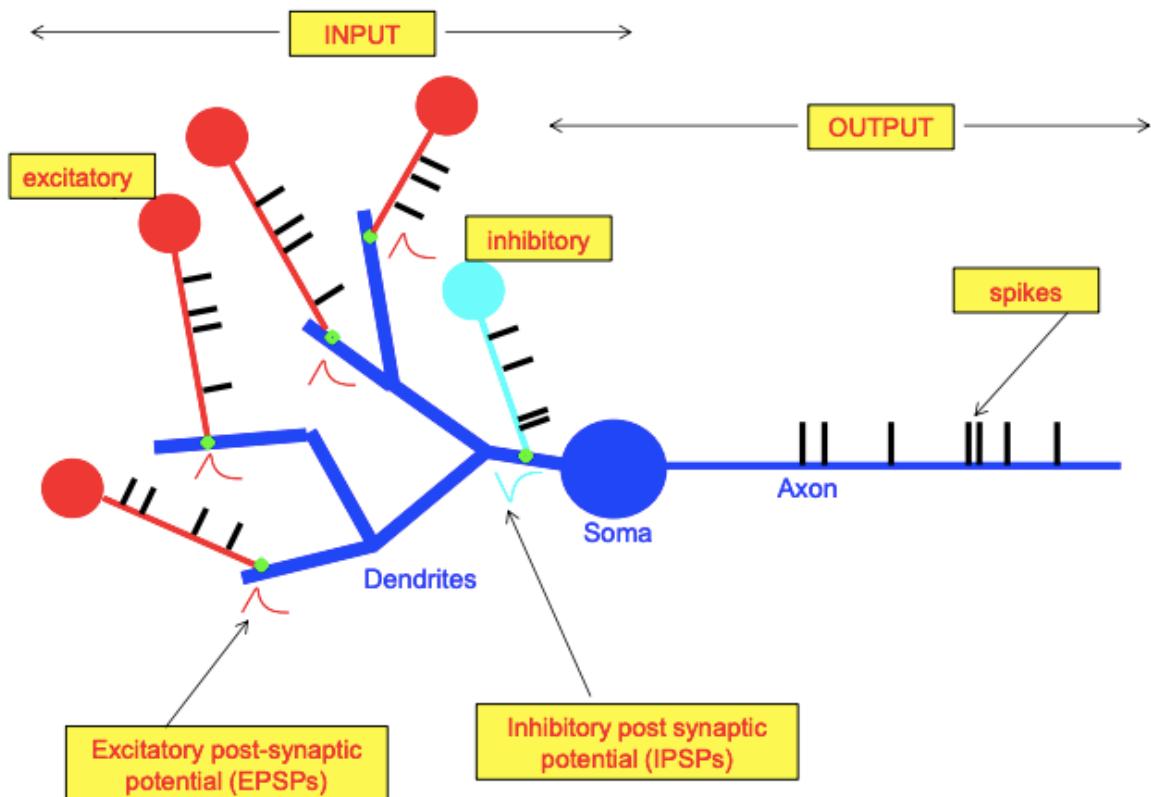


The **dendritic tree** which is **local**, the **axonal ramification branching**, which could be rather **global**, sometimes go to another part of the brain, sometimes make a lot of **synapse locally**.

## The Neuron as I/O Device Part I

In this part, the neuron will be considered as **an input/output device**.

# The neuron as an input-output **electrical** device (conceptual, details will follow)



The red neuron: the **pre-synaptic neuron** which make synaptic contact with the post-synaptic neuron (axons)

The blue neuron: the **post-synaptic neuron** (the receiving neuron) (dendrites)

When the pre-synaptic neurons make contact with the post-synaptic neurons, they locally make a little change in voltage/potential, which is called **the positive synaptic potential locally**. The red neurons are called **excitatory cells**, these cells try to **activate** the post-synaptic cell. (**action potential signals**)

**Excitatory** means that these red cells through transmission of action potentials, reaching the Soma, **generate post-synaptically in the dendrite locally**. They generate positive signal which I call excitatory post-synaptic potential.

The green neuron: also make contact with the blue neuron but tries to **inhibit** the post-synaptic neurons. The green neuron are **inhibitory cells** which generates a **locally negative voltage**, in order to **dampen the activity of the post-synaptic neuron**.

**Inhibitory** means this particular interneuron typically local, sends a set of spikes that reach this synapse. And when it reaches this synapse, the spike, it **generates post-synaptically in this dendritic location**, a negative signal, an **inhibitory post-synaptic potential**.

All the signals are transported from the red cells and the green cell to the blue cells. We should **plus the excitatory and minus the negatory** all sum over the dendritic tree. Then the post-synaptic neuron will make a decision depending on the input signals whether to generate an output (spikes) or not.

This axon may connect to another post-synaptic cell.

When inventing the Neuron Doctrine, Cajal did not know that there are synapses. He did not know that there are **two types of synapses, excitatory and inhibitory**. But he realized that the dendritic tree is the receiving, receptive part of the cell. And that the axonal tree is the output part of the cell.

### Summarization

Neurons are input/output devices. The input consists of two types of synapses, of two types of inputs: the excitatory input and the inhibitory input. The former tend to excite to try to make the cell fire, and the latter tend to dampen to inhibit and control the output.

Basically, spikes can be considered as ONE or ZERO (exist or not). They are very elementary barcode of the brain.

### Question

Does the inhibitory neuron always locate more closer to the dendrite of the post-synaptic than excitatory neurons?

not really it is just showed in the model in the figure above

But what does the **inhibitory post-synaptic potential** mean? Does that means **negative current** or **negative voltage**?

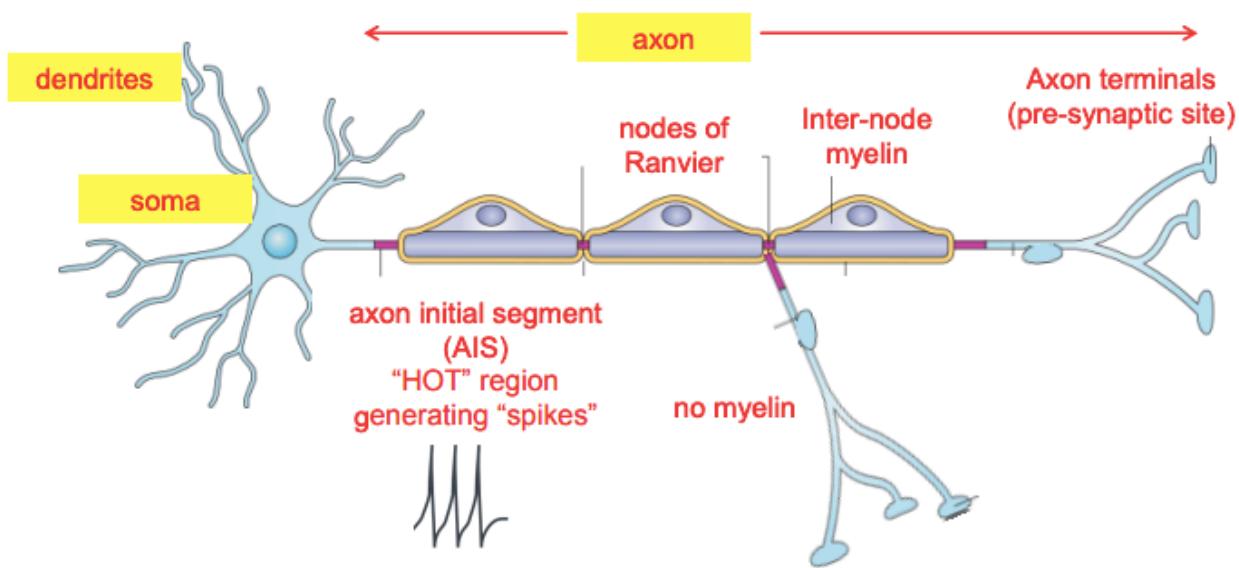
An inhibitory postsynaptic potential (IPSP) is a kind of synaptic potential that makes a postsynaptic neuron less likely to generate an action potential.

Inhibitory presynaptic neurons release neurotransmitters that then bind to the postsynaptic receptors; this induces a change in the permeability of the postsynaptic neuronal membrane to particular ions. An electric current that changes the postsynaptic membrane potential to create a more negative postsynaptic potential is generated, i.e. the postsynaptic membrane potential becomes more negative than the resting membrane potential, and this is called hyperpolarisation.

## The Axon

### Typical morphology of a neuron

# Typical morphology of a neuron



Poliak & Peles  
Nature Reviews Neuroscience 4, 968-980 (December 2003)

## 1. The axon initial segment

Notice that just at the exit from the soma, there is a part called **the axon initial segment**. It is important to remember that the number of axons initial segments per neuron is 1.

This region is **hot**, because it is the **initiation of the spike**. The hot region is a bare piece of membrane consisting of **very special ion channels** which enable the generation of the spike.

The spike then will travel along the axon. They propagate from the initiation spot to all the branches of the axon.

## 2. The node of Ranvier

Notice the gap between the internodes are called **the node of Ranvier**. In the node of Ranvier there is no isolation which means that these little gaps are not isolated by the myelin. As a result, these are also hot regions. Spikes can be boosted in the nodes of Ranvier.

## 3. The Internode

Between the node of Ranvier there are sections called **the internode**, which are **myelin sheath**. It is a kind of wrapping sheet to isolate the axon.

The myelin is lipid wrapping of the piece of the axon, resulting in that the piece of the axon is electrically isolated from the outside.

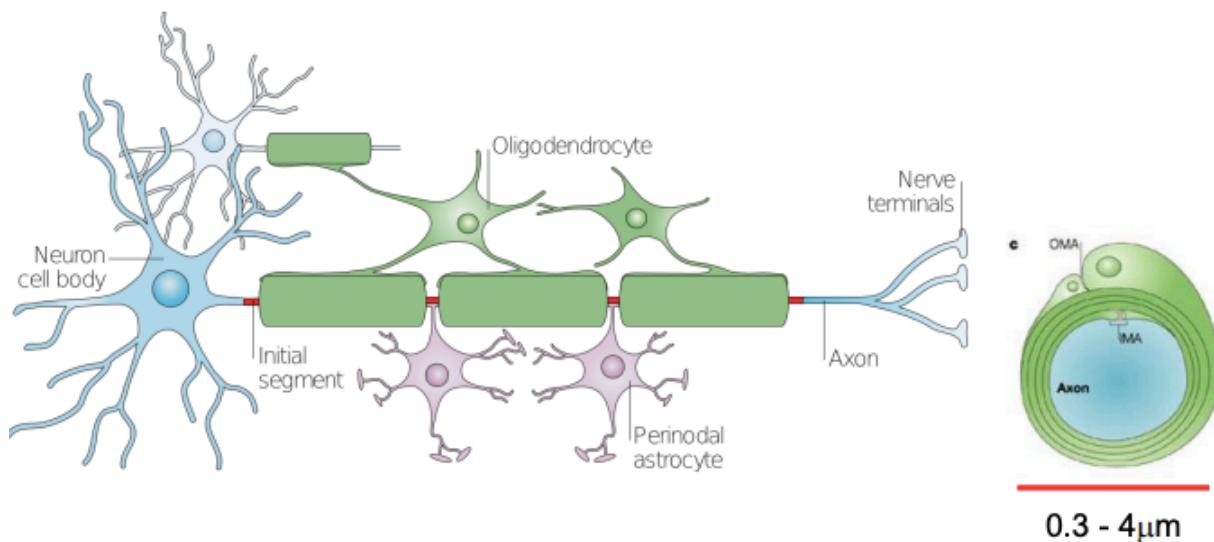
## 4. Axon terminals

At the ends of an axon, we can see some **varicosities** or **boutons**, that consist the neurotransmitter (synapses). They consist chemical that will interact with the next neuron. And the number of boutons (varicosities) per axon is about  $5 \times 10^3$ .

Notice there are no myelin in the varicosity, that means that the varicosities are *open* and *bare*.

### The myelin of axons

## The myelin of axons



**Myelinating glial cells, oligodendrocytes in the central nervous system (CNS) or Schwann cells in the peripheral nervous system (PNS), form the myelin sheath by enwrapping their membrane several times around the axon.**

Poliak & Peles  
Nature Reviews Neuroscience 4, 968-980 (December 2003)

The internodes of an axon are wrapped by another cell which is not neurons but called **Myelinating glial cells**, sometimes also called **Oligodendrocyte**. They are responsible for wrapping the axon in a particular regions (**the internodes**) but leaving the particular important gaps (the nodes of Ranvier).

That is what we called a **myelinated axon**. They distribute in our CNS (even though not all the neurons are myelinated). *But notice that each myelinated axon also contains pieces that are not myelinated.*

The dendrites never have a myelin. So if there is myelin, it must be on the axon. But if there is no myelin, it is very hard to tell whether it is a dendrite or an unmyelinated axon.

### Question

Does Perinodal astrocyte showed in the fig contribute to boosting and amplifying the signal that travels along the axon?

Several studies have demonstrated the presence of perinodal astrocyte processes at nodes of Ranvier in the central nervous system, suggesting that, in addition to the axon and oligodendrocyte, astrocytes participate in the formation of mature central nodes. The specific association between perinodal astrocyte processes and nodal membrane develops at the time of, or soon after, the appearance of relatively differentiated nodes of Ranvier.

Black, Joel A., and Stephen G. Waxman. "The perinodal astrocyte." *Glia* 1.3 (1988): 169-183.

### The node of Ranvier in Axons



Notice **the hot region** the node of Ranvier has **many specific membrane ion channels**.

These node of Ranvier are very important elements that contribute to the propagation of the signal (action potential) successful along the axon. They can **boost or amplify** the action potential in these hot regions. Without the node of Ranvier, the propagation of the action potential is made possible attenuating due to the fact that along the axon. The nodes of Ranvier are so hot that each time a signal arrives they makes it big and then it goes there and the next node makes it big.

### Questions

Which ion channels make the node of Ranvier so special? What are the ion channels that give the node of Ranvier the ability to be boosted or amplified?

sodium and potassium (mainly)

### Summarization

## A typical axon in the central nervous system (CNS summary)

1. A single, **highly branched**, thin ( $\mu\text{m}$ ) process emerging from the soma. Branched locally but may extend far (many centimeters and even meters) away from the soma
2. At the “hot” **axon initial segment** (AIS) the spike (“action potential”) is initiated and then propagates along the axon
3. Covered with myelin (isolating) lipid sheath, with intermittent small gaps – the **nodes of Ranvier** (where “hot” – excitable ion channels reside)
4. Decorated with **frequent swellings** (axonal boutons) – where the neurotransmitter “hides” (the pre-synaptic site)

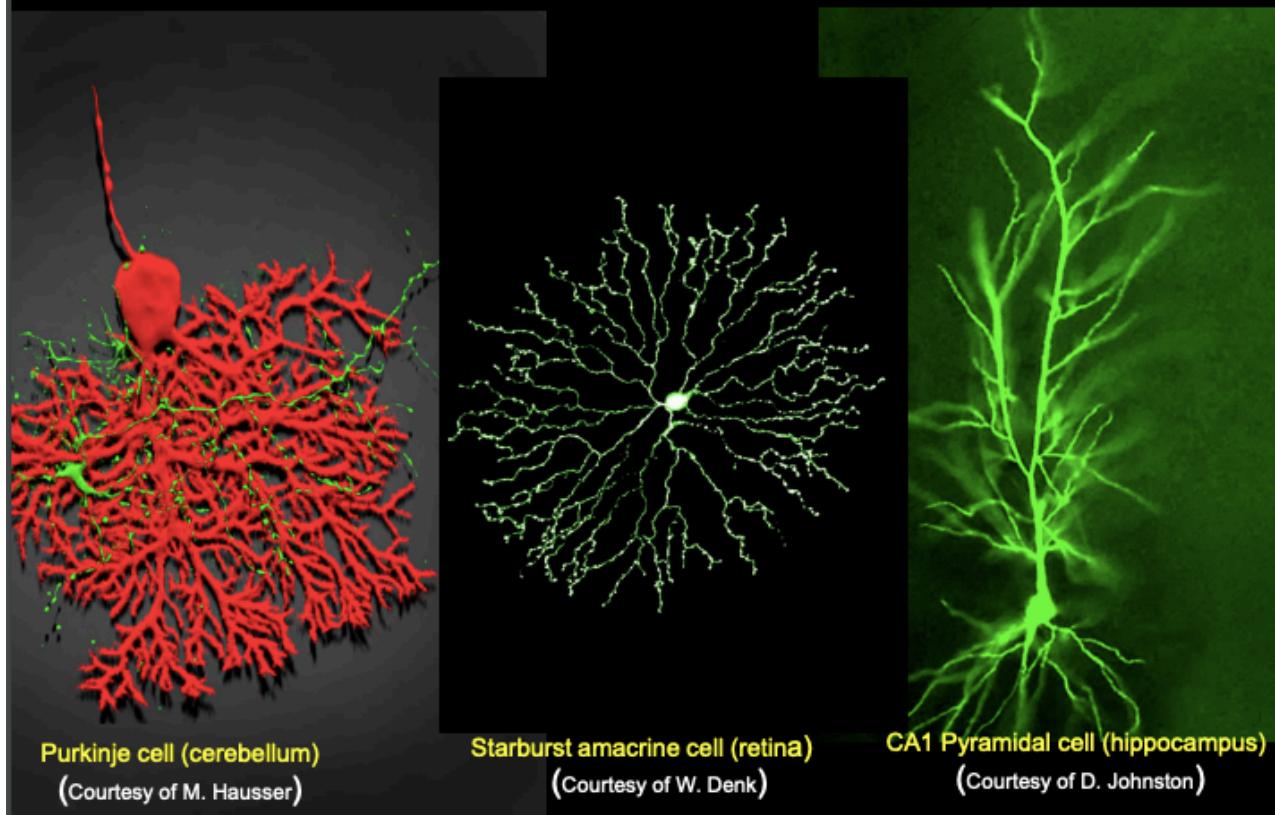
The axon is the output electrical device of neurons,  
It generates and carries electrical signals called spikes

Notice that axons can extend locally or in a very long distance. In addition, axons also have many *branches*.

## The Dendrite

Some typical dendrites look like:

## Dendrites

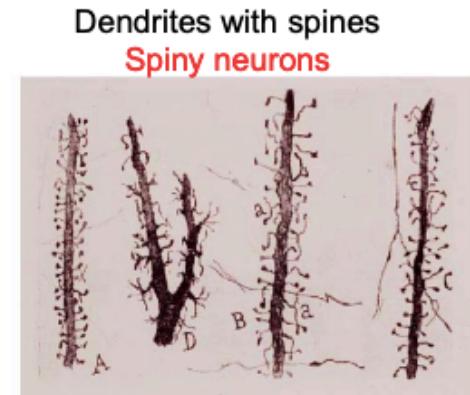
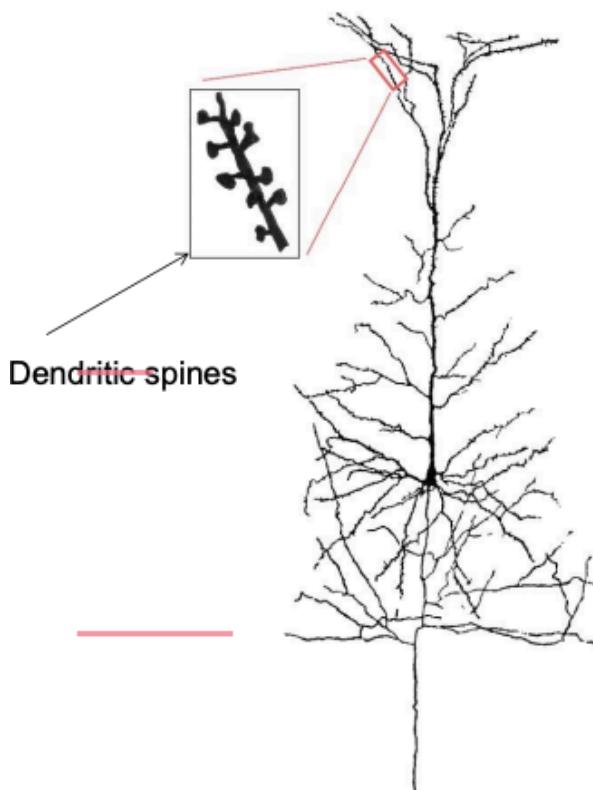


Interestingly, we notice that in the first dendrite of Purkinje cell, there is an axon crossing (making contact).

### Dendritic spines

If you zoom into a dendritic tree, you will see that it consists of all these little appendages, all these small branches. So many **dendritic spines** emerging out from the dendrites. **Dendritic spines** are the regions where **synapses** are made onto.

## An example: The layer 5 cortical pyramidal cell (the “psychic” cell by Cajal)



### Typical numbers

Total dendritic area – **20,000  $\mu\text{m}^2$**

Number of dendritic spines/cell – **8,000**

Spine area – **~1  $\mu\text{m}^2$**

Number of converging inputs (synapses/cell) – **10,000**

In some cells like Purkinje cell we have 200,000 synapses per one dendritic tree.

The dendritic tree of cortical pyramidal cells are covered with these unique structures—dendritic spines (in many species like human, cat, rat, and etc.)

But notice that not all the neurons are **spiny**. Some of them are non-spiny and **smooth**.

## Neuron Type

There are many different ways to classify neurons:

# Neuron types

- Classification by **anatomical features** (“the face” of dendrites and axons)
- Classification – functional (e.g., **Excitatory** (principal) vs. **Inhibitory** (inter) neurons)
- Classification using **electrical/spiking activity pattern**
- Classification using **chemical characteristics**
- Classification using **gene expression**

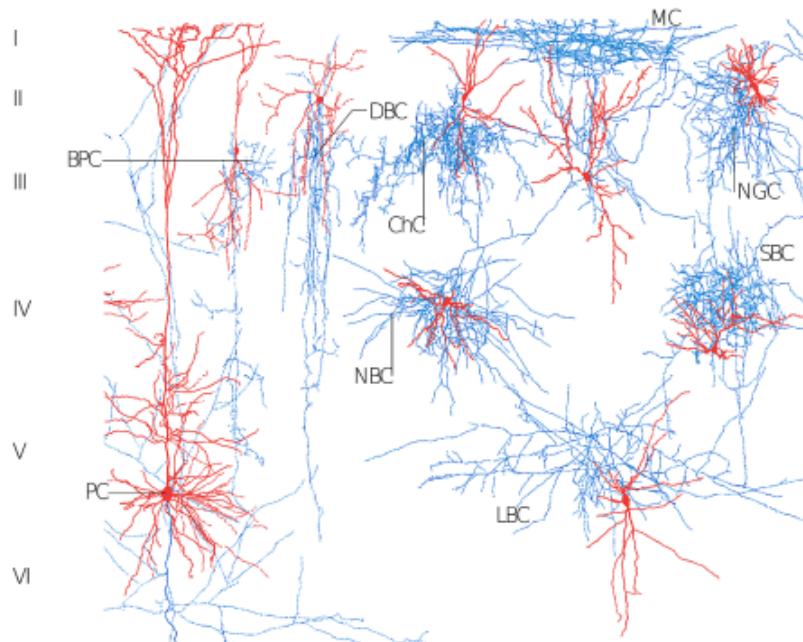
The number of neurons in your brain is close to 100 billion or 100 million ( $10^{11}$ ).

Just as we mentioned in the img, we can classify neurons by using electrical/spiking activity pattern. Some cells like to fire more spikes while some cells like to fire less spike. And also with the different patterns of activity.

Also, because today we can actually stain chemicals, we can classify neurons by their chemical characteristics.

Or using gene-expression profile.

# Microcircuit of the Neocortex



**Principal neurons**  
(excitatory) - axon projects to other brain regions

**Interneurons (inhibitory)** – local axonal projection

Z. J. Huang, G. Di Cristo & F. Ango  
Nature Reviews Neuroscience 8, 673-686 (September 2007)

## The principle neurons versus the interneurons

### 1. Principle Neurons

Usually, we say that this big excitatory pyramidal cells. And other excitatory cells, where they have this axonal projection, out of this local region. We call them **projection, or principal neurons**. Because they are principal in the sense that, they **send from local processing outside to other regions through long Axons**.

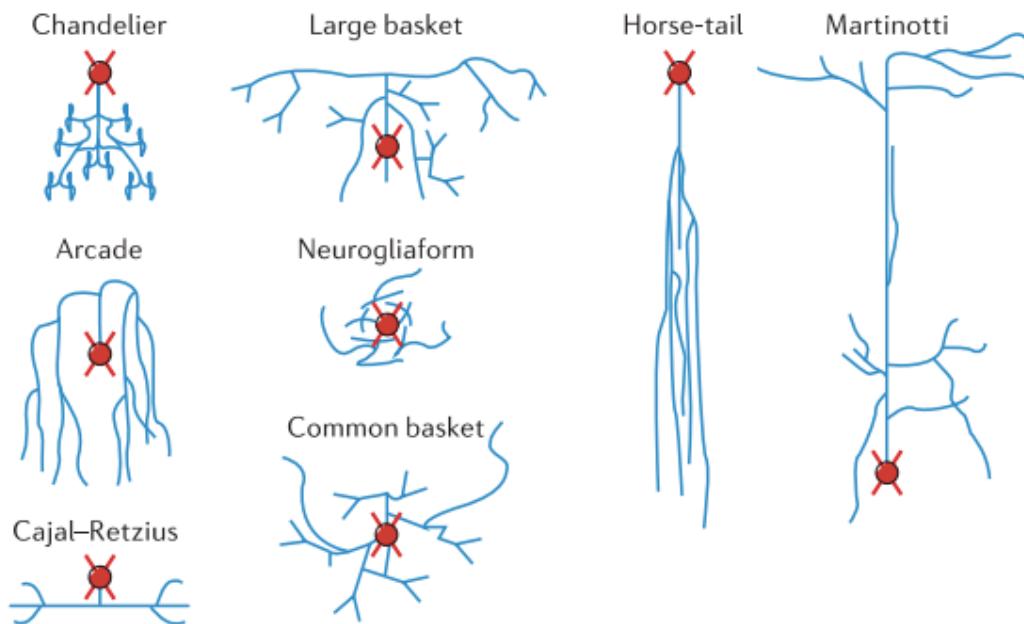
So principals versus interneurons. It's an important classification to try to understand the system of this local inhibitory control. And more **globally sending information to other regions**. Especially **excitatory information**.

### 2. Interneurons

Usually, inhibitory neurons enter neurons because there are inter, they are **inside the region**.

## Using morphology to classify inhibitory neurons (Interneurons)

## Morphometric-based classification of (inhibitory) *interneurons*



*DeFelipe et al., Nature Review neuroscience, 2013*

They use **morphology** (the **dendritic tree** as a signature) to identify different types of interneurons.

### Question

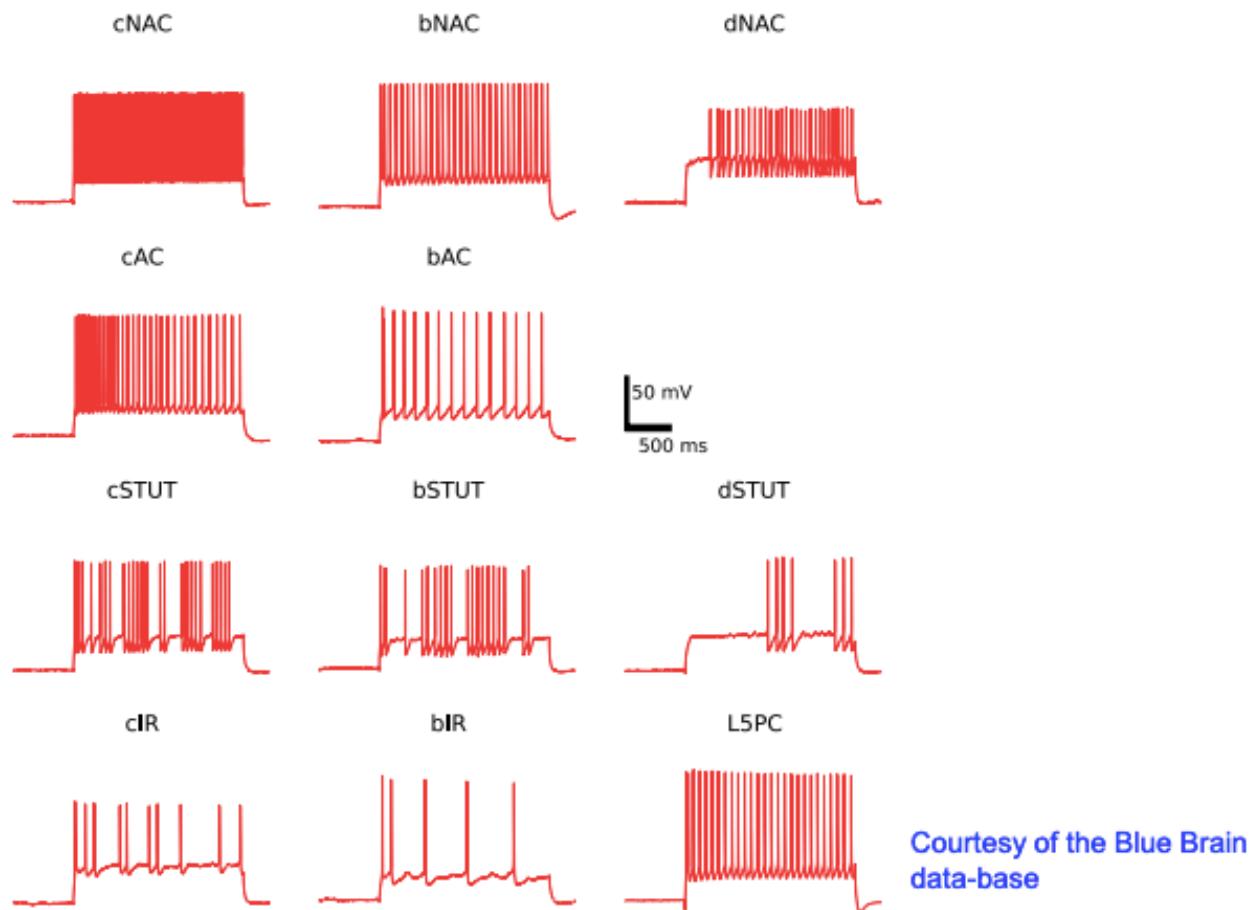
Does the morphology of each interneurons relate to their specific functions?

cortical interneurons (CIN) populations are highly heterogeneous. CINs have been reported to account for up to 50 distinct transcriptional signatures in the cerebral cortex (Tasic et al., 2018; Tasic et al., 2016; Zeisel et al., 2015; Harris et al., 2018). **The most prominent diversified characteristics of CINs relate to their inherent morphology, which includes specialized shapes and orientations of dendrites and axons to provide guidance in defining their dendritic and axonal innervation fields** (Somogyi and Klausberger, 2005; Klausberger and Somogyi, 2008).

Miu, Kai-Kei, et al. "The construction of 3D cognitive networks from iPSCs through precise spatiotemporal specification." *iPSCs in Tissue Engineering* (2021): 45-76.

### Using spiking patterns to classify electrically-based neurons

## Electrically-based neuron classification (based of spiking patterns)



Courtesy of the Blue Brain  
data-base

### Question

What kind of information can be delivered by different spiking patterns?

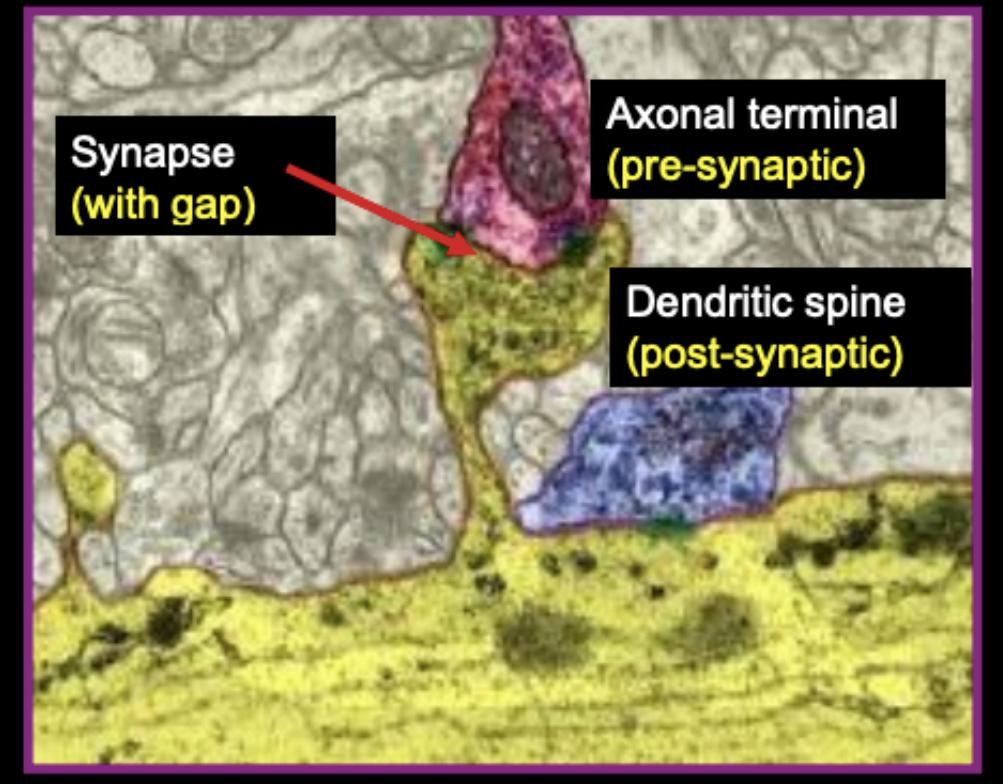
I think it is a problem for computational neuroscience

## The Synapse

### The definition of the chemical synapse

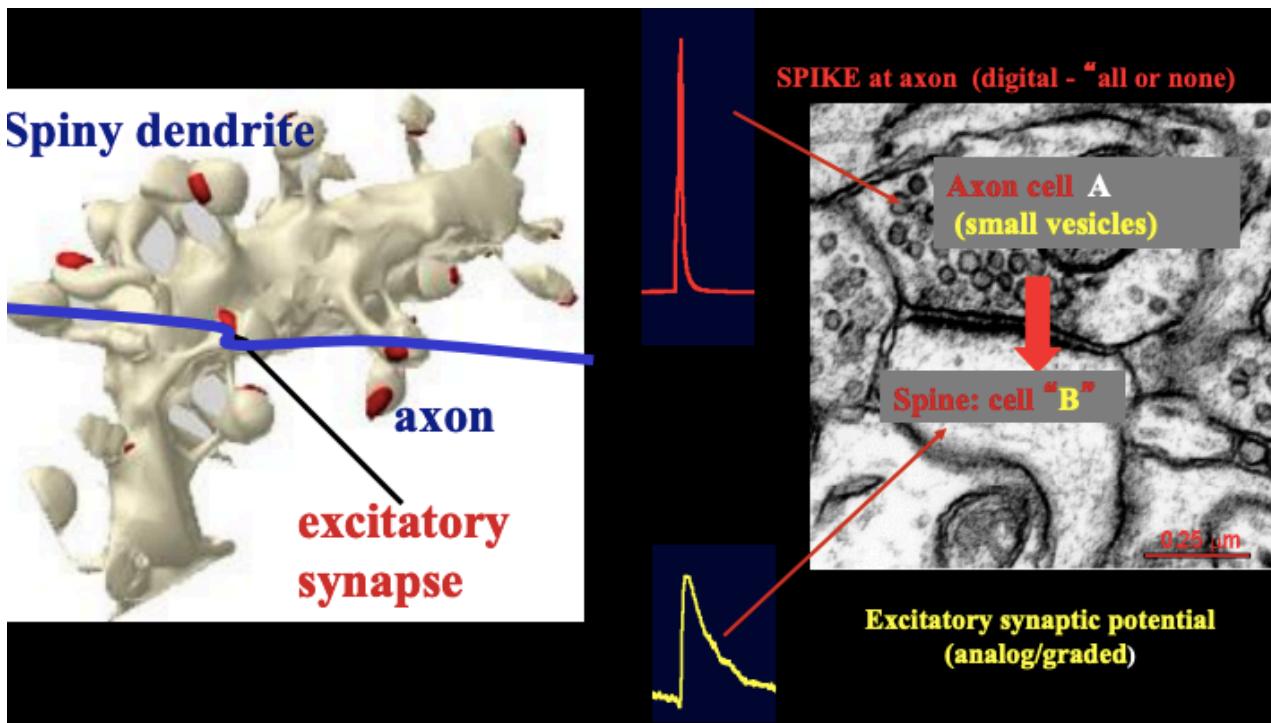
A (chemical/electrical) device that connects **axon** of neuron A to **dendrites** of neuron B.

# A chemical synapse formed between axons and dendrites



So the synapse consists of three elements:

1. Axonal terminal (pre-synaptic)
2. Synapse (with gap)
  - | can only be seen in electron microscope
3. Dendritic spine (post-synaptic)
  - | does not physically touch with pre-synaptic



Notice that the synapse showed in the left is a typical excitatory type which will be discussed in later course.

And if we goes to a higher resolution, EM, electron microscope, we can see the axon showed in the right. The spheres or vesicles in the axon cell A consisting of the neurotransmitter. Here you may have 5,000 molecules of neurotransmitter.

And here in the head of the dendritic spine, there are **receptors** waiting to receive the transmitter.

For pre-synaptic, the spike is the trigger for releasing mechanism of the transmitter from the vesicle into the gap. (The red signal in the fig)

Post-synaptically, if receiving the transmitter, will have the yellow signal just like the yellow one showed in the fig. In the dendrite, you will see the post-synaptic potential. It could be **excitatory post-synaptic potential** which tries to excite the post-synaptic cell. It could be **inhibitory post-synaptic potential** with a negative sign, which would try to reduce the activity.

Interestingly, we can think about a synapse as a digital to analog converter. And this analog signal, post-synaptically, may gain different amplitudes.

### 1. strong synapses

And this analog signal, post-synaptically, may gain different amplitudes. So I can speak about strong synapse, meaning that, for a given spike, the synapse may generate large post-synaptic potential.

### 2. weak synapses

And I can think about weak synapses. So for the same spike, you will get a weaker post-synaptic signal, a smaller or maybe even nothing.

### 3. silent synapses

I can speak about the silent synapses, where the action potential here does not release vesicles. Does not release transmitters. So if you would record here, you will not see voltage change. You will not see potential. This would be a silent synapse.

However, the term is more commonly used to describe a *postsynaptically silent* excitatory synapse, where glutamate release fails to elicit a detectable AMPA receptor-mediated response.

### Question

How to differentiate these three kind of synapses (strong, weak and silent)?

Actually we can use systematic quantification methods on the synapses

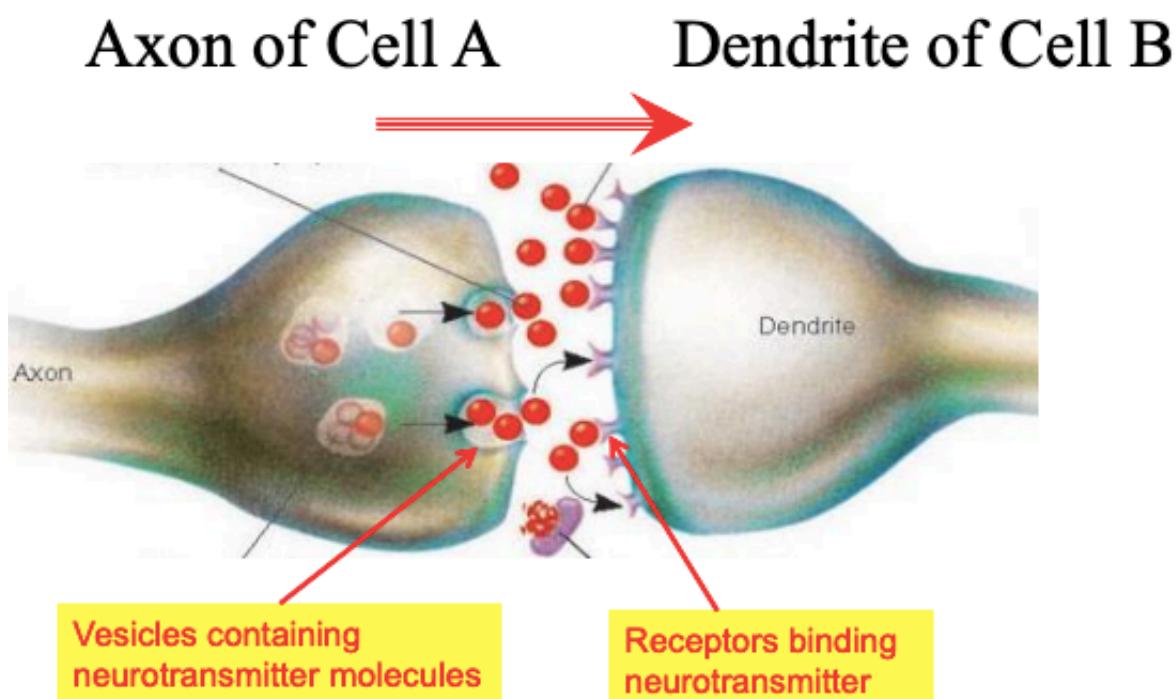
[Systematic Quantification of Synapses in Primary Neuronal Culture](#)

Why the synapse showed in the fig is a typical excitatory synapse?

chemical synapse vs electrical synapse

There are two different kinds of synapses present within the human brain: chemical and electrical. Chemical synapses are by far the most prevalent and are the main player involved in excitatory synapses. Electrical synapses, the minority, allow direct, passive flow of electric current through special intercellular connections called gap junctions. These gap junctions allow for virtually instantaneous transmission of electrical signals through direct passive flow of ions between neurons (transmission can be bidirectional). The main goal of electrical synapses is to synchronize electrical activity among populations of neurons.

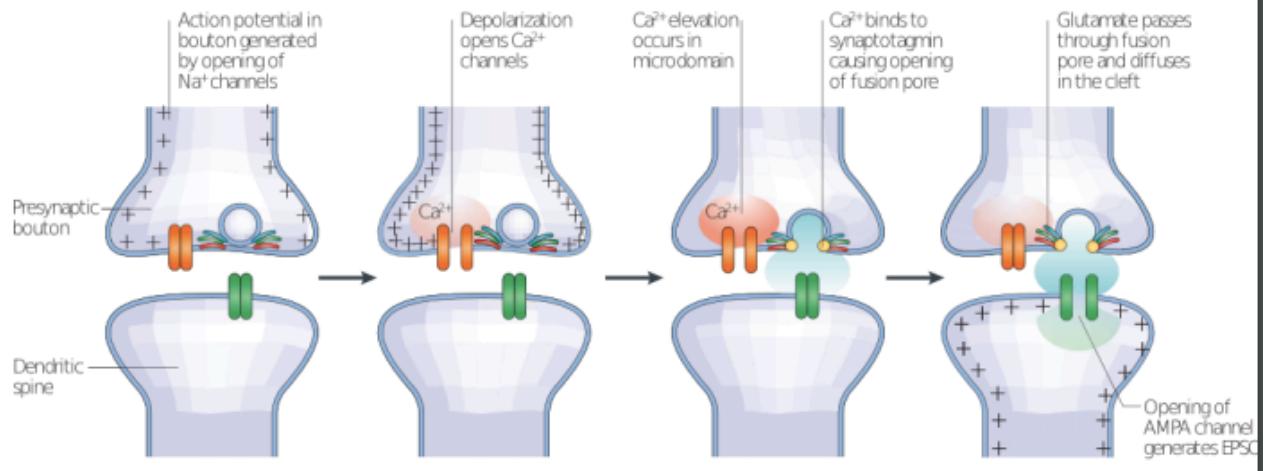
## The Chemical Synapse



The synapse is **a transmission line** between the axon firing spike and the dendrite receiving the transmitter responding with generation of post-synaptic potential.

**The synapse is a chemical entity.** But the pre-synaptic and the post-synaptic are electrical activities.

## Vesicle quantal release



And because these synapses are the very fundamental units of the brain and they are chemical. So you can manipulate the chemistry in this region by certain drugs. Gaps of chemical elements makes the nervous system very **plastic** accessible to effects of drugs and also effects of changes in the connectivity.

### Questions

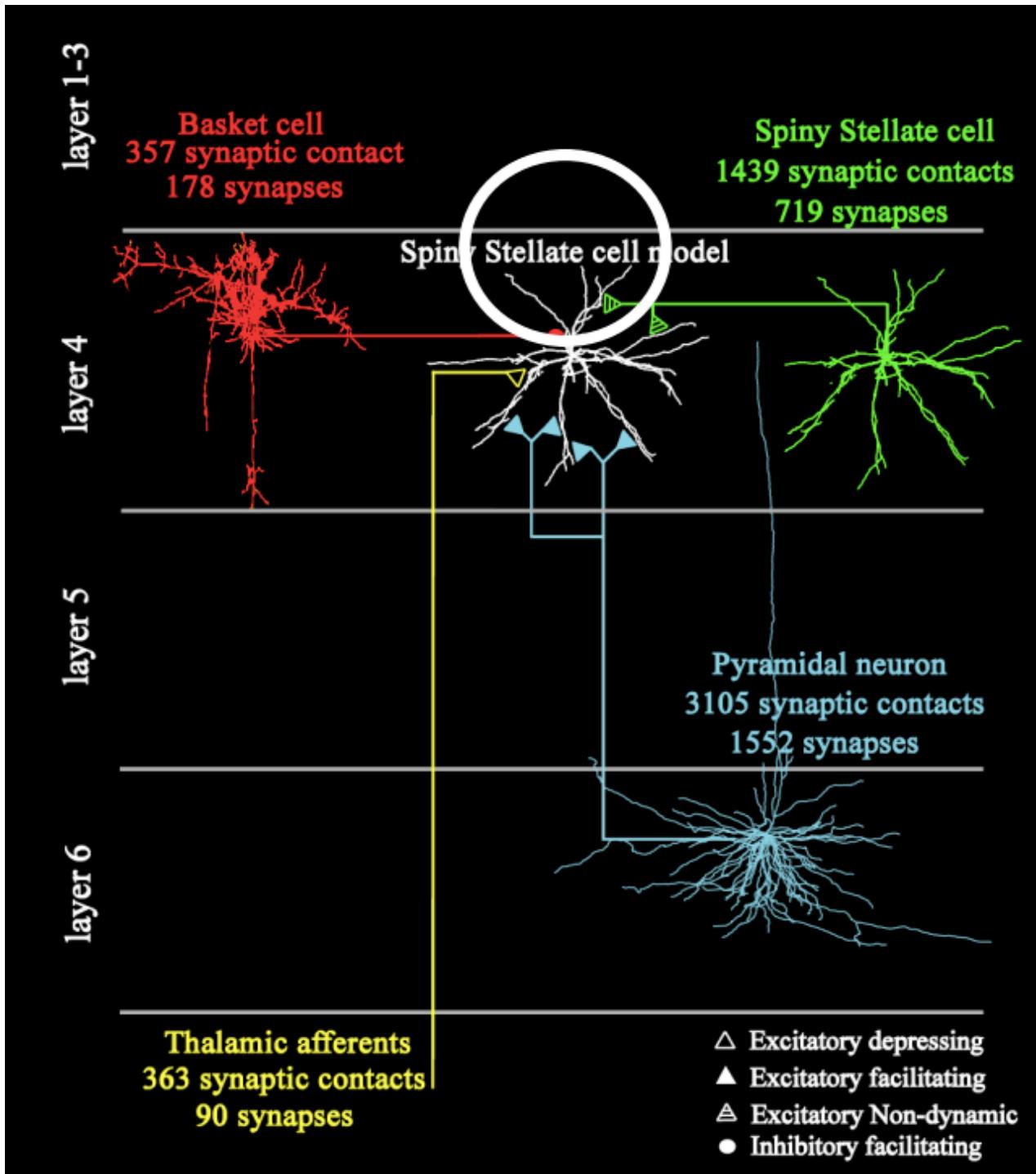
How does the vesicle in pre-synapse sense the electrical signal and begin to release the chemistry?

Which chemical is excitatory and which is inhibitory (to the post-synaptic)?

What are the particular methods to manipulate the synapses by using drugs?

## The Neuron as I/O Device Part II

**What neurons "see" when embedded in the (cortical) circuit**



The figure shows a piece of a cortex. There are many different cell types.

These cells interact with each other via synapse. The prof said that the green cell is making excitatory synapse to the white cell. The red cell is making maybe inhibitory synapse to the dendrite of the white cell.

So **Question** again:

Does the inhibitory neuron always locate more closer to the dendrite of the post-synaptic than excitatory neurons?

## *L4 Spiny Stellate Cell covered with (excitatory and inhibitory synapses)*

*355 Synapses formed  
by Smooth Cells*



*360 Synapses formed by  
Thalamic Neurons*



*L4 Spiny Stellate Cell*

*1430 Synapses formed by  
other Spiny Stellate Cells*



*3105 Synapses formed by  
Layer 6 Pyramidal Neurons*

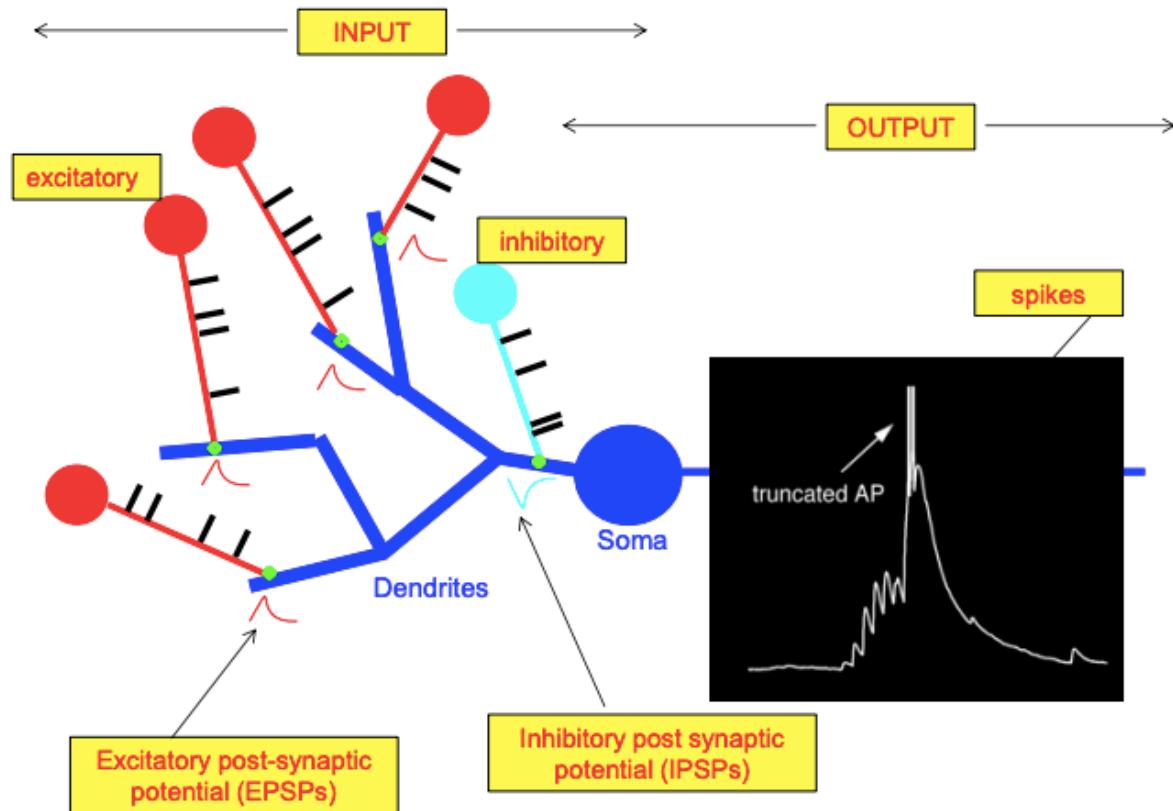


This L4 Spinay Stellate cell is absolutely decorated with different types of synapses. And each one conveys a particular electrical signals, sometimes inhibitory, sometimes excitatory.

### **Summarization**

# The neuron as an input-output electrical device

(SUMMARY after you've been learning)



Eventually all these synapses sum up at the cell body. From everything it converges, it flows, the signal flows into the cell body, and they start to **generate voltage change at the Soma and at the initial segment**.

Just as the black fig showed in the fig. All the input signals build up, one on top of the other, excitatory (wave crest), inhibitory (wave troughs), excitatory (wave crest), inhibitory (wave troughs), excitatory, excitatory, excitatory, excitatory. And at some point, at some voltage, they may **reach the threshold for action potential generation**.

Eventually the axon initial segment should decide, did i reach the threshold or not? If I did not reach the threshold, no spike.

If I reached the threshold, boom, there is a **spike**, and when there is a spike or many spikes, you see them, when there is a spike, you see them flowing. You see them flowing one spike after the other spike, into this axon, effecting the next stage, the next chain, in this interaction.

## Question

If the initial segment can decide whether the threshold has been reached or not, then can the signal be reduced at the node of Ranvier to below the threshold?

Axonal boutons, Axon nerve ends

# WEEK 3: Electrifying Brains-Passive Electrical Signals

In lesson 3 we will discuss the cell as RC circuit and its passive electrical signals.

## A resistor-capacitor (RC circuit)

A resistor–capacitor circuit (RC circuit), or RC filter or RC network, is an electric circuit composed of resistors and capacitors. It may be driven by a voltage or current source and these will produce different responses. A first order RC circuit is composed of one resistor and one capacitor and is the simplest type of RC circuit.

RC circuits can be used to filter a signal by blocking certain frequencies and passing others. The two most common RC filters are the high-pass filters and low-pass filters; band-pass filters and band-stop filters usually require RLC filters, though crude ones can be made with RC filters.

Source: [https://en.wikipedia.org/wiki/RC\\_circuit](https://en.wikipedia.org/wiki/RC_circuit)

## Ohms law

Ohm's law states that the current through a conductor between two points is directly proportional to the voltage across the two points. Introducing the constant of proportionality, the resistance, one arrives at the usual mathematical equation that describes this relationship:

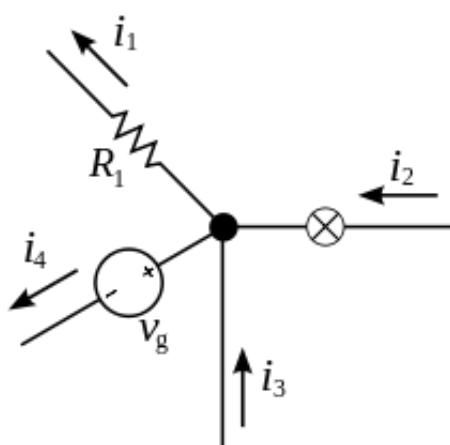
$$I = \frac{V}{R}$$

## Kirchoff's law

Kirchhoff's circuit laws are two equalities that deal with the current and potential difference (commonly known as voltage) in the lumped element model of electrical circuits.

This law, also called Kirchhoff's first law, Kirchhoff's point rule, or Kirchhoff's junction rule (or nodal rule), states that, for any node (junction) in an electrical circuit, the sum of currents flowing into that node is equal to the sum of currents flowing out of that node; or equivalently:

The algebraic sum of currents in a network of conductors meeting at a point is zero.



$$\sum_{k=1}^n I_k = 0$$

## Supplementary Materials

### Voltage Clamp

The voltage clamp is a technique used to control the voltage across the membrane of a small or isopotential area of a nerve cell by an electronic feedback circuit. The voltage is normally stepped to a family of levels, matching preset command patterns, and the current supplied or absorbed by the circuit to hold the voltage at each level is measured. This current is equivalent to the ionic current flowing across the membrane in response to the voltage step.

In contrast, the current clamp circuit controls the amplitude of the injected current (e. g. via a microelectrode) and allows the voltage to vary. Injection of a depolarizing current across an excitable membrane may be sufficient to generate an action potential (also called an 'impulse' or 'spike'). Membrane voltage changes cause membrane conductance changes, due to the opening of populations of ion channels, which then lead to changes in the sodium and potassium currents through those channels. The balance or imbalance in these currents determines whether or not an impulse is generated.

### Electrical properties of cell membrane

#### Rall Model for the passive neuron (WEEK6 material)

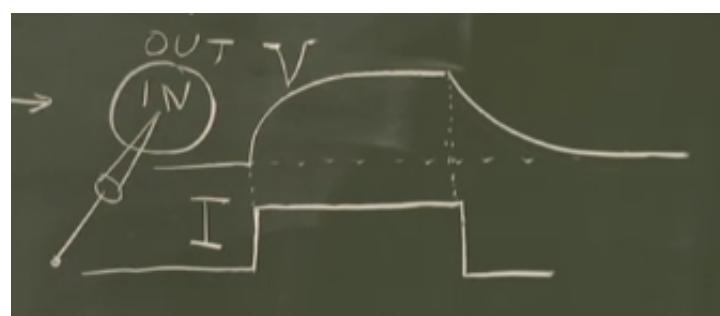
#### Nernst Equation

## The Cell as a RC Circuit

Core:

1. neuron as passive R-C circuit (anatomical structure - electrical representation)
2. the membrane time constant ( $\tau_m$ )
3. temporal summation of repeated inputs - "electrical memory"
4. excitatory (E) and inhibitory (I) synapses
5. E and I interaction

In the middle of 20th century, people found that when given a constant positive current inside the cell body, the membrane would exhibit a voltage change looks like:



the voltage grows with time

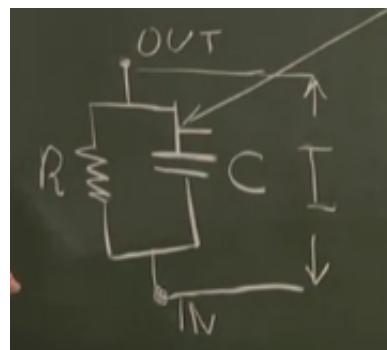
And when the current injection got seized, the voltage slowly dropped back into zero

**suggesting the cell cannot be seen as a mere resistance, if the neuron cell is a resistance, the voltage should be like  $I^2 R$**

notice the cell was given a **step current pulse**

and it is a common property of all the cell

But it reminded scientists that the cell exhibits a behavior like a R-C circuit.



this patch a membrane can be considered as a R-C circuit (part of it inside the cell body while part of it outside the cell body)

When injected current  $I$  between the two sides of such a circuit, the response of the cell will look like the first fig.

It takes time to grow while I inject the current and after injecting the current, when I stop injecting the current, no current anymore. The voltage between the two sides of these circuits is attenuating with time to zero.

**An RC circuit is a good first approximation to the actual behavior of cells, when they received kind of a step current.**

The voltage in a passive RC circuit increases as **(1- exponent)** during a step current injection ( $I$ ) across the two sides of the circuit.

The voltage in a passive RC circuit decreases **exponentially** at the end of the current injection.

## The Voltage Equation for the Passive Cell

According to the **Kirchoff's law**:

**Capasitor Current + Resistor Current = Injected Current**

The voltage equation would be like:  $C \frac{dV}{dt} + \frac{V}{R} = I$

Actually, current can only flow outside through the resistance. And it can **charge the capacitance**. So if a positive current gets injected, then the capacitance is charged inside. And **the inside of the cell become positive**. (just like the figs above)

And this called **depolarizing**.

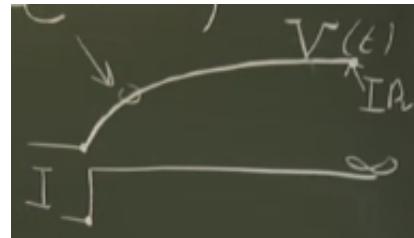
Then we will have the solution:

$$V(t) = IR(1 - e^{-\frac{t}{RC}})$$

Let us look at 2 extreme conditions:

$$t = 0, V(t = 0) = 0$$

$$t = \infty, V(t = \infty) = IR$$



It basically means that if the current maintains for a long enough time, the voltage will finally reach the maximum (IR).

## The Membrane Time Constant

For  $V(t) = IR(1 - e^{-\frac{t}{RC}})$ , what happens when  $t = RC$ ?

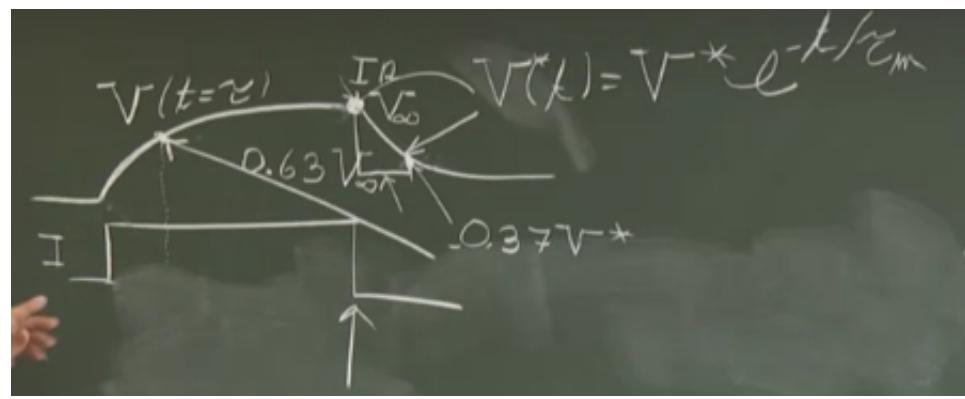
Notice that  $t = RC$  is a very important value which is called  $\tau$  or sometimes  $\tau_M$  ( $\tau_{membrane}$ )

So  $\tau$  symbolizes the value of  $RC$ , it is in units of time

$$t = RC = \tau, V(t = \tau) = IR(1 - \frac{1}{e}) = 0.63IR$$

So this means. That after  $t$  equal tau, I get the voltage gets into **63% of the maximal voltage** that it reaches. So here we get, at this location, 0.63, 63% of, the infinity.

Now here is another problem is that how would the voltage decay if the current is completed?



$$V(t) = V \cdot e^{-\frac{t}{\tau_m}}$$

**Basically that means 1  $\tau$  after the injected current is completed, the voltage will get attenuation to 63% from the start.**

So both the growth and the decay are mirror-image of one each other.

$\tau_m$  is called the membrane time constant.

## Summarization

This is a passive system and a R-C circuit is a good representation. During the current injection, the voltage develops like -1 exponent. And after the current injection-finishing the injection-the voltage decays like exponent.

The controlling parameter  $\tau_m$  controls the timescale-how fast the voltage develops and how fast the voltage attenuates. After the injection, the timescale is all governed by the membrane time constant  $\tau_m$ .

For example, if the membrane time constant is long. This means it will take long time for the voltage to attenuate, long time.

If the time constant is short, it will be much shorter to attenuate, or to build up.

So the membrane time constant controls how fast the membrane voltage respond to current.

The decay of the current after finishing the injection is called **the electrical memory of the cell**.

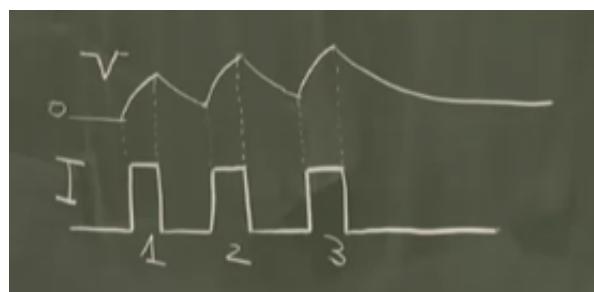
Show time constant means that the cell gets rid, develops fast voltage and gets rid of the voltage. and slow time constant means that it takes very long to get rid of this voltage.

R is another parameter. R as an input parameter defined **the maximum voltage** you can get.

Basically,  $\tau_m$  and R are the two critical parameters for understanding passive RC circuit, which is at first passive linear approximation for biological membrane and in particular, neuronal membrane.

## Temporal Summation

Now instead of injecting a constant current, try **inject intermittent current** (a repetitive current with intermissions). How would the voltage response to it?



The voltage wil response in a buildig up and summatting way, due to the repetitive current.

Finnaly, by stopping injecting current, the voltage starts to attenuate and back to resting, which is called **resting potential**.

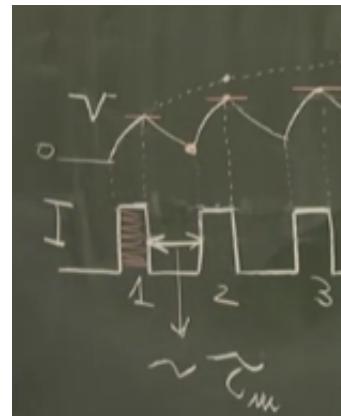
Notice **if it is not too long the time difference, then the reminiscence the remainders of the previous voltage here will be the initial condition for the next buildup**.

This phenomena is called **Temporal Summation**

One response, and then the second one on top of the first response, and then the third one on top of the second response, and they summate one on top of the other.

**And this is because you have a memory to the system, electrical memory and all due to the fact the cell has a membrane time constant  $\tau_m$ .**

Interestingly, IR is the maximum voltage a cell could ever get. But if injected in some intermissions, the voltage would exhibit in peaks and will be always less than the voltage injected continuously.



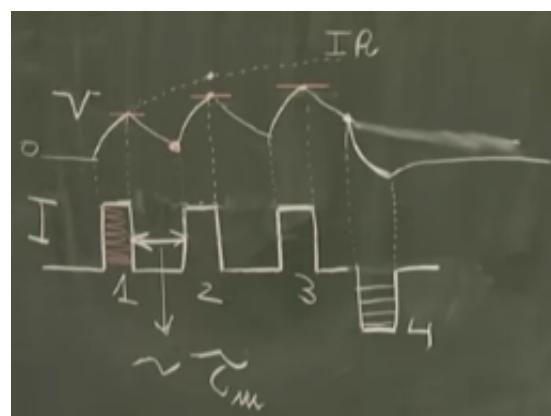
It is similar in the consequence input like synaptic inputs. One after the other after the other, that will tend, the voltage response, will tend to summate one on top of the other.

### Question

what is the maximum intermission of the repetitive current to build up all the peaks before the voltage gets to attenuate?

$\tau_m$

Now what would have happened for example if the cell is injected with a negative current?



A injected negative current will push the voltage down into a negative direction.

And if the negative current is strong enough, the voltage might go very much below, even below the resting potential (depending on how strong this negative current is.) **And the negative current is called hyper polarizing current.**

When the injection is completed (when the injecting of the current is ceased), the voltage will attenuate back into the resting potential.

Notably, it will be also a summation of a positive response (which is called depolarization) and a negative response (which is called hyper polarization).

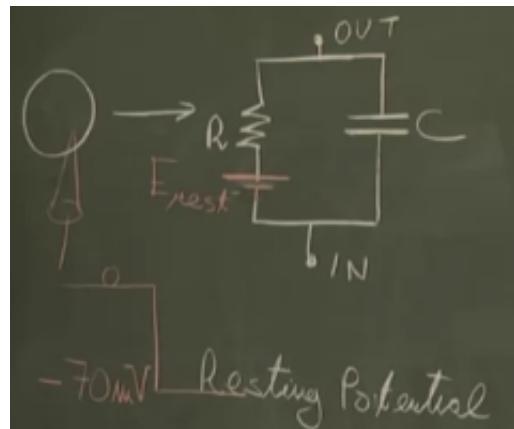
So this interplay between positive currents trying to depolarize the cell, negative currents trying to carry the voltage back or even more negative relative to the initial state. **This interplay between positive and negative is exactly what synapses are doing.** Because as we'll hear soon, some synapses inject positive current, some synapses inject negative current in the cell.

## The Resting Potential

A drop (from 0 to -70 milli volts) in voltage can be observed when an electrode penetrates into the cell, suggesting that **the cell is more negative than the outside.**

The inside of the cell is about minus 70 milli volts more negative than the outside of the cell always.

This is called resting potential  $E_{rest}$



Depolarization means less negative than resting potential

Hyperpolarization means more negative than resting potential

In our brain, these **electrode** injecting current into neural cells are **synapses** (or synaptic inputs).

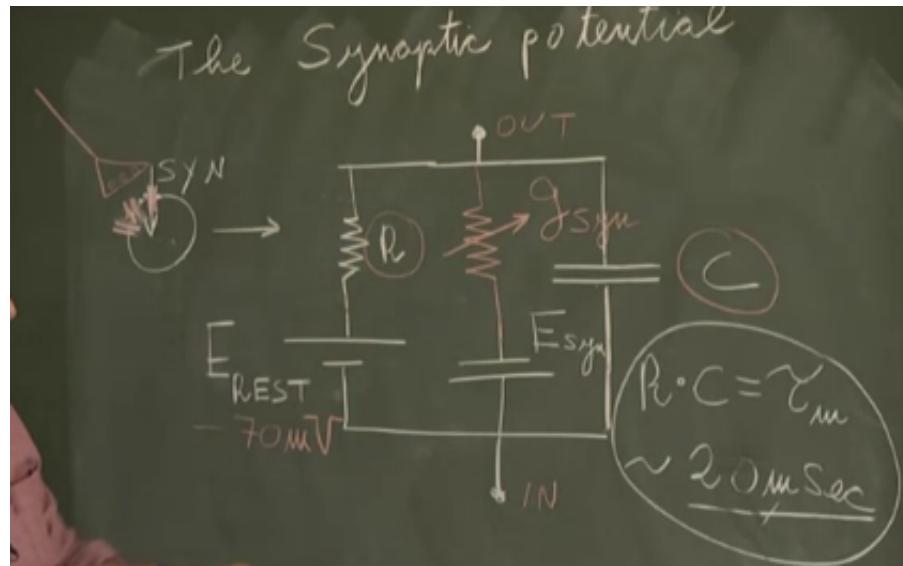
## The Synaptic Potential Part 1

In human brain,  $\tau_m = RC \approx 20ms$

20~5 milliseconds

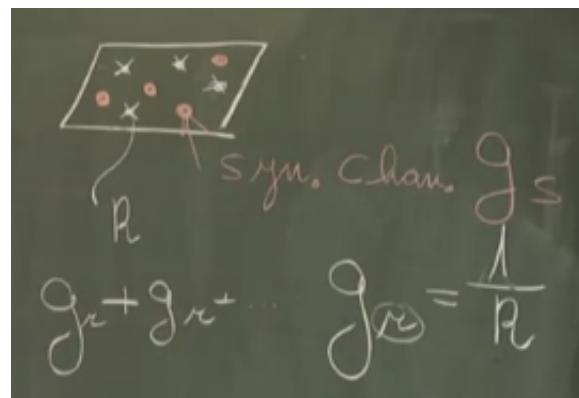
depending on how leaky is the membrane of the particular cell

a synapse can be considered as an electrical device. And **the ion flow caused by transmitter from pre-synapse** can be considered as the **injected current**.



An **ion channel** on the cell membrane can be considered as **a resistor and a battery** as showed in the fig. And these red ion channels enable particular specific ions to flow **either from the outside to the inside or from the inside to the outside**, depending on which channel is being opened.

## The Synaptic Conductance

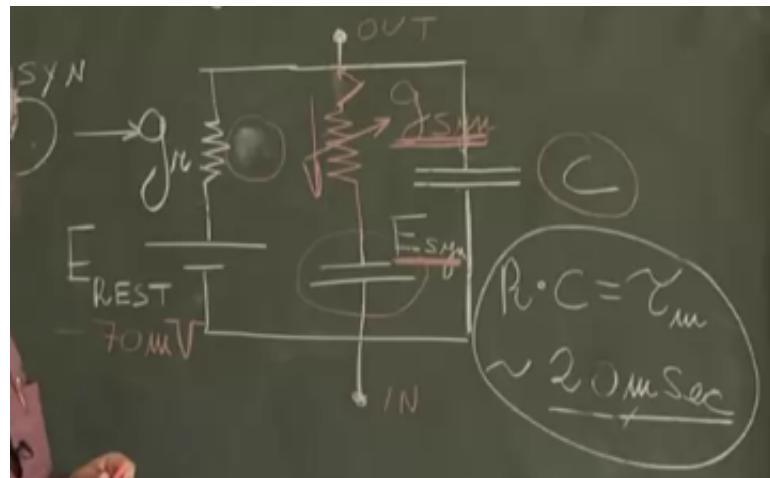


Imagine in a patch of the post-synaptic membrane, there distribute 2 kinds of different ion channels. The **white ones are the passive channels**, which are always opening. The **red ones are synaptic channels**, which *open only when the transmitter is being released and interacts with the receptors on the post-synaptic membrane*.

Assume that the conductance of a passive ion channel (white) is  $g_r$ , so the sum of all the conductance of passive ion channels is  $\sum g_r = \frac{1}{R}$

notice that conductance is one over the resistance

And the conductance of a synaptic ion channel (red) is  $g_s$  ( $g_{synap}$ )



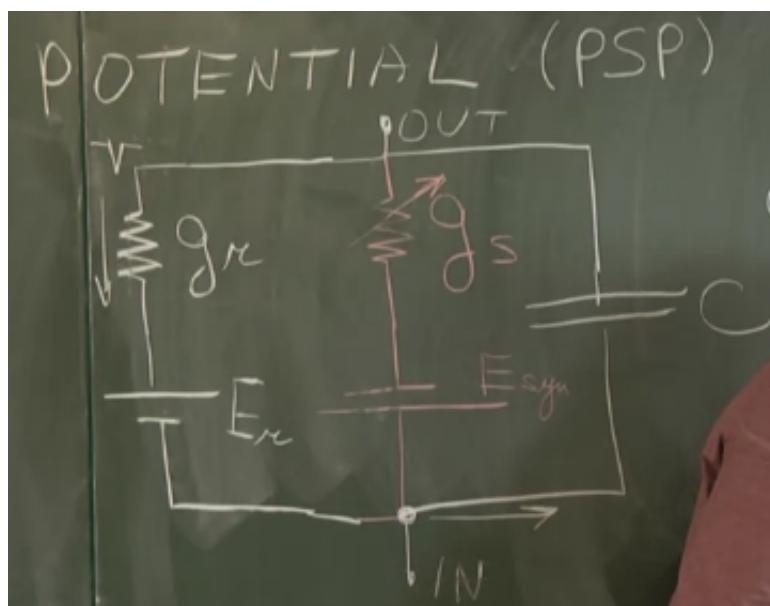
So look back at the previous fig. The white circuit is always opening. But **the red circuit is tentative, which would open only if there is a transmitter, a reaction with a receptor.** And this current, that will flow here, will be called the **Synaptic Current.**

Because of these two new elements within the postsynaptic membrane, I will get a voltage that will be called the **synaptic voltage.** But before talking about the synaptic channels, let's take a look at synaptic battery. What is this synaptic battery? What makes a battery for the synapse?

## The Synaptic Battery

The current flow along the concentrate and depending on the specific ion channels if the transmitter meets the receptor.

## The Synaptic Potential Part 2



Then we have the new equation:

$$C \frac{dV}{dt} + g_r(V - E_r) + g_s(V - E_s) = 0$$

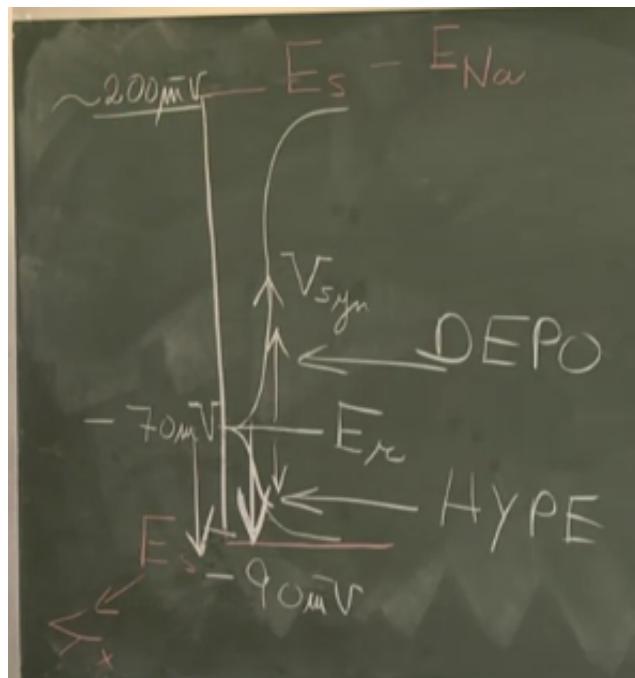
There are three types of current: **the capacitive current**, **the passive current (the resting current)** and **the synaptic current**. The sum of them must be 0. Because there is no extracellular, meaning there is no external current going into the cell.

So I need to solve this equation in order to get this  $V$ , which is the voltage being generated by the synapse, by the fact that there is a synaptic conductance. There is a voltage change and I'm interested in this voltage change. I want to know what is the change of voltage due to the opening of the conductance of the synapse, that I will call the post-synaptic potential.

## The Voltage Equation for the Synapse and EPSP and IPSP

$$V(t) = \frac{g_r E_r + g_s E_s}{g_r + g_s} (1 - e^{-t(g_r + g_s)/c})$$

The synaptic battery is the ceiling of the synaptic voltage.



**EPSP:** excitatory post-synaptic potential (generate depolarization)

**IPSP:** inhibitory post-synaptic potential (generate hyperpolarization)

Some of the synapses tend to do negative voltage, some synapses tend to do positive voltage relative to the resting potential typically. The more excitatory synapses you have in your cell, the more the cell will be more active.

## Summary

PSP in real cell: Summation of EPSP and IPSP

That if this voltage becomes enough positive, enough depolarizing, crossing a certain threshold you will get a new phenomena from the cell, the spike.

# QUIZ

1. Injection of a constant positive current into a neuron will: Select all the correct answers (could be more than one)

Charge the internal side of the membrane capacitance with positive ions

Result with less negative membrane potential (depolarization)

2. Select all the correct answers : The following equation  $V(t) = IR(1 - e^{-t/RC})$  describes:

The maximal voltage  $V = IR$  that may be attained during the injection of a step current I.

The development of membrane voltage following a step current injection to a passive isopotential cell.

3. Select all the correct answers : What is the membrane time constant  $\tau_m$ ?

$$\tau_m = RC$$

The time that it takes for the membrane potential to rise to about 63% of its steady state value following a long step current pulse.

4. Mark all the correct sentences

The voltage in a passive RC circuit increases as (1- exponent) during a step current injection (I) across the two sides of the circuit.

The voltage in a passive RC circuit decreases exponentially at the end of the current injection.

5. What is a typical resting potential of a neuron?

$$-70mV$$

6. Select all the correct answers: What does the term "temporal summation" mean?

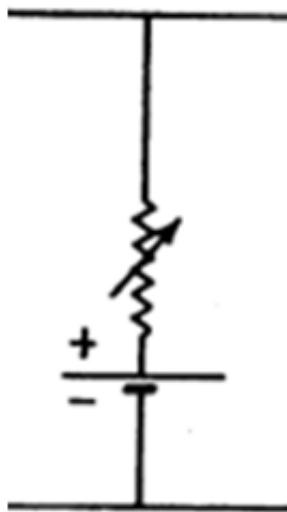
The voltage response to repeated inputs to the cell will build up one response on top of the other.

The RC properties of neurons cause the neuron's membrane to activate an 'electrical memory' and thus, the voltage response to a later input may summate with that of an earlier input.

The timing of synaptic inputs to the cell determines the integration (summation) of these inputs.

7. Select all the correct answers: What is the direction of the (positive) current flow in the following circuit?

# Out



# In

Outward (from In to Out)

8. Select all the correct answers: Potassium (K<sup>+</sup>) concentration is higher inside the neuron than in the outside. The opening of potassium ion channels in the cell's membrane will result in:

- Flow of K<sup>+</sup> ions outside of the cell
- Hyper-polarization of the cell's membrane

9. Mark the correct sentences regarding the EPSP (Excitatory Post Synaptic Potential):

- The EPSP results from the opening of synaptic (transmitter-gated) membrane ion channels associated with a positive battery
- The opening of transmitter-gated sodium channels will result with an EPSP

10. Mark the correct sentences regarding the IPSP (Inhibitory Post Synaptic Potential)

- IPSP results from the opening of synaptic channels associated with a (inward directed) negative battery
- Opening of transmitter-gated potassium channels will result with an IPSP

11. Select all the correct answers: Activation of an EPSP at t=0 and then an IPSPs at  $t = \tau_m$  will result with:

- A PSP- post synaptic potential that is smaller (less depolarized) than the EPSP alone
- First depolarization then hyperpolarization

## WEEK 4: Electrifying Brains-Active Electrical Spikes

In the previous module we learned that:

1. neurons are electrical devices
2. Membrane behaves as an RC circuit
3. synapses operate by opening a new cross-membrane conductance attached with a battery.

We will discuss:

1. The excitable (spiking) axon
2. The Hodgkin & Huxley experiment
3. Space clamp and voltage clamp
4. Membrane conductances/currents underlying the spike
5. The H&H model for spike initiation
6. Spike propagation in axons
7. From synapses to spikes

single neuron carries two signals: synaptic potentials in dendrites and spikes in axon.  
and the synaptic potentials generate spike

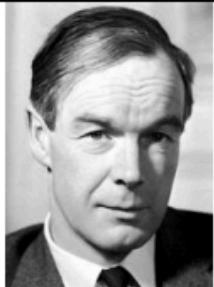
## The Hodgkin Huxley Experiments

The advantage of choosing squid: it has a giant axon (wide and thick)

a half of a millimeter (500 micrometer)

so it enabled Hodgkin-Huxley to penetrate axially through the axon with a wire (with a electrode) inside

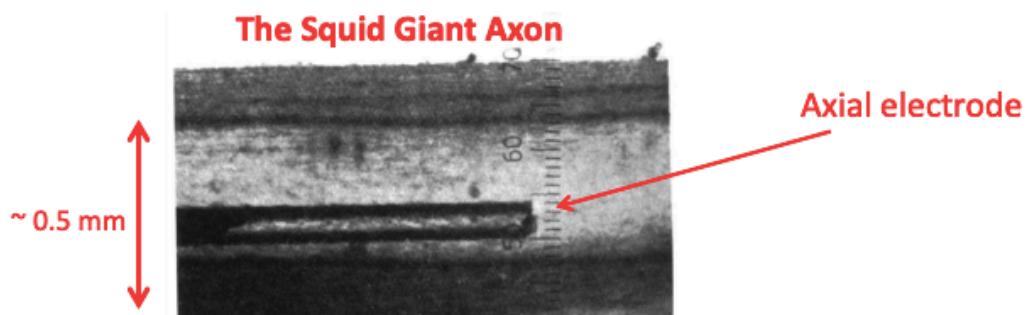
## THE SPIKE - Hodgkin and Huxley (H&H) – NOBEL 1963)



Sir Alan Lloyd  
Hodgkin



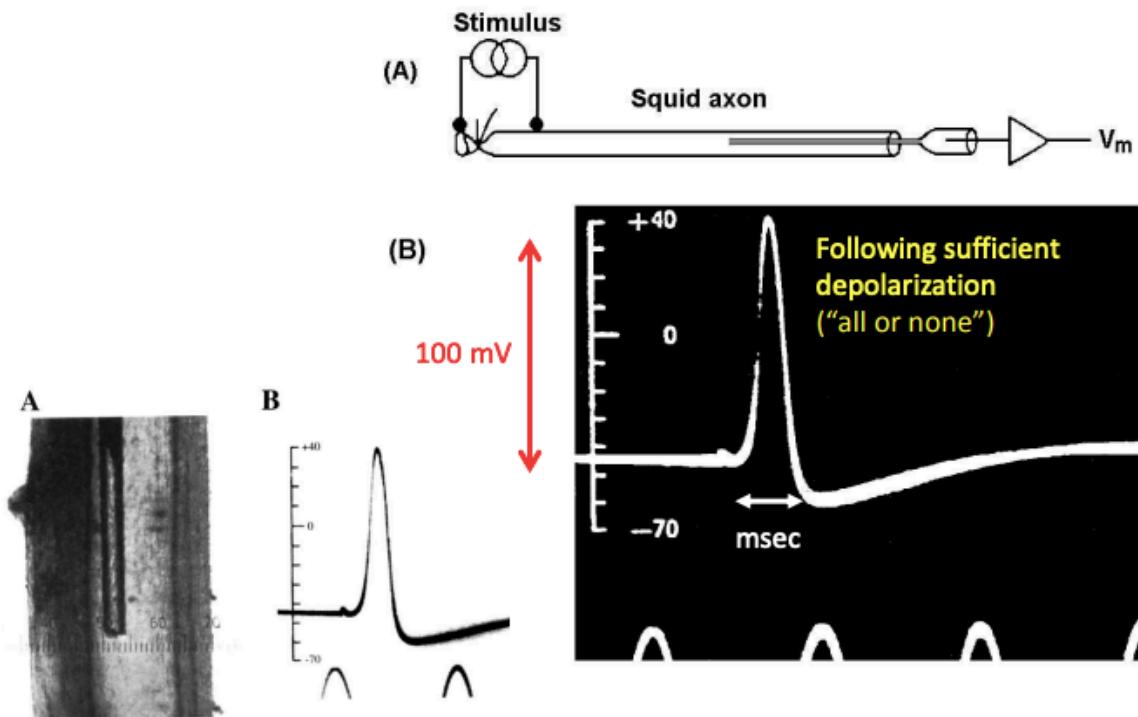
Sir Andrew Fielding  
Huxley



we can penetrate an electrode into our axon but we cannot do axially electrode in our real axon

The first intracellular recording of a spike:

**First direct (intracellular) recorded action-potential (spike)  
in the squid giant axon (Hodgkin and Huxley, 1939)**



the spike starts from minus 60 or minus 50 and goes up until cross the zero, becomes even more positive inside than outside. and this is called **over shoot**

remember that the resting potential is more negative inside than outside

then the spike finishes itself and repolarize back into the resting potential (even below the resting potential)

this is called **hyperpolarization (undershoot)**

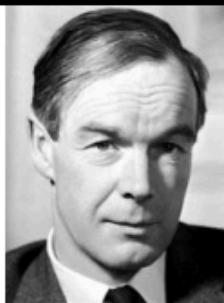
this is a transient phenomena. after a few milliseconds (depending on temperature), the spike disappears

the experiment was done in a cold temperature, 6.3 centigrades.

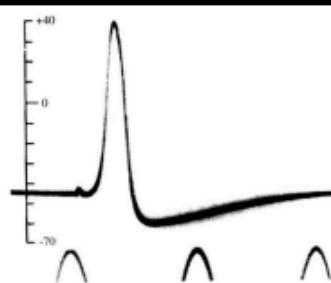
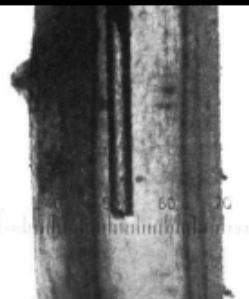
That is a general universal phenomena almost generated in all the nerve cells. And the **question of Hodgkin-Huxley** was what are the **membrane mechanisms in the axon that enables this fantastic phenomena**, all or none phenomena. The spike is called **an all or none phenomena** is because **if the stimulus was not strong enough, there would not be an action potential**.

### Hodgkin & Huxley Equations

## The H&H equations for spike initiation *The triumph of theory*



Sir Alan Lloyd  
Hodgkin



Sir Andrew Fielding  
Huxley

$$I = C_m \frac{dV}{dt} + g_{Na} h m^3 (V - V_{Na}) + g_K n^4 (V - V_K) + G_L (V - V_L) \quad (1)$$

$$\frac{dm}{dt} = \alpha_m (V) (1 - m) - \beta_m (V) m \quad (2)$$

$$\frac{dn}{dt} = \alpha_n (V) (1 - n) - \beta_n (V) n \quad (3)$$

$$\frac{dh}{dt} = \alpha_h (V) (1 - h) - \beta_h (V) h \quad (4)$$

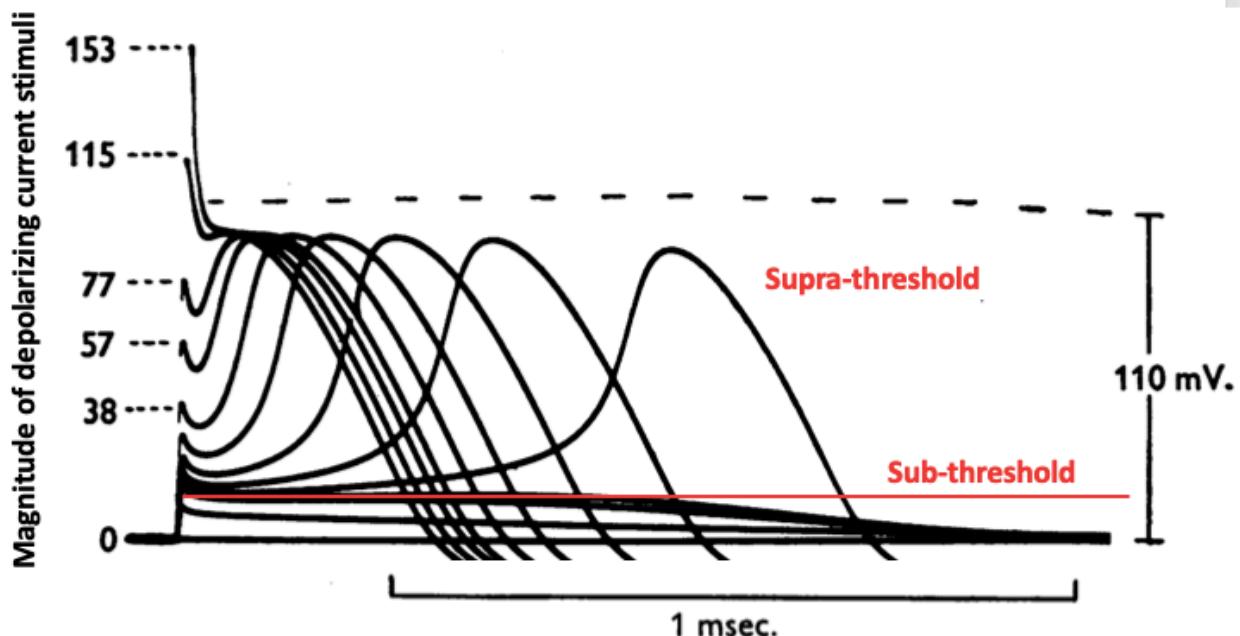
The core of this lesson

They capture the action potential mathematically

Each of the parameters here derives from experiments. If we solve this equation for voltage, then we will get the solution and will behave like a connection potential.

## The All or None Spike and the Voltage Clamp

### The “all or none” nature of the spike



Hodgkin, Huxley and Katz, 1952

#### threshold

If you cross the voltage threshold, you suddenly see that the voltage, instead of going down, it goes up. And boom, it generates this new phenomena, the spike, the action potential.

And if you inject even a stronger current, you will get an action potential that looks similar. So, the stronger current you inject, you get an earlier spike.

Notice that these spikes have the **same shapes**.

If your injected current is below the **sub-threshold of depolarizing**, you will not get a spike.

**the sub-threshold is about 10 millivolts above the rest from minus 70 to minus 60, or from minus 60 to minus 50**

If you injected current is above the sub-threshold, the current will be considered within the **supra-threshold**, and you will get a spike.

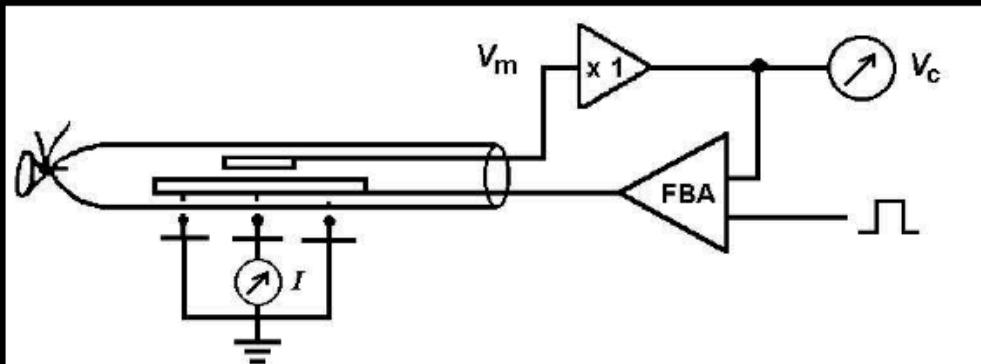
**What are the membrane currents underlying the spike?**

What makes the membrane of the axon excitable? What makes the membrane of the axon enabled to after reaching a certain voltage, to generate this all or none phenomenon? What are the properties of the axon?

So Hodgkin and Huxley developed 2 techniques: **the voltage clamp** and **the space clamp**.

## The Voltage Clapm & The Space Clamp

### The voltage clamp (+ space clamp) *The technique that made the whole difference*



**Space clamp** - making the (long) axon effectively isopotential via the insertion of an axial conductive wire.

**Voltage clamp** – enables the experimenter to dictate the desired voltage difference between the inside and the outside of the membrane.

The electronic feedback system injects current to exactly counterbalance the (**excitable – voltage-dependent**) membrane current.

*Developed by Kenneth Cole and George Marmont*

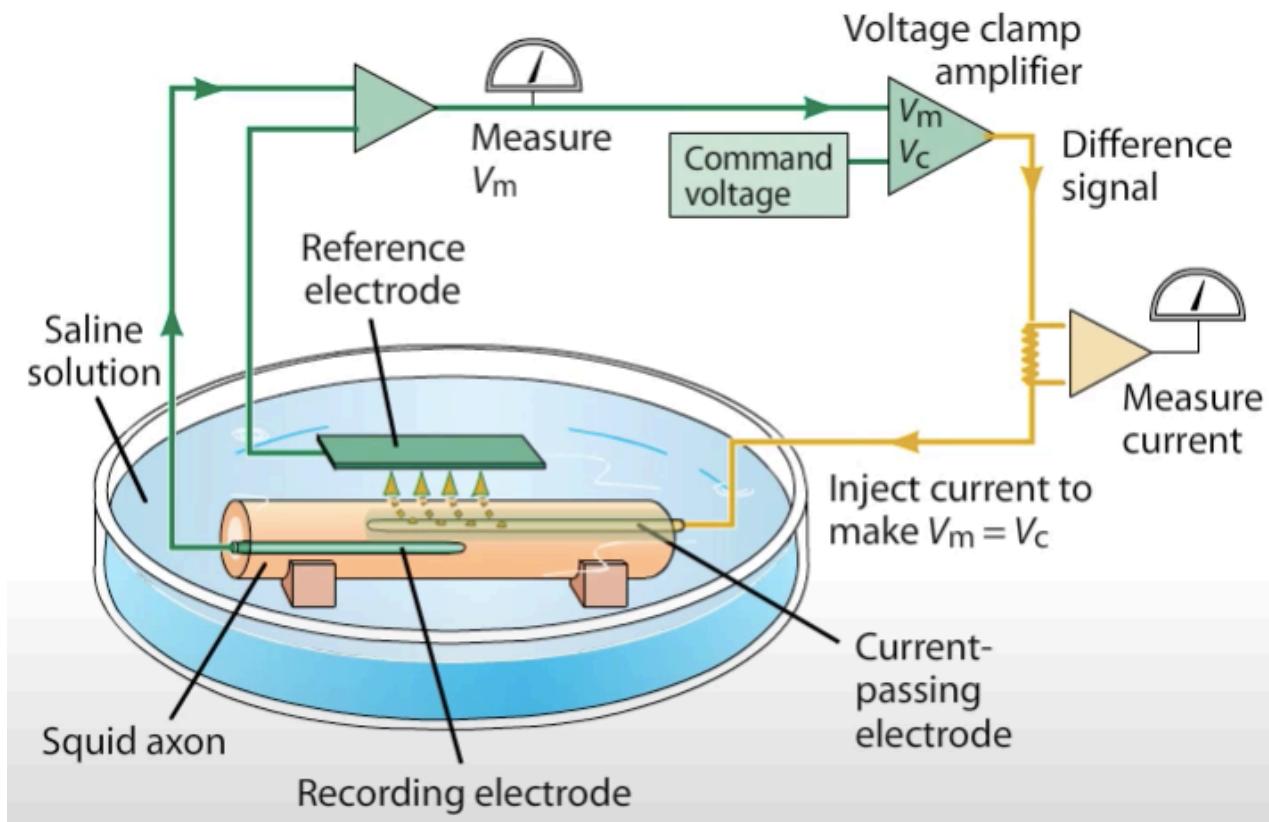
## The Space Clamp

The space clamp technique means, that you take an axial or long axon and, and makes it electrically **isopotential**. What does it mean? It means that when you put place inside the axon, an axial, an axial resistance, low resistance inside the axon, all the points along the axon become isopotential.

Electrically, because of this resistivity that is low, actually there is no voltage draw between this point and this point and this point and this point. So, on the inside of the axon becomes isopotential. Whenever there is a spike here immediately there is a spike there, isopotential. So, the **whole membrane becomes isopotential**.

So this is called space clamp, because you clamp the space.

## The Voltage Clamp a.k.a. Vc



Basically the voltage clamp is in order to make  $V_m = V_c$  so the membrane voltage is close to the command voltage

$V_m$  is the membrane voltage

$V_c$  is the command voltage (the desired membrane voltage) and is set by investigator

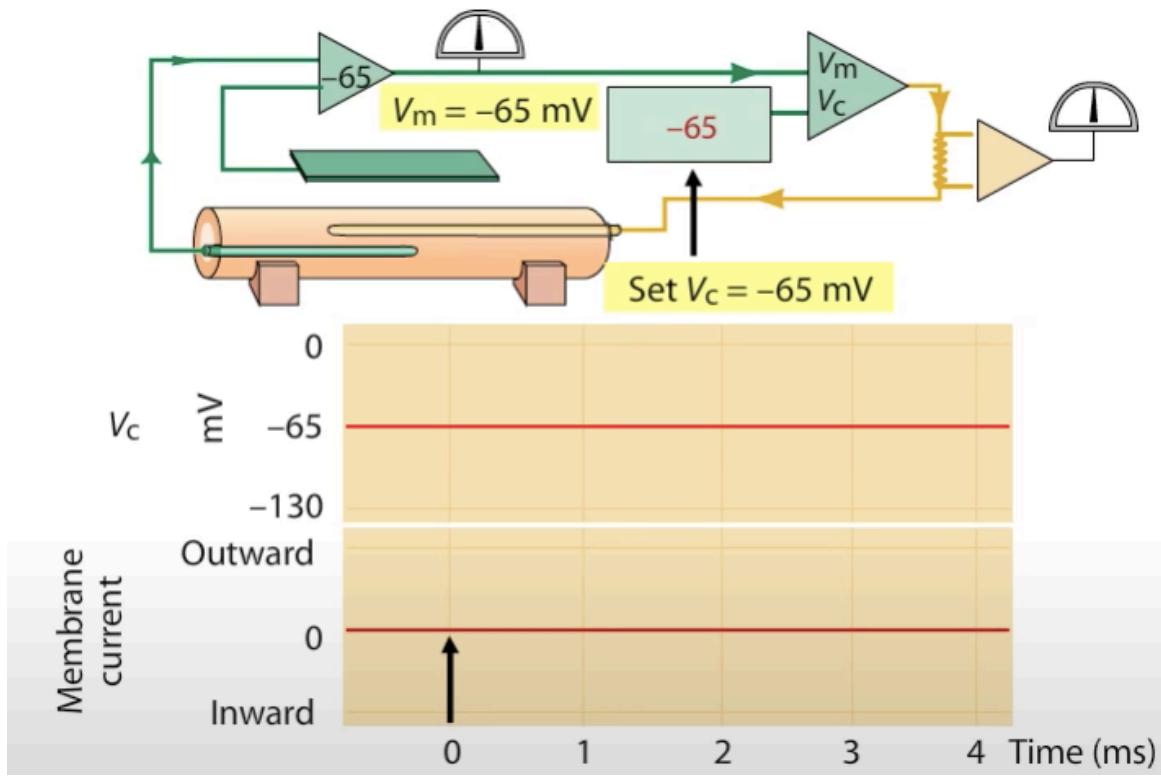
the difference between  $V_m$  and  $V_c$  is compared by a comparator. if  $V_m$  is not equal to  $V_c$ , this comparator generates a different signal. This different signal is used by the voltage clamp amplifier to generate a current which will be injected into the axon via the current passing electrode in order to make  $V_m = V_c$

This feedback circuit keeps the membrane voltage as close to the command voltage as possible

Finally the amount of current required to keep  $V_m = V_c$  (the injected current current) can be measured and recorded.

This means that is voltage-gated ion channels open and closed over time in response to change in  $V_m$  imposed by the voltage clamp the current generated by this channels can be recorded and analyzed.

### Experiment 1

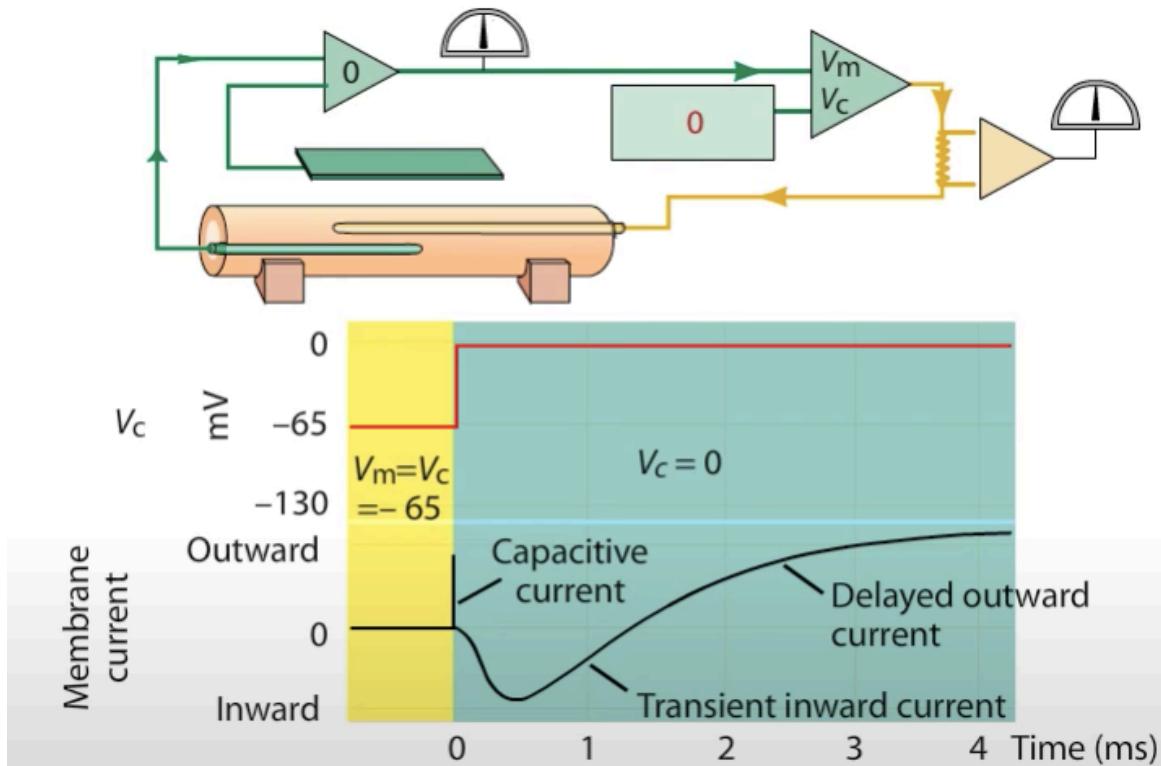


$0$  is the start point

$V_c$  and  $V_m$  are identical (both  $-65$  millivolts), so there is no change in  $V_c$  and  $V_m$

### Experiment Two

Then set  $V_c$  to  $0$  millivolts



a brief capacitive current is seen followed by a characteristic pattern of **inward** and **outward current** current.

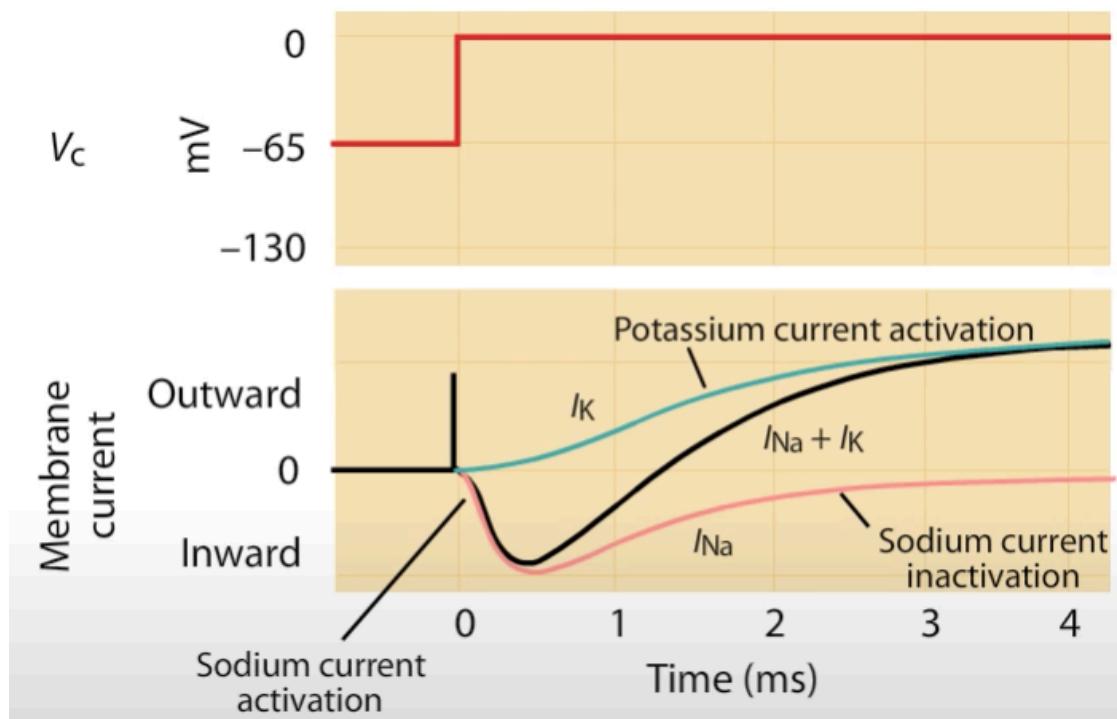
The capacitive current occurs because the step from one potential to another alters the charge separation and thus the electrical potential across the membrane.

Once the new potential is reached there's no more capacitive current initially  $V_c$  is at the holding voltage (-65 millivolts) which is identical to the resting potential.

When  $V_c$  is adjusted to 0 millivolts, the voltage clamp amplifier injects current to push the membrane potential to 0 millivolts.

Now different types of ion channels in the axon membrane open and close such that one sees an initial surge of inward current followed by a more slowly developing outward current the late or delayed outward current.

The transient inward and delayed outward phases of the current trace recorded after the command voltage was set to 0 millivolts **correspond to the sodium and potassium conductances** measured during an action potential.



In fact, the inward and outward currents are separated.

One of them, **the early current is carried by sodium ions** and is thus called **sodium current  $I_{Na}$** . Sodium channels are set to be **voltage-gated** because they **activate rapidly in response to depolarization** not only because the sodium conductance to activate but also cause it to decrease over time or inactivate.

**The other current is carried by potassium ions** and is called the **potassium current**. Voltage-gated **potassium channels activate more slowly than sodium channels** and do not show inactivation in axons.

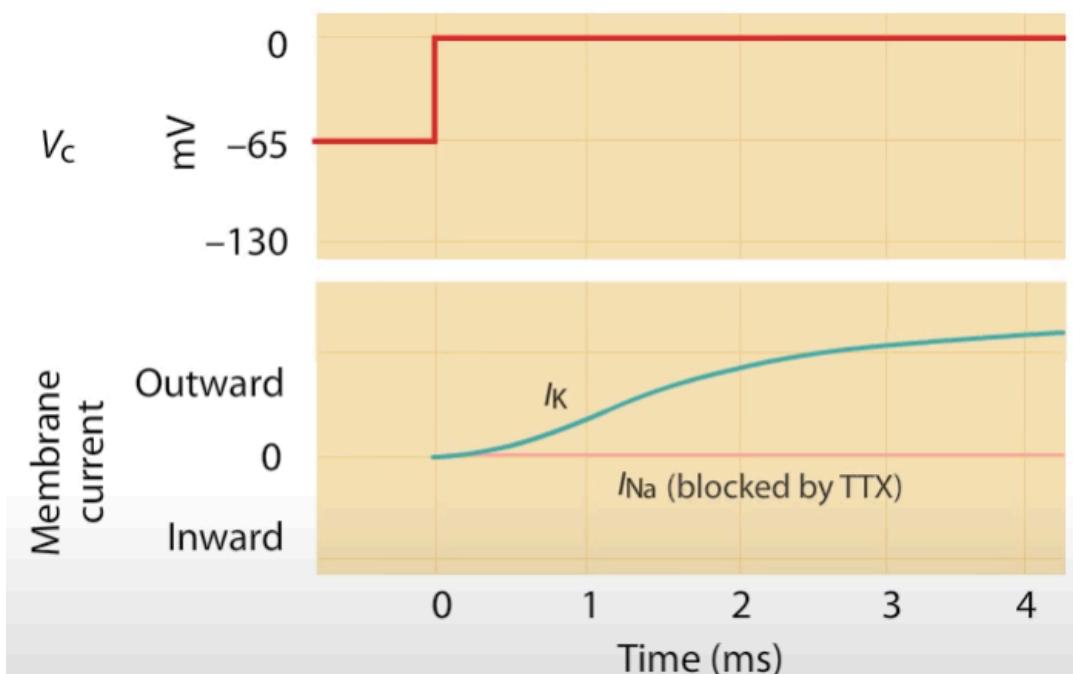
### Specific Blocking Agents

How do we know which ions carry these inward and outward currents?

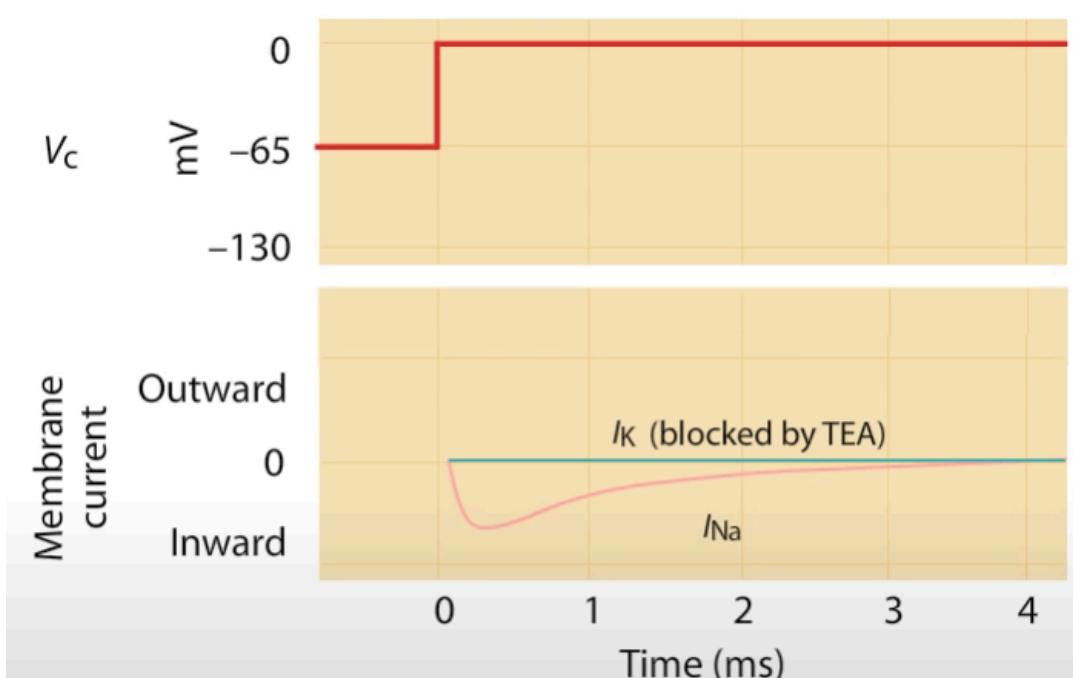
The answer is **specific blocking agents**.

Specific blocking agents can be used in studies to dissect out the currents that underlie the action potential.

For example, **TTX (tetrodotoxin)** is a toxin found in pufferfish and in the skin or certain frogs and salamanders, can specifically blocks sodium channels. In the presence of TTX, only potassium channels open during the voltage clamp depolarization. So these potassium channels can be studied in isolation.

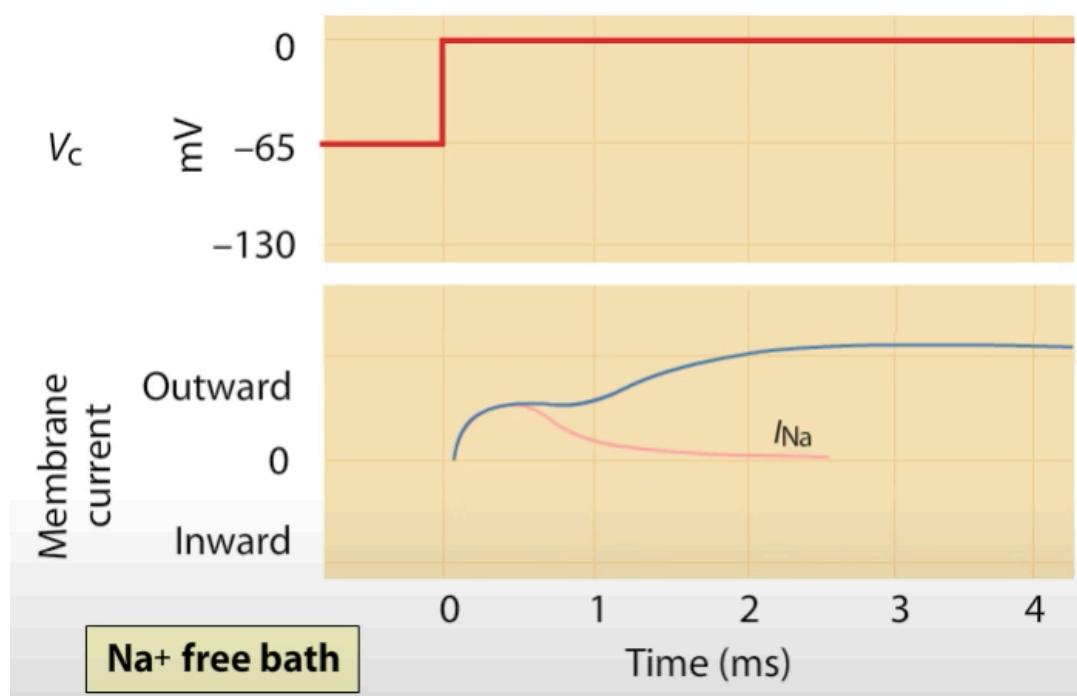


**Tetraethylammonium (TEA)** is a large organic cation which can **specifically blocks potassium channels** and therefore allows us to isolate the sodium current.



Plus, **since the sodium current is an inward current depended on extracellular sodium concentration it can be eliminated by removing all external sodium**. Under this condition, the recorded current is similar to the current seen in the presence of TTX which blocks the sodium channels.

But there is one major difference that there is an initial outward. Because even though there is no external sodium, there is still sodium present inside the axon. This sodium can flow outward down its concentration gradient through the open sodium channels.



The **voltage clamp** is a technique used to control the voltage across the membrane of a small or isopotential area of a nerve cell by an electronic feedback circuit.

You don't want the membrane of the axon to behave independently, as it wants to behave, and generate a spike. You want to fix the voltage, to clamp the voltage between the inside and the outside. The idea is that you want to **clamp the voltage**. You want to **set the voltage**, to **fix the voltage between the inside and the outside of the, of the membrane of the axon**.

Basically, V<sub>c</sub> is making the generation of the current voltage-dependent. Mostly from the voltage clamp, which enables to record direct currents through the membrane because you inject exactly the same current in the opposite direction.

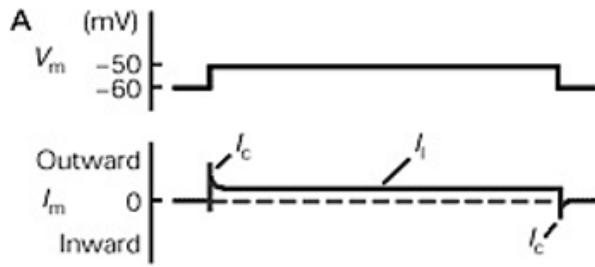
The essence of this advance was that the **ionic currents** could be **separated from the capacitive currents** and studied directly as a function of voltage by combining three strategies:

1. creating a length of membrane whose potential was uniform throughout (controlled by the axial wire)
2. controlling the voltage of this length of axon with electronic feedback
3. applying abrupt, step changes of voltage in order to charge the membrane's capacitance quickly and restrict the capacitative current to the time before the ionic current developed

# Membrane Currents Underlying the Spike

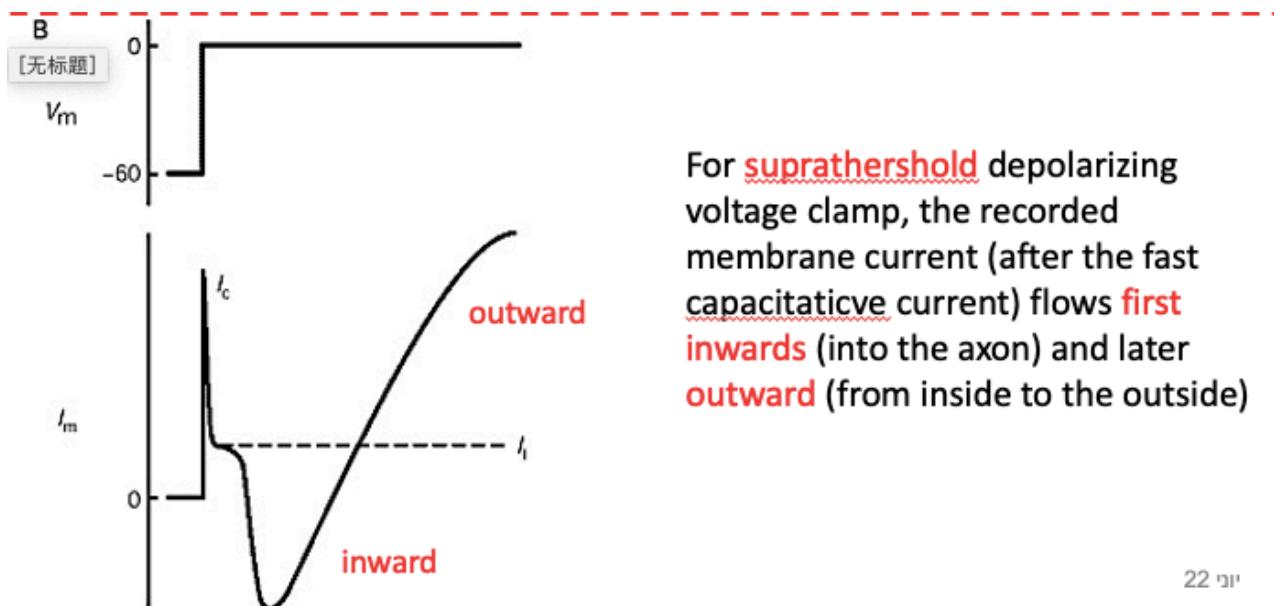
Firstly we try the **subthreshold regime**. Capacitive current is sensitive to the change in voltage. But there is still **resistive current**. And it behaves like a passive circuit.

## Membrane current in response to voltage clamp (VC)



For **subthreshold** depolarizing voltage clamp, the recorded membrane current is the current that flows via the leak (passive) conductance + a small **capacitative current** (at start and end of the VC)

Then we depolarize the cell further to the **superthreshold regime**. The voltage jumps from -60 millivolts to 0 millivolts.



For **suprathreshold** depolarizing voltage clamp, the recorded membrane current (after the fast **capacitative current**) flows **first inwards** (into the axon) and later **outward** (from inside to the outside)

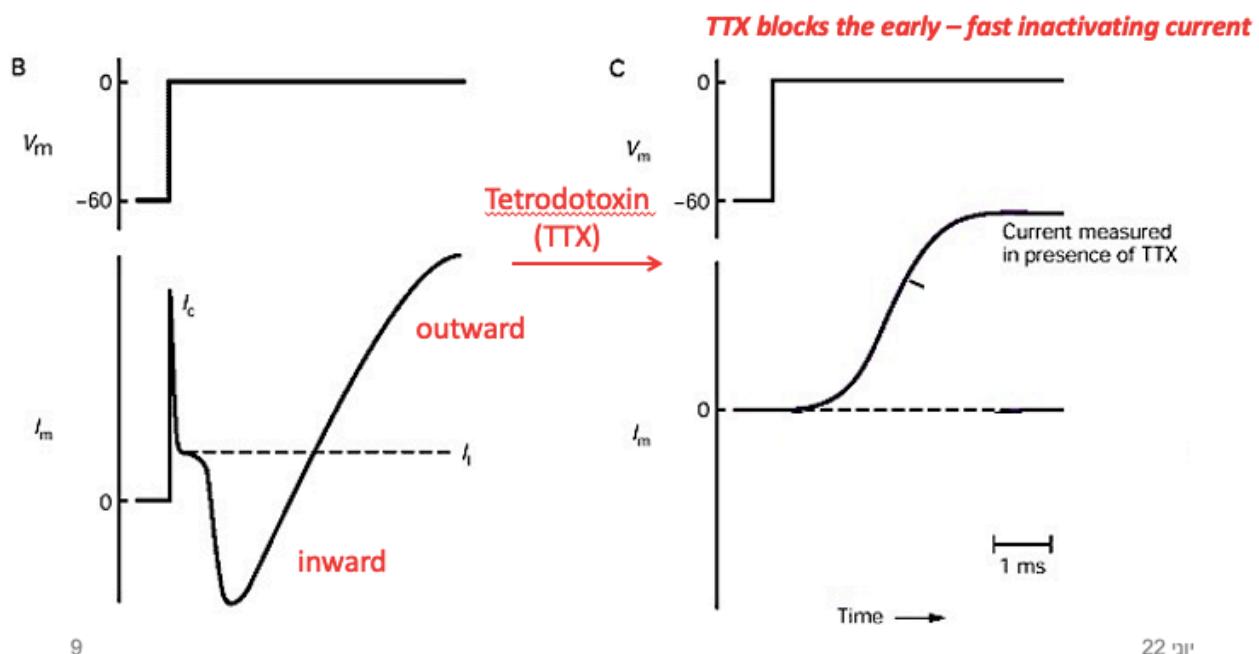
22.iii

As long as you hold the voltage fixed, you will get first a fast early inward current, and then it reverses and then inactivates and becomes an outward current so it is a biphasic current.

What Hodgkin and Huxley also found is that you can block these two currents separately. If you put TTX a very low concentration in the dish, you can get rid of one of those currents:

## Separating voltage-dependent active (excitable) currents Using pharmacological agents

2 different currents flow via the membrane during the spike



9

22.11.

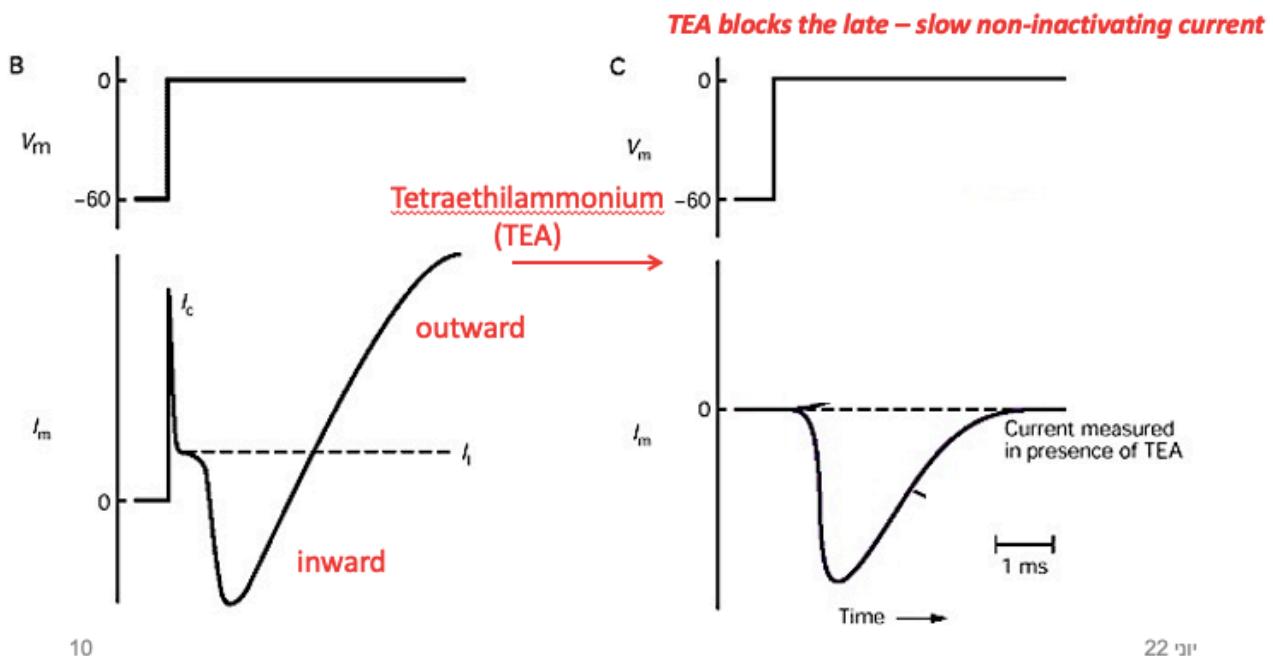
TTX will only leave you an outward phase of the current.

So using pharmac, pharmacology, using pharmacology agents, or drugs, using drugs, you start to separate two currents.

Hodgkin and Huxley also found that TEA is useful:

## Separating voltage-dependent active (excitable) currents Using pharmacological agents

2 different currents flow via the membrane during the spike



TEA will only leave you an inward phase of the current.

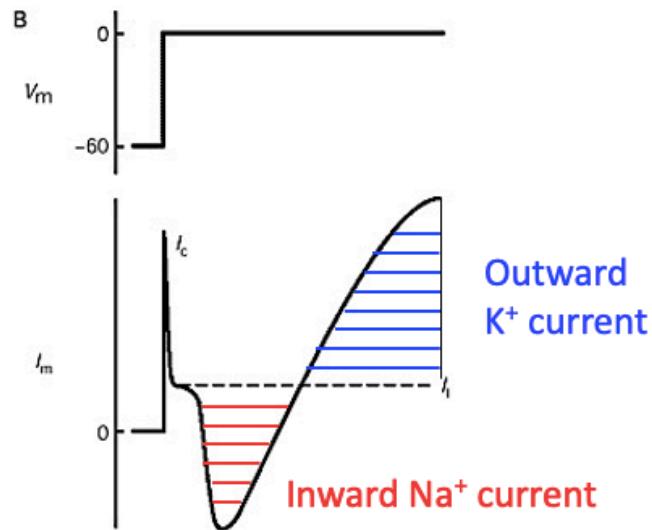
So Hodgkin and Huxley using this separation technique came to a conclusion that **the current response may contain two different currents**.

In addition, they also found that **changing the external concentration of sodium and potassium** can cause different results.

And they found that **the sodium current is an early on inward current that flows from outside inside**. So, very **early on**. Just after your voltage clamp, some ion channels for sodium apparently open. And these sodiums enables the flow, can flow from outside into the cell.

But if you continue the voltage clamp, you will see the inward sodium ends or inactivates. And later on with time, there is a second phase, which is an outward phase. This is the blue current here, and they show that this consists of potassium ions. So potassium at this, at this time the potassium flows from inside, outside. This is the outward current.

**Changing ion concentration at bath with giant axon showed that early current is carried by  $\text{Na}^+$  ions and late one by  $\text{K}^+$  ions**



(Red part)

So this current has two phases upon it: the activation phase and the inactivation phase of the inward, first inward current. We call it **fast inactivating sodium current**.

Activate fast and inactivate fast

(blue part)

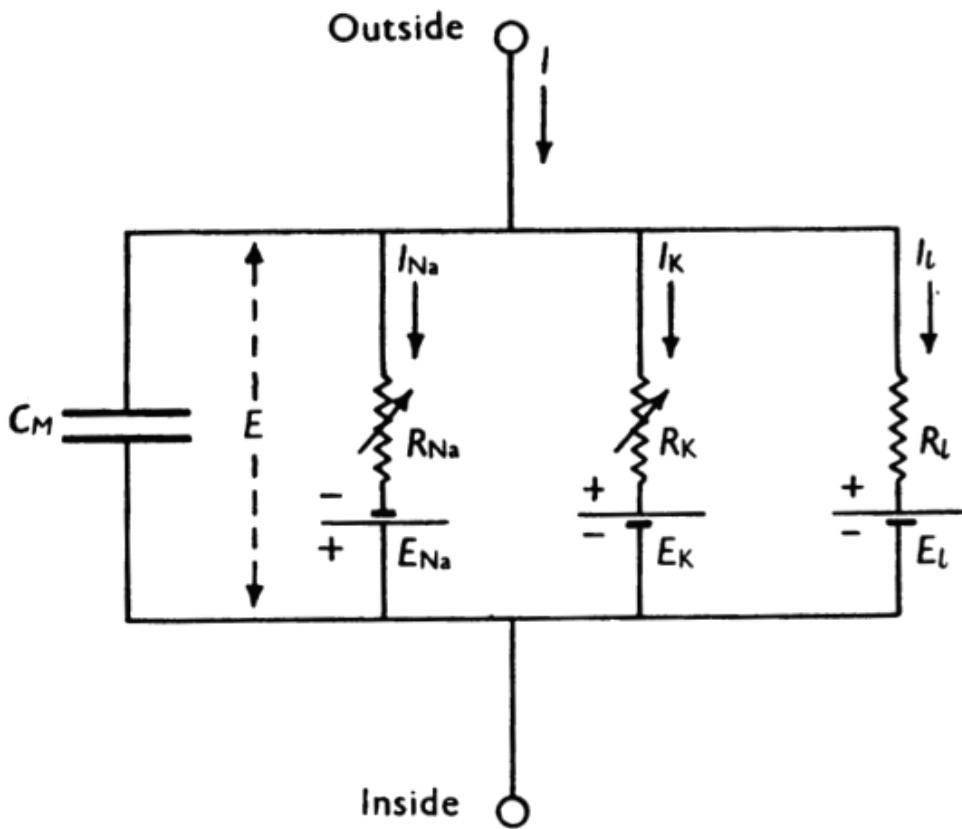
later potassium current and seems not to be inactivated

it will remain open as long as the voltage hold fixed

So Hodgkin and Huxley drew the electrical circuit in 1952:

The classical conceptual jump of Hudgkin-Huxley in understanding the action potential

## The electrical circuit for the squid axon (excitable) membrane



circuit for the axonal membrane

$I_l$

leak or passive channels as always there are all these channels are passive static. they don't depend on anything. ( $R_l$  for  $R_{leak}$  and  $E_l$  for  $E_{leak}$ )

**The sodium conductance**

with a **positive battery inside** so wherever this conductance, which is voltage-dependent, called **excitable** because it is a voltage-dependent.

And when I clamp the membrane supra-threshold, I get current flow, sodium current flow from outside to the inside.

**The potassium conductance**

with a **negative battery inside** so wherever you open this conductance, potassium actually flows from the inside to outside like it is here.

# Modeling the Membrane Currents

**Ion currents ( $K^+$  and  $Na^+$ ) for various depolarizing voltage clamp  
(and extracting respective ion conductances)**

$$I_K = g_K (V_m - E_K); \quad I_{Na} = g_{Na} (V_m - E_{Na})$$

$g_K$  conductance of the potassium channels

$g_{Na}$  conductance of the sodium channels

$I_K$  Potassium current (can be measured)

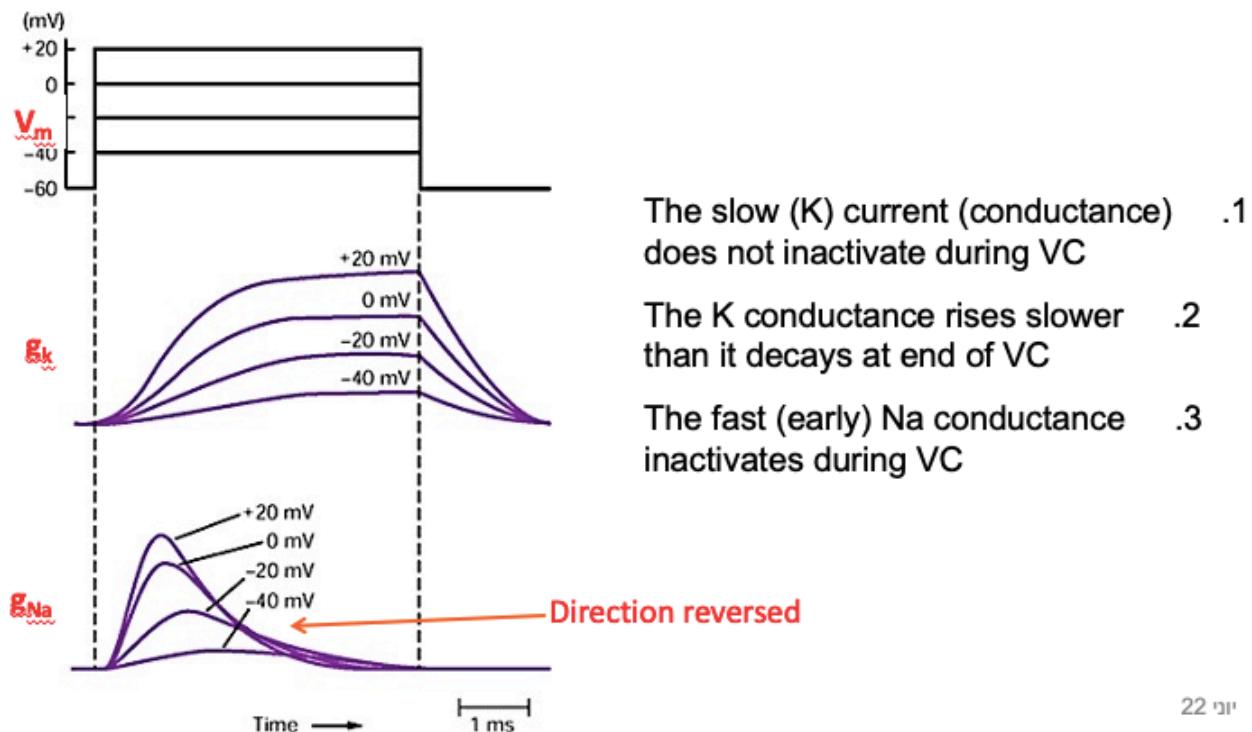
$I_{Na}$  sodium current (can be measured)

$V_m$  if the voltage is fixed then the voltage clamp will give the value

$E_K$  depends on the concentration difference between the outside and the inside of potassium (the potassium battery)

$E_{Na}$  depends on the concentration difference between the outside and the inside of sodium (the sodium battery)

And if you know  $I_K$   $I_{Na}$   $V_m$   $E_K$   $E_{Na}$ , then you can calculate  $g_K$   $g_{Na}$



22.11

## Potassium Conductance

You can see that the conductance of the potassium, becomes stronger and stronger, as you depolarize more and more, the membrane.

So the larger the voltage clamp, the more conductance opening of a voltage-dependent conductance. That's the reason why you change the voltage clamp, you get more and more conductance.

It will take time to open the potassium conductances and by the way **this time becomes faster as your voltage clamp more stronger**.

In addition, **the more you depolarize the voltage clamp, the higher conductance you will get.**

And when you stop the voltage clamp, you will see the continuation of the potassium conductance to its resting venue.

So this is a voltage-dependent conductance. This ion channels that are sensitive to voltage.

They will not inactivate during the voltage clamp. And they are slow conductance change.

### Sodium Conductance

Even though the current is inward, the conductance is always positive. (direction reversed)

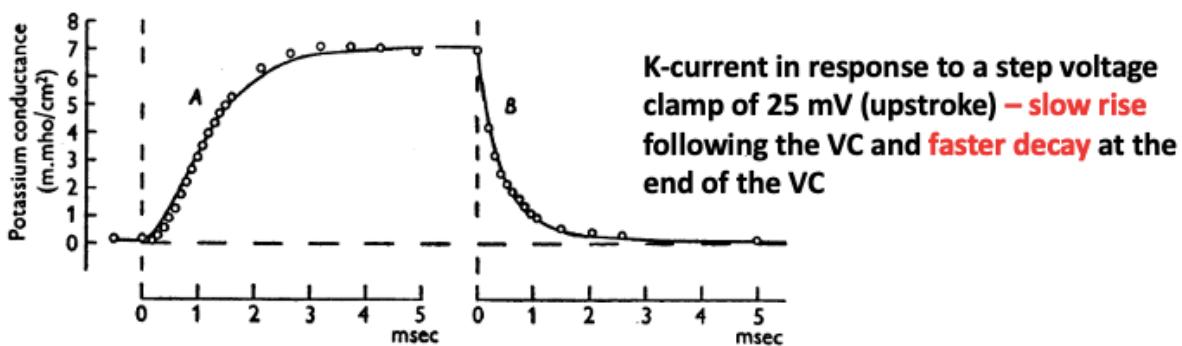
**Sodium conductance responds fast.** So as soon as you have voltage clamp, very early on, you get a conductance change.

When the depolarization is more and more extreme you get more and more conductance.

If you continue to voltage climb, the conductance will fade away. Somehow it inactivates, and it disappears during the voltage climb.

### Fitting an equation for $I_k$

#### **Fitting an equation for the K current (K-conductance) during/following VC**



Mathematically – the rising phase of K-current can be described as a power of 4 (namely as  $(1 - \exp(-t))^4$  and the decay as  $\exp(-4t)$ )

And the maximum of  $g_k$ :

$$g_K = \bar{g}_K n^4$$

**n represents the proportion of K-ion channels in the open state**

*"These equations may be given a physical basis if we assume that potassium ions can only cross the membrane when four similar particles occupy a certain region of the membrane..."* Hodgkin AL, Huxley AF. 1952 J Physiol (Lond) 117:500–544

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n is an activating parameter, it is a voltage-dependent parameter.

when n=0, there is no potassium conductance

when n=1, the potassium conductance is going to the maximum

For a particular voltage clamp, n gets its value somewhere between 0 to 1.

**n depends on both voltage and time.** So n represents the proportion of K-ion channels In the open state.

#### The exponent 4

This power 4 means that this potassium channel is open. Only if exponent 4 particles, if 4 gates in the channels are open so that the channel enables the flow of the current through the channel.

## Fitting K current for different VC depolarizing values

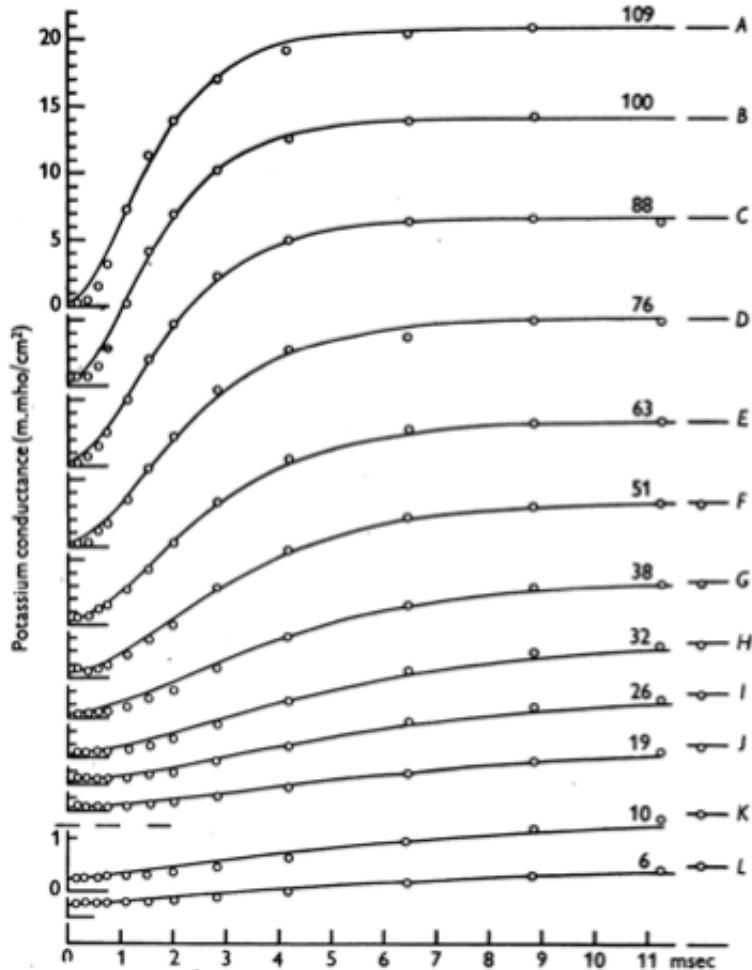


Fig. 3. Rise of potassium conductance associated with different depolarizations. The circles are experimental points obtained on axon 17, temperature 6–7°C, using observations in sea water and choline sea water (see Hodgkin & Huxley, 1952a). The smooth curves were drawn from eqn. (11) with  $g_{K0} = 0.24 \text{ m.mho/cm}^2$  and other parameters as shown in Table 1. The time scale applies to all records. The ordinate scale is the same in the upper ten curves (A to J) and is increased fourfold in the lower two curves (K and L). The number on each curve gives the depolarization in mV.

with voltage, you get more and more activation. So  $n$  becomes more and more close to one.

And the conductance will get faster activated if using higher voltage. ( $n$  is increasing faster and faster with depolarization faster and faster)

## Hodgkin-Huxley Equations Understanding

$$C \frac{dV_m}{dt} = -g_L(V_m - E_L) - g_{k^+}(V_m - E_{k^+}) - g_{Na^+}(V_m - E_{Na^+})$$

When parameters  $n$ ,  $m$ , and  $h$ :

$$C \frac{dV_m}{dt} = -g_L(V_m - E_L) - n^4 g_{k^+}(V_m - E_{k^+}) - m^3 h g_{Na^+}(V_m - E_{Na^+})$$

What we need to understand is when  $n$ ,  $m$  and  $h$  changes separately.

At least we know they are relying on the **voltage** and **time**.

$$n = f_1(v, t)$$

$$m = f_2(v, t)$$

$$h = f_3(v, t)$$

Now we know that  $n = [0, 1]$ , if  $n = 0.2$ , which means that 20% of the gates are open, and the **probability** is  $1 - n = 1 - 0.2 = 0.8$ , which means that 80% of gates are closed or the probability of finding closed gate.

Then we have:  $\frac{dn}{dt} = P_{closed}(c \rightarrow o) - P_{open}(o \rightarrow c)$

P stands for population

$P_{closed}(c \rightarrow o)$  for **closed gates to be open**

$P_{open}(o \rightarrow c)$  for **open gates to be closed**

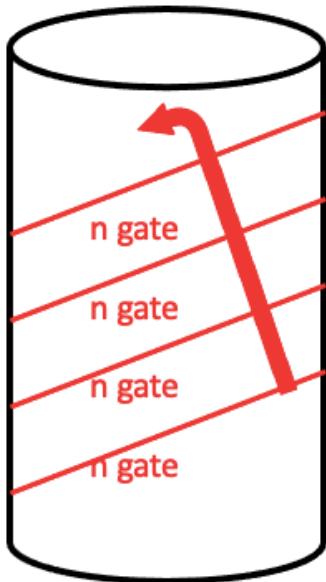
We can add in the **rate of change**:  $\frac{dn}{dt} = (1 - n)\alpha_n - n\beta_n$

These are equations Hodgkin and Huxley used, but they are not used today.

## The H&H Spike Model

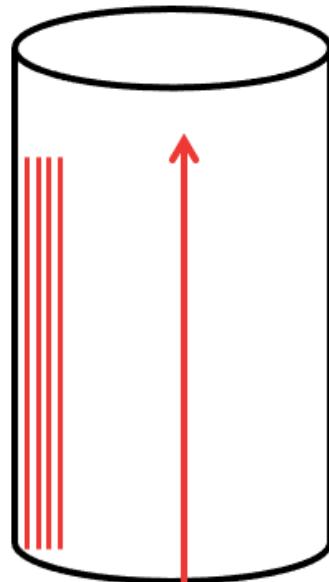
Graphical interpretation of H&H model for the K channel

Closed K channel (by 4 n gates)



4 n gates open with depolarization

Open K channel (by 4 n gates)



Gate closed: 0

Gate open: 1

n can be considered as the probability of a gate being open. n lies between 0 to 1.

There is no half open channel, there is either open channel or closed channel.

## The activation function, $n$ , and the rate functions $\alpha_n$ and $\beta_n$

$$g_K = \bar{g}_K n^4,$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

where  $\bar{g}_K$  is a constant with the dimensions of conductance/cm<sup>2</sup>,  $\alpha_n$  and  $\beta_n$  are rate constants which vary with voltage but not with time and have dimensions of [time]<sup>-1</sup>,  $n$  is a dimensionless variable which can vary between 0 and 1.

You need four  $n$  to open the channel. Only if all the four of  $n$  open, potassium will flow through the channel.

The  $n$  parameter relies on the other parameter  $\alpha_n$  and  $\beta_n$

$\alpha_n$  and  $\beta_n$  are (only) voltage dependent

$\alpha_n$  shifts the close state to the open state

$\beta_n$  shifts the open state to the closed state

Depending on voltage and depending on time, you move from the closed state to the open state as a function of voltage and time.

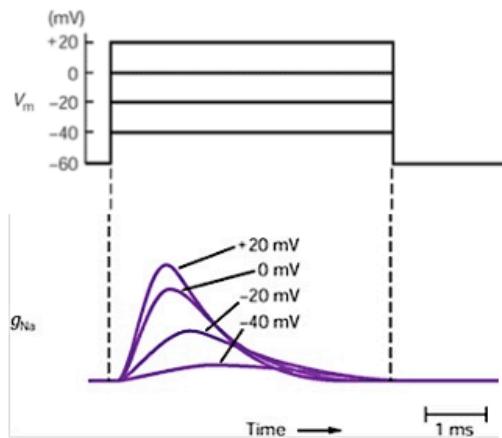
Alpha becomes larger with voltage, and as this becomes larger, it moves the closed state to the open state.

Beta becomes smaller with voltage, so less is moved from the open state to the closed state.

And eventually if the voltage is big enough, and the depolarization is big enough, most of the channels will be in their open state. So  $n$  will be close to 1.

## Sodium

Similar procedure is used to extract the activation ( $m$ ) and inactivation ( $h$ ) parameters for the Na current



$$g_{\text{Na}} = m^3 h \bar{g}_{\text{Na}},$$

$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_m m,$$

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h h,$$

Because Sodium current will inactivation, so we will need another parameter to measure the inactivation of sodium current.

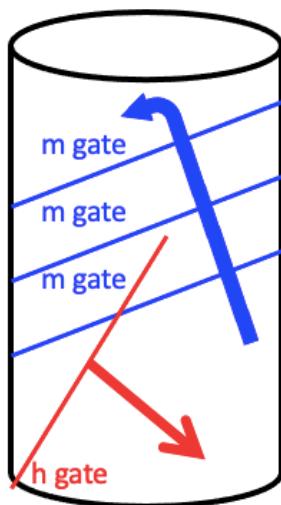
### the inactivating variable

$m^3$  to describe the opening of the channel during the depolarization (opens fast)

$h$  to describe the close of the channel during the depolarization (closes slowly)

### Graphical interpretation of H&H model for the Na channel

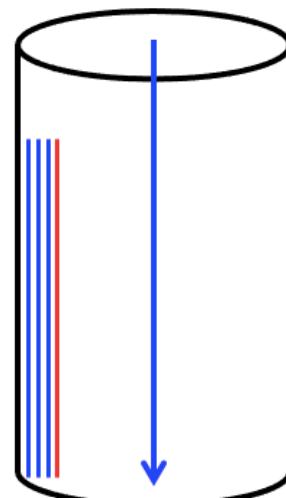
Na channel (by 3 activated  $m$  gates and 1 inactivated  $h$  gate)



3 (fast)  $m$  (activated) gates open with depolarization

1 (slow)  $h$  (inactivated) gate closes with depolarization

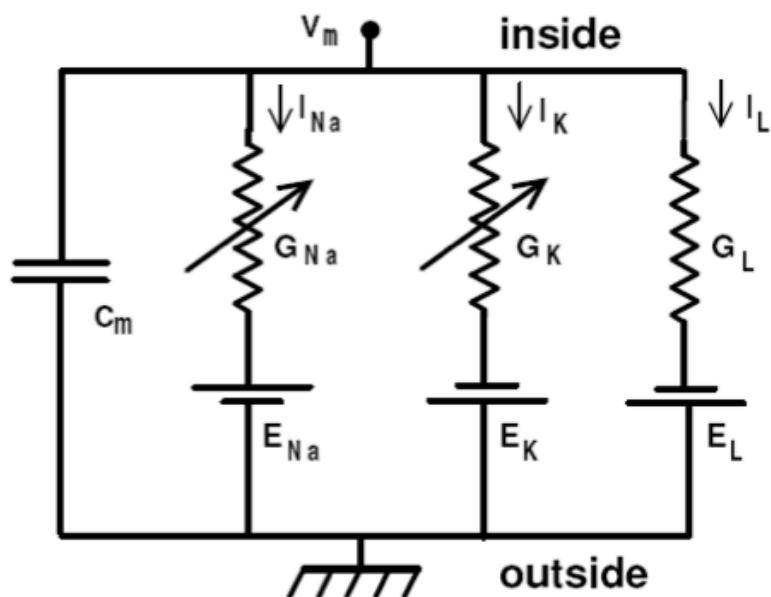
Open Na channel  
Na outside



you have a fast gate that opens early on, enables the flow of sodium from the inside to the outside early on. And this is **the beginning of the spike**, when sodium goes in there is depolarization due to the sodium.

Sodium goes in, but with time, there is this closing of this **h gate**, this red gate. And if it is closed there is no sodium in anymore.

### Summary



$$I = C_m \frac{dV}{dt} + g_{Na} h m^3 (V - V_{Na}) + g_K n^4 (V - V_K) + g_L (V - V_L) \quad (1)$$

$$\frac{dm}{dt} = \alpha_m (V) (1 - m) - \beta_m (V) m \quad (2)$$

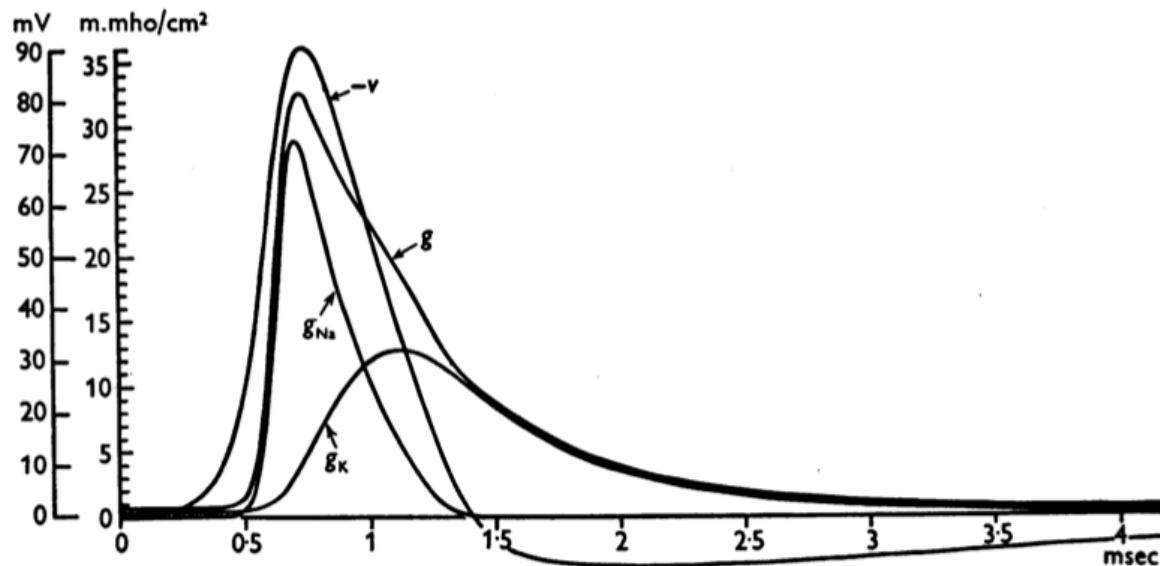
$$\frac{dn}{dt} = \alpha_n (V) (1 - n) - \beta_n (V) n \quad (3)$$

$$\frac{dh}{dt} = \alpha_h (V) (1 - h) - \beta_h (V) h \quad (4)$$

The circuit and the grand equation

describes the actual potential current  $I$

## **Overlay of the action potential (voltage) and underlying Na and K conductances**



**Fig. 17.** Numerical solution of eqn. (31) showing components of membrane conductance ( $g$ ) during propagated action potential ( $-V$ ). Details of the analysis are as in Fig. 15.

When you solve the equation for  $V$ , you will get this spike.

When it becomes more positive inside due to extra sodium ions, there is an extra depolarization here. The spike starts to grow. When the spike starts to grow there is even more sodium channels going in. More sodium channel going in, more depolarization, **more depolarization more sodium channel open, more sodium channel open, more depolarization and so on.**

This is the **positive feedback** between **depolarization** and **conductance for sodium**

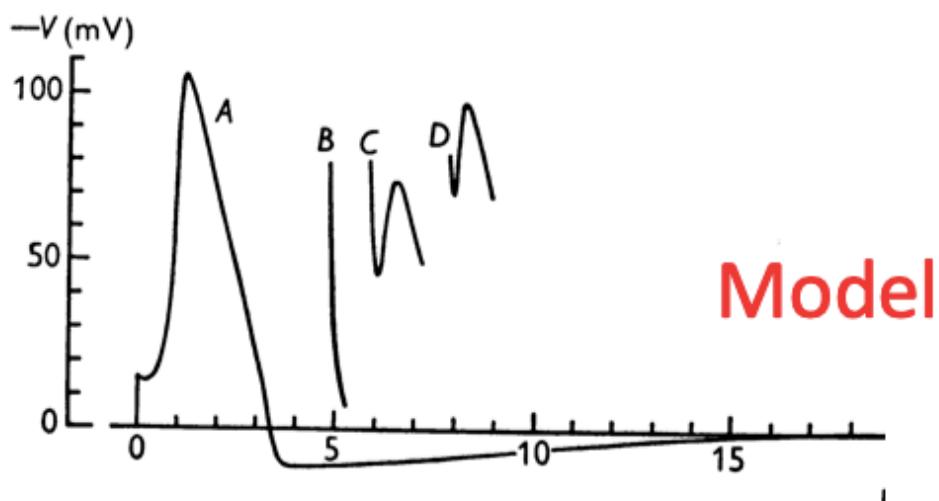
But the sodium conductance will turn to inactivation thanks to  $h$ , even though it is slower than  $m$

Then due to the spike and depolarization, the activation of the potassium starts.

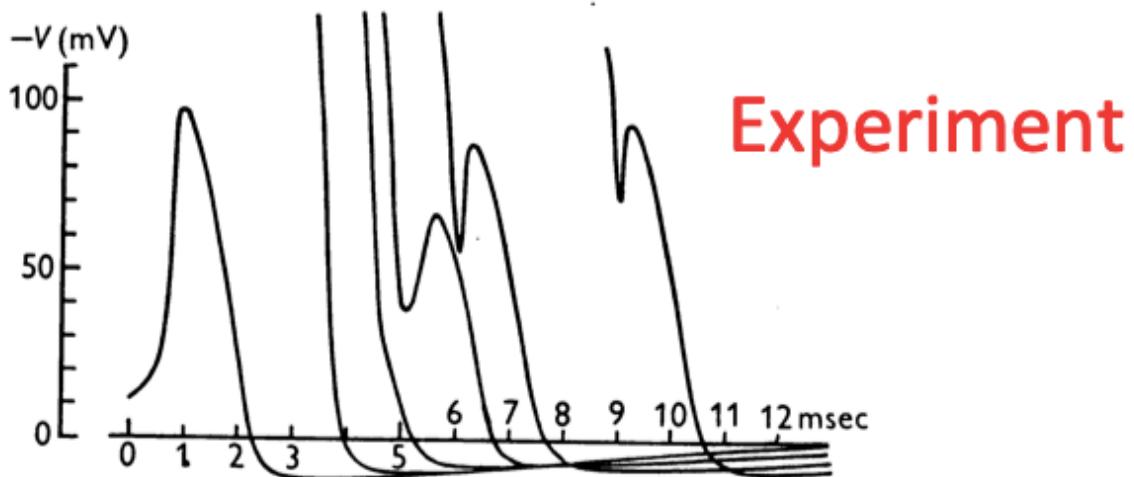
So here ( $\text{msec}=2$ ) the **potassium conductance is larger than the rest**. This extra potassium conductance enables the flow of potassium channel ions from inside to outside. This makes the inside even more negative than the resting potential. **With time, the voltage of the spike goes back slowly, slowly to rest. The conductance of the potassium goes also slowly, slowly to its resting value.** And eventually, the spike ends.

**The refractory Period**

## The refractory period



Model



Experiment

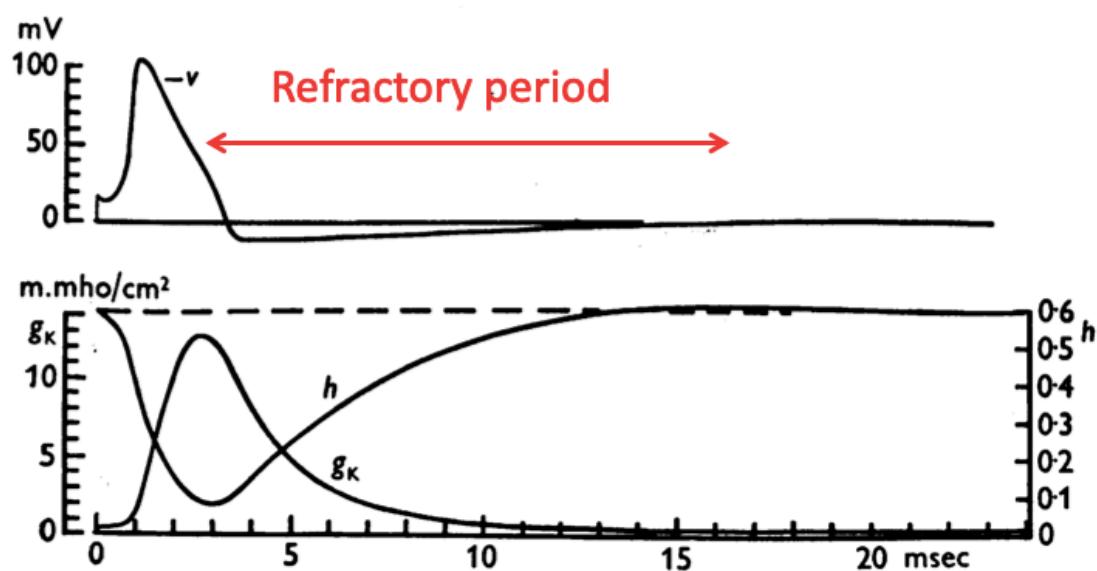
Very early on after the first action potential, you cannot get a second action potential.

You have to wait enough time for a second stimulation to get the second action potential.  
(about 10 milliseconds)

This means that the frequency of action potential is limited in actions.

**The source of the refractory period**

## H&H explanation for the refractory period



Slow recovery from **Na inactivation (h)** and slow kinetics of K conductance, both make the following spike impossible (**absolute refractory**) or hard (**relative refractory**) to be initiated.

$h$ , the inactivation variable. When  $h$  is close to 0, the sodium channel is closed. No matter what you do, you cannot get a second spike. Because there is no extra sodium current.  $h$  is slow and responsible for what we call the **absolute refractory period**.

Also, the sodium conductance impedes the spike.

So the two parameters **h inactivation** and **potassium activation** both are responsible for the refractory period.

Before everything is recovered, you can only get partial spikes; but after recovered, you can get full-blown spikes.

So the cell cannot generate a spike attached to another. There will always be a difference in time between the first spike and the second spike.

Now we know the frequency of the "clock" is about 100 hertz (100 spikes per second).

## QUIZ

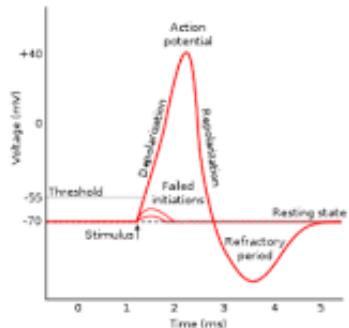
- What is typical amplitude of a spike? (from the cell's resting potential to the peak of the spike)  
~100mV
- What is a normal duration of a spike? (the width at its half amplitude)  
1-2 msec
- Injection of a brief 200 pA depolarizing current into the squid giant axon resulted with a single spike, increasing the stimulus to 300 pA:

Select all the correct answers (could be more than one)

Will trigger a spike with a similar shape.

May trigger a train of spikes.

What is a train of action potentials?



Action potentials in neurons are also known as "nerve impulses" or "spikes", and **the temporal sequence of action potentials generated by a neuron** is called its **"spike train"**. A neuron that emits an action potential, or nerve impulse, is often said to "fire".

Will trigger a larger spike.

Will trigger a shorter spike.

4. An Isopotential axon is a/an

Select all the correct answers (could be more than one)

axon with the same membrane voltage along its whole length (space clamp)

axon cannot be isopotential as when the spike starts at one location it is not yet initiated in another location

5. With the voltage clamp (VC) technique:

Select all the correct answers (could be more than one)

The voltage-gated ion channels in the axon open or close in response to the assigned membrane potential.

The experimenter may fix the membrane voltage at different pre-determined values.

The VC system injects a current to counter balance the membrane currents.

The experimenter measures the voltage change in response to the opening of the voltage gated channels.

6. Suprathreshold depolarizing voltage clamp in the squid giant axon will activate membrane currents. Mark the correct order of the currents in the cell:

Capacitive Current, inward current (into the axon), outward current

7. Mark the correct sentence for the squid giant axon membrane:

Sodium current is a fast inward inactivated current.

8. Mark the correct sentence for the squid giant axon membrane:

Potassium current is a slow outward non-inactivated current.

9. A poison **blocks the inactivation of sodium channels** in an axon and **keeps the inactivating variable (h) at its resting value**. What will change in the action potential (AP)?

The AP will become broader

because the inactivating variable h has a high resting value which allows  $Na^+$  flows inside from outside

10. According to Hodgkin and Huxley (H&H) model, the potassium activation variable (n) depends on?

Voltage and time

11. Mark the correct sentences about the potassium conductance ( $g_k$ ) according to the H&H model:

Depolarizing the membrane will increase n

We may interpret the potassium ion channel as having 4 identical gates

$g_k$  depends on the maximal potassium conductance and on n raised to the power of 4

because  $g_k = \bar{g}_k n^4$

12. According to H&H model, what is the reason for the termination (repolarization) of the spike?

Select all the correct answers

Opening of the outward K-conductance

Inactivation of the sodium current due to the closing of the h-gate

13. Mark the correct sentences about refractory period:

The refractory period restricts the maximal firing rate of nerve cells

In the absolute refractory period the cell can never generate a spike

The refractory period is caused by close-to-zero values of h

## WEEK 5: Neurons as Plastic/Dynamic Devices

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1. Learning in the brain - fast examples
2. The purpose of learning ("action perception loop")
3. Functional plasticity (without anatomic change)
4. Structural plasticity
5. Discussion on memory: embedding memories? copy memories?

New technology: The Clarity Method

to make the whole brain completely transparent

# The Brain Learns

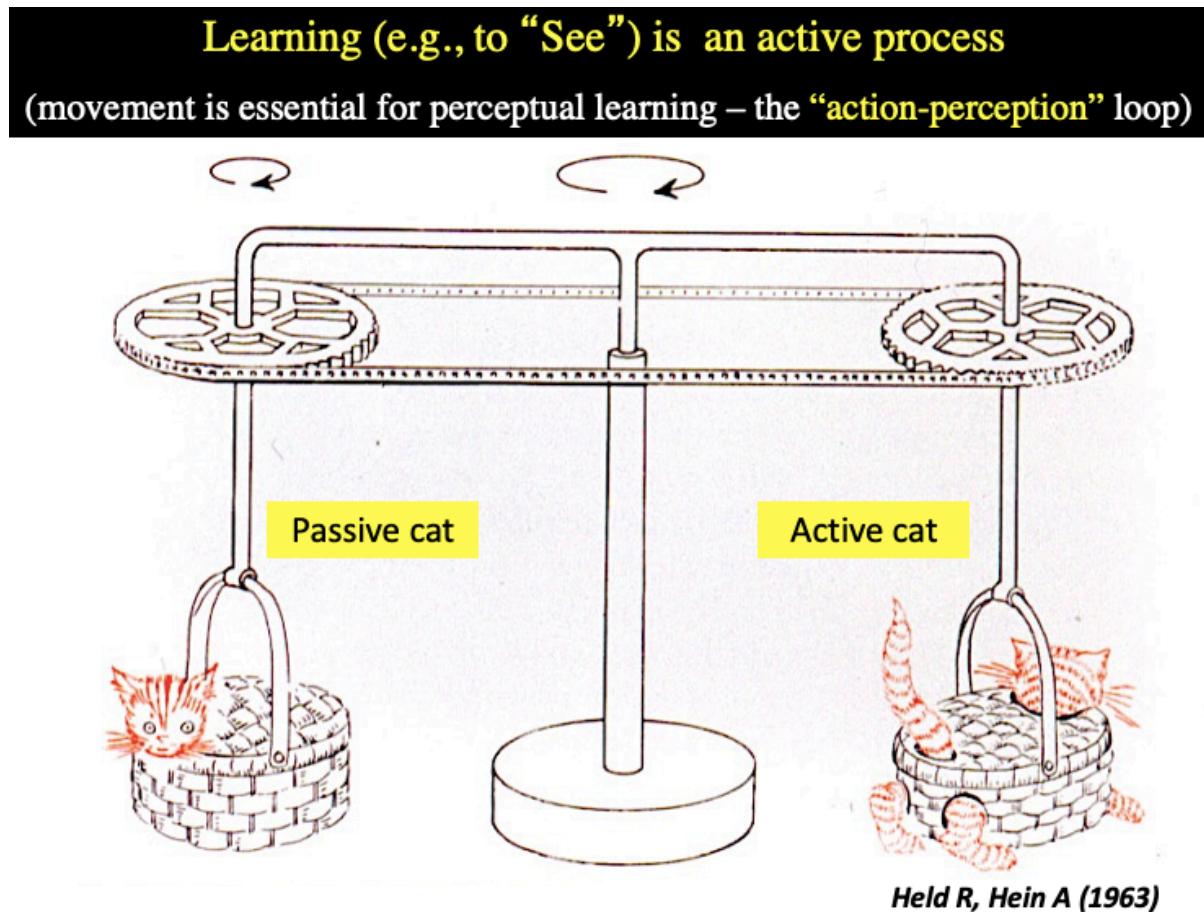
Sensory Substitution (by Amir Amedi)

using sound to describe objects for the blind

Learning enable us for:

1. General useful predictions
2. Categorize the world
3. Create consensus among us for successful interactions

Remark #1: Experiment by Held and Hein (1963)



The well-known experiment on vision performed by Held and Hein: They harnessed a pair of kittens to a carousel (see the figure). One of the kittens was harnessed but stood on the ground and was able to rotate around by itself, while the other, being placed in the gondola, was only moved passively.

## Learning is an active process

and movement is essential for perceptual learning (movement generate changes in the world, visual system need to be correlated with the movement)

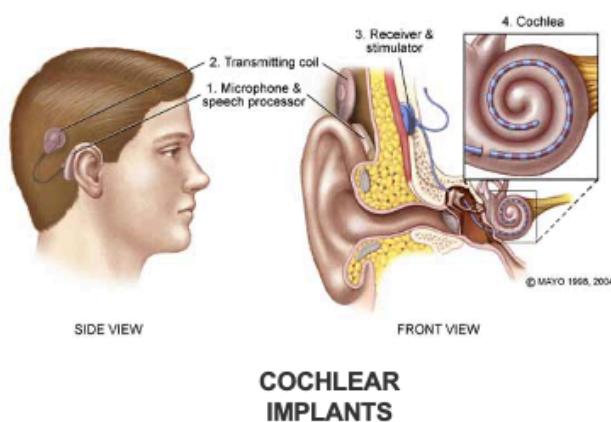
there is a critical period in the early age (so do speak something can not be relearned)

## Action Perception Loop

## Remark #2: Cochlear Implants

## Remark #2

The brain reconstruct “reality” from minute/very-partial information  
(e.g., cochlear implants)



Based on memory and learning you'll eventually build some reality. You can rebuild your reality based on very sparse and incomplete information. And your brain reconstruct information.

# Mechanism Sub-Serving Learning and Memory

We know that brain is constructed by nerve cells and that gives the brain plasticity. But what is the underlying mechanism of plasticity?

"There is a notable increase in intellect among men dedicated to deep and continued mental exercise."

S. Ramon Y Cajal

Cajal also supposed that there is no correlation between the weight of the brain and intelligence.

He thought that "nerve cells do not multiply as do muscle cells". He was wrong here.

## cerebral gymnastics

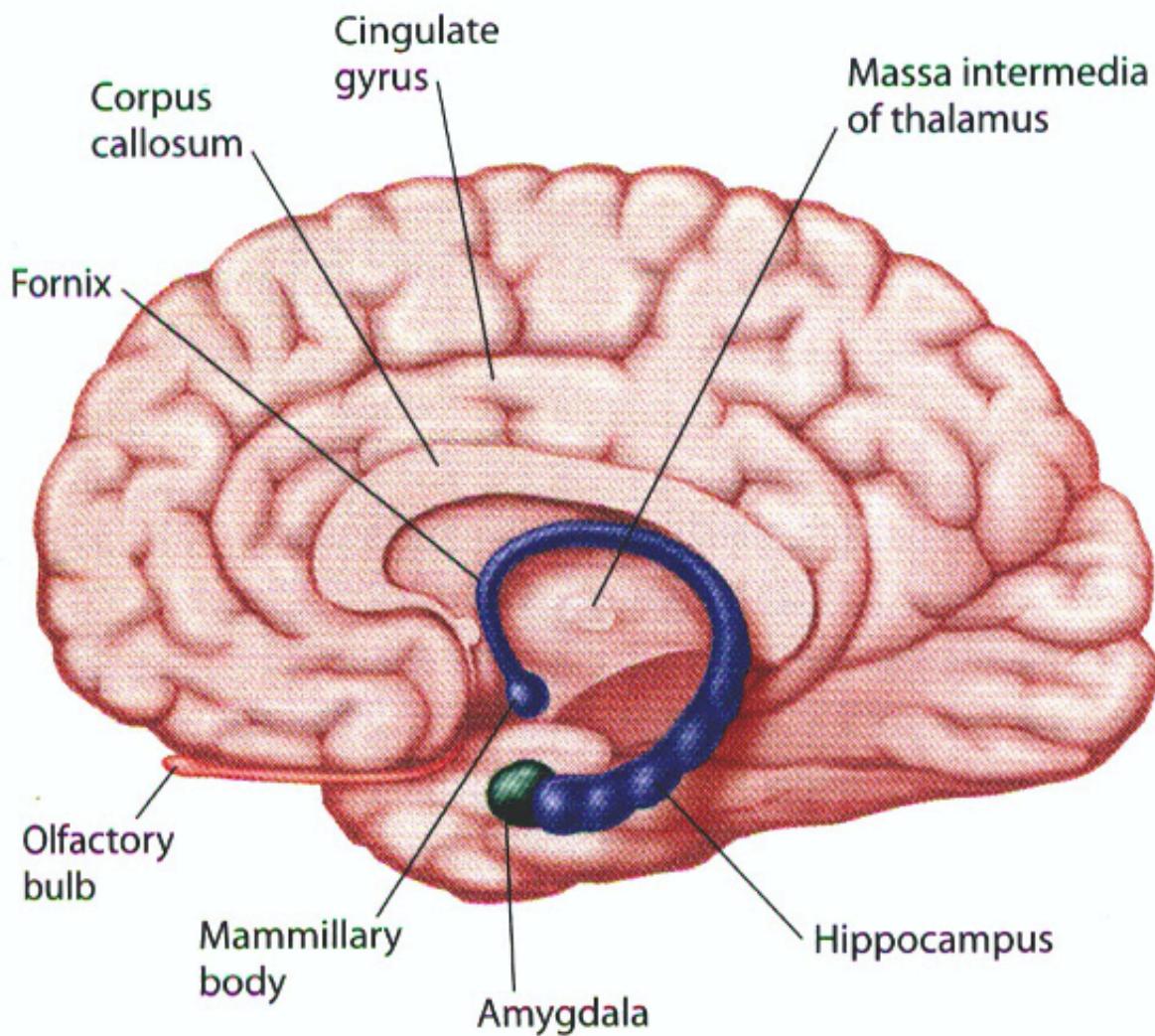
"There must be something changed in the brain during the process of learning"

meaning you cannot learn something new without some fundamental change in the brain

## Structure Plasticity

Existing cells-existing neurons make new branches and connections. This is what we called *structure plasticity*. The reason underlying structural change in the brain, underlying the new memory.

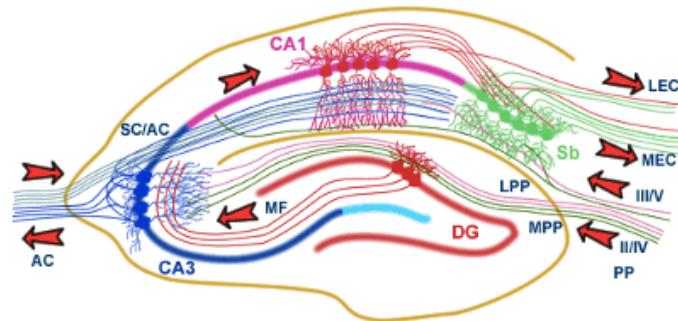
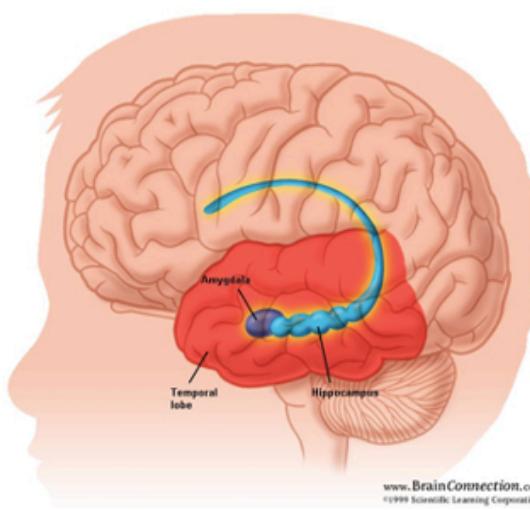
"The cerebral cortex is similar to a garden filled with trees (the pyramidal cells) can multiply their branches, they don't multiply themselves, but only the branches, sending their roots deeper and producing more and more varied and exquisite flowers and fruits."



Hippocampus is the very important region for learning and memory in the case of human, rats, cats and monkeys.

We know that very fundamental learning processes are happening in the hippocampus. But the capability of the brain to learn, to change is not only performed on the hippocampus. They also happen on the cortex.

# Storing our memories - The hippocampus



Hippocampus is built from unique types of neurons.

But what is the mechanism? What are the rules for learning plasticity in nervous tissues?

There are three possible mechanisms underlying learning and memory.

## A few possible neuronal mechanisms sub-serving learning and memory

1. **New nerve cells** grow - new functional neural networks are formed for exhibiting new learned items - **structural plasticity**

Cajal did not accept this theory. He did not think it does exist.

This theory supposes that a group of new cells (neurons) are born and then new functional networks are being generated (because there is a set of new cells). And this new networks underlies new memory.

2. **New synaptic** connections (new functional neural networks) are formed - **structural plasticity**

mentioned by Cajal

It assumes that new synaptic connections, new spines are growing, new axons, new synapses are formed, new functional networks are being created. **Not because there are new cells but because there are new connections.**

It is about structural plasticity because there is a new structure - a new synapse, a new axon, a new dendrite, a new spine.

3. **Strength of existing** (synaptic) connections change - (new functional neural networks) - **functional plasticity** (by Donald Hebb)

It assumes that existing synapses become stronger or weaker. It is not that you build new synapses but you use old synapses in a different way. A synapse may transfer information better or worse than before. So maybe existing synapses may change their efficacy.

This functional plasticity again generates a new kind of active networks not because you address or you generate new synapses but you use old synapses.

## Functional Plasticity

The "Hebb Hypothesis"

### The "Hebb hypothesis"

*"When an axon of cell A is near enough to excite cell B or repeatedly or consistently takes part in firing it, some growth or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased"*

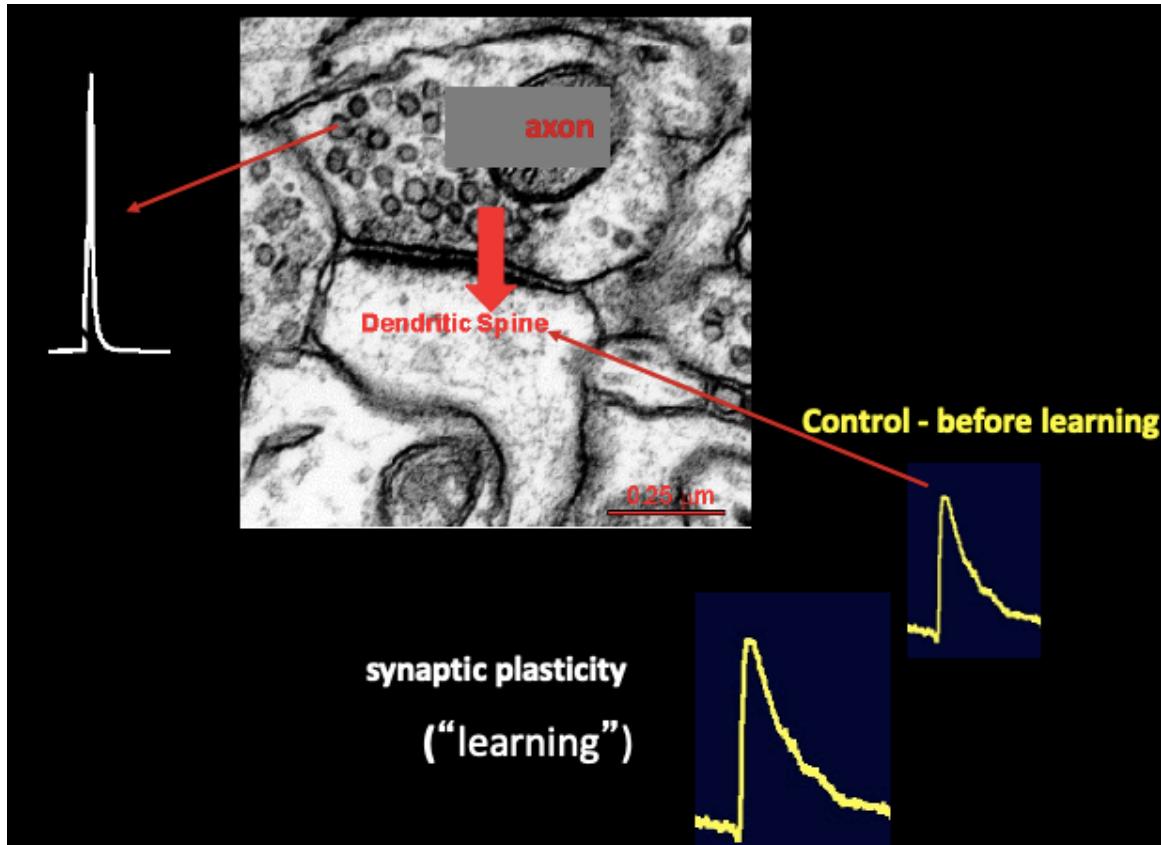
Donald Hebb (1949)

OR: **“Fire together wire together”**

If cell A is involved with firing cell B again and again (not only cell A and cell B but with other cells) sufficiently enough time, some changes between the cells take place, and eventually cell A becomes more and more effective in activating cell B. (**Strengthening the synapse among cell A and B**)

It was a formative hypothesis, until 20 years later, it has been proved that **Hebb rule is indeed implemented at some (hippocampal and cortical) synapses**

showing that **the synapse (between cell A and cell B) is very plastic**



cell A gives spike to cell B, and cell B generates EPSP

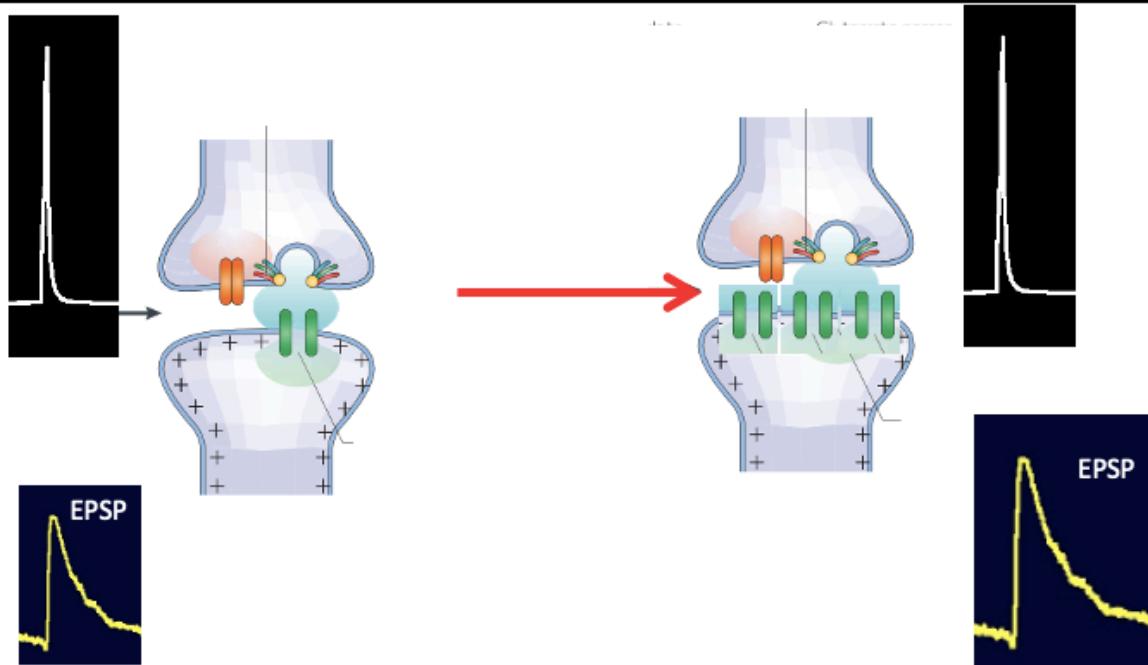
somewhat cell A fires cell B sufficiently timed, something about the connection is changed, and cell B and the connection become more effective.

**The synapse becomes stronger, for the same spike from cell A you will get a bigger EPSP from cell B.** It is a stronger synapse, more depolarization due to the same spike. So this is what Hebb is saying, if the connection between cell A and cell B is active enough time, then the weak synapse will become a stronger synapse.

What could be a mechanism for making the synapse stronger?

# Synaptic plasticity/mechanisms

E.g., insertion of additional receptors to the post-synaptic membrane



## 1. Post-synaptically

One possible mechanism is that the synapse becomes more effective for a given spike. Making more potential post-synaptically due to **the insertion of new receptors in the post-synaptic membrane**.

So it basically means that the post-synapse may have more receptors. So the same spike generate post-synaptically a larger EPSP.

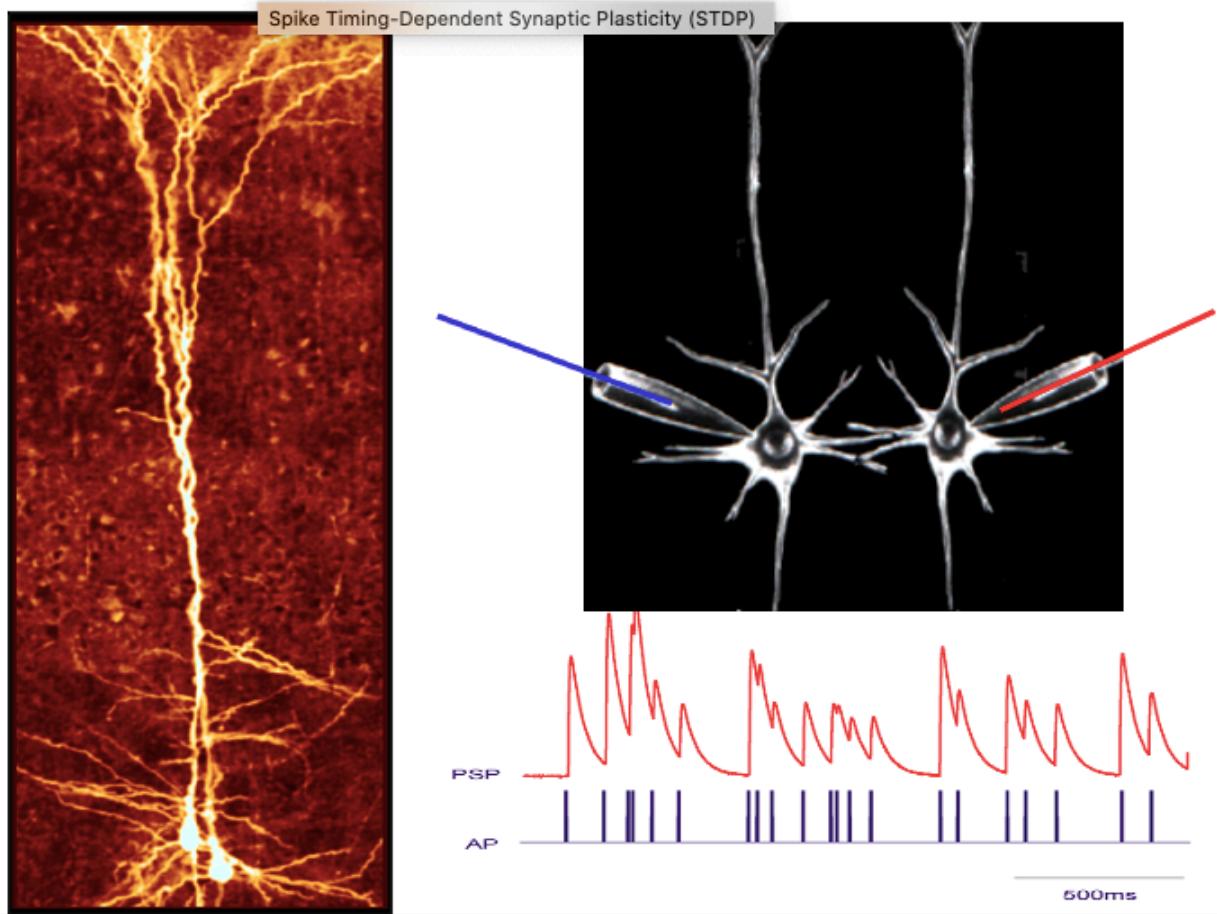
**The same transmitter release opens more ion channels post-synaptically, thus generating a larger EPSP.**

## 2. Pre-synaptically

**The same spike would release more transmitters.**

So how do we study what really happens in the synapse?

# Biophysics of learning (when do synapses change?)



The idea is that today, with new techniques, we can record, both in the In Vivo case, in the whole brain, but typically in slices. You can record from two cells in a brain slice, for example, in the cortex. You implant an electrode here and here, in these two cells. And you start to ask the question, what makes this particular synapse, if they are connected synaptically between here and here, what makes the synapse between these two cells more or less effective.

So you really can stimulate the blue cell, you can record synaptic potential in the red cells, and you can try to manipulate things until you find what could be the mechanism for synaptic plasticity. What are the conditions for the synapse to become stronger, to have more receptors, to respond stronger to a spine? What could be the conditions? Now, you can **manipulate each sense separately**, and so you can **control the condition and find out what are the conditions**.

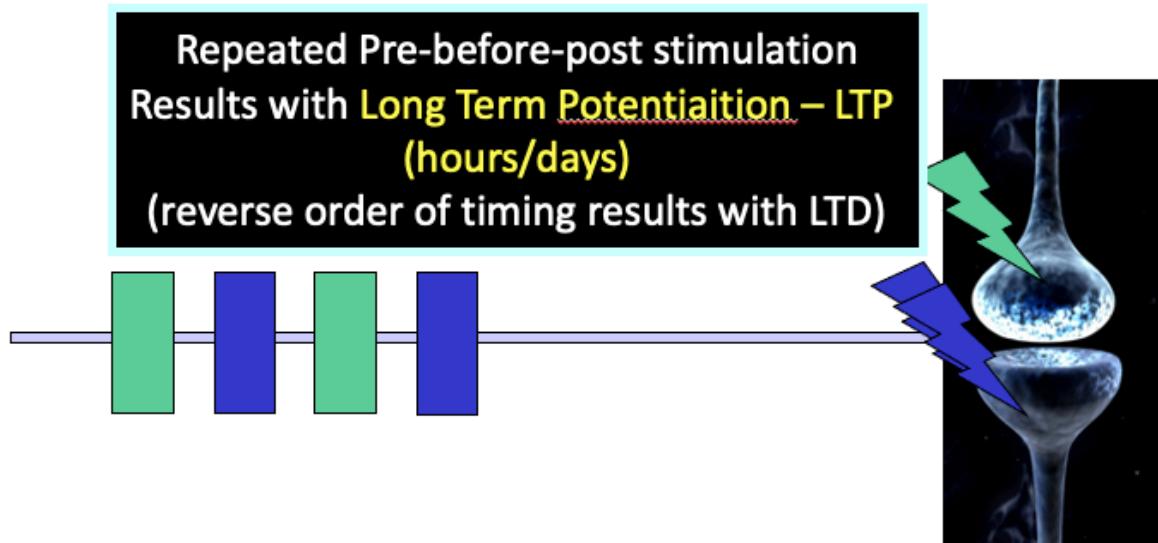
Technology 15 years ago

And they found a very fundamental mechanism called **Spike Timing-Dependent Synaptic Plasticity (STDP)**

## Spike Timing-Dependent Synaptic Plasticity (STDP)

This particular condition makes the synapse - the connection stronger.

# Spike Timing-Dependent Synaptic Plasticity (STDP)



using electrode to generate pre-synaptic spike, a post-synaptic spike, a pre-synaptic spike, a post-synaptic spike... repeatedly.

After enough of this repetition, the synapse becomes stronger. You will get a larger EPSP.

And repeated this **pre-before-post stimulation** results with **Long Term Potentiation - LTP (hours/days)**

which means that could last minutes long, maybe days, maybe lifetime, but long.

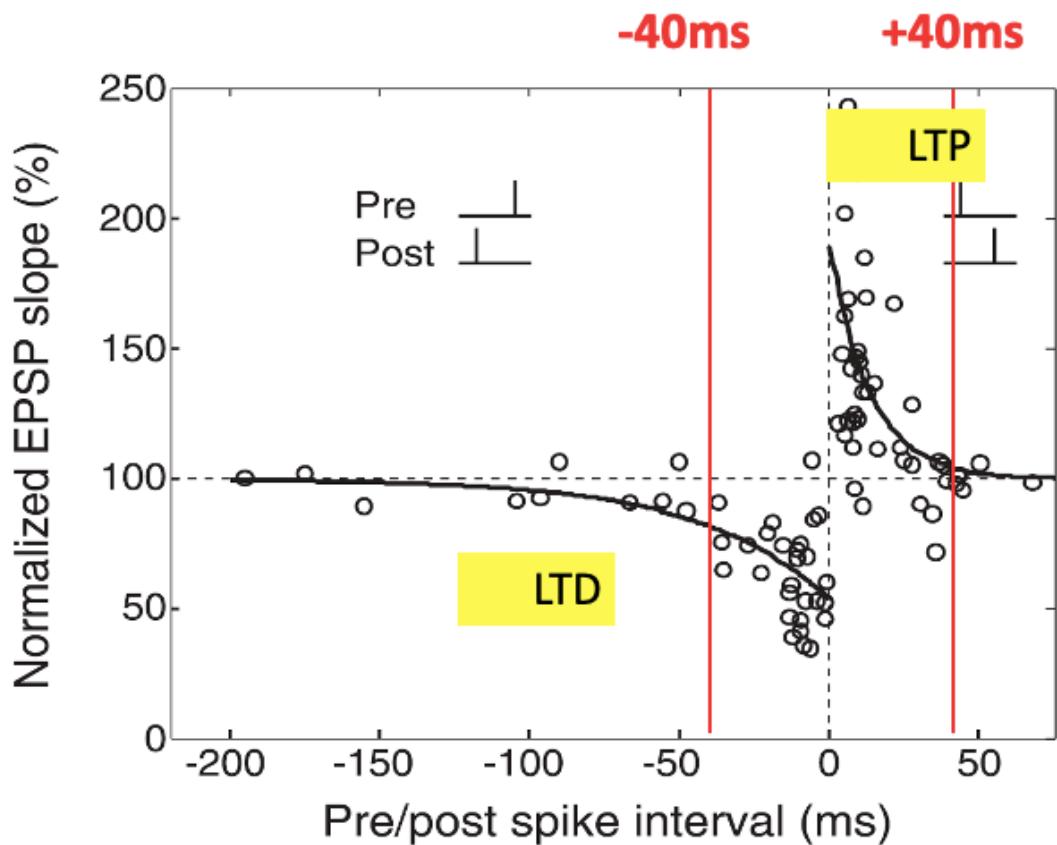
So after this kind of pre-, post-, pre-, post-, enough time, you will get an **enhancement of the synapse**.

If reverse the order of timing results with **LTD - Long Term Depression**

if doing the post-, pre-, post-, pre- stimulating order, the synapse will become weaker

Experimental results

# The STDP window



There is a very narrow time window for this mechanism to work.

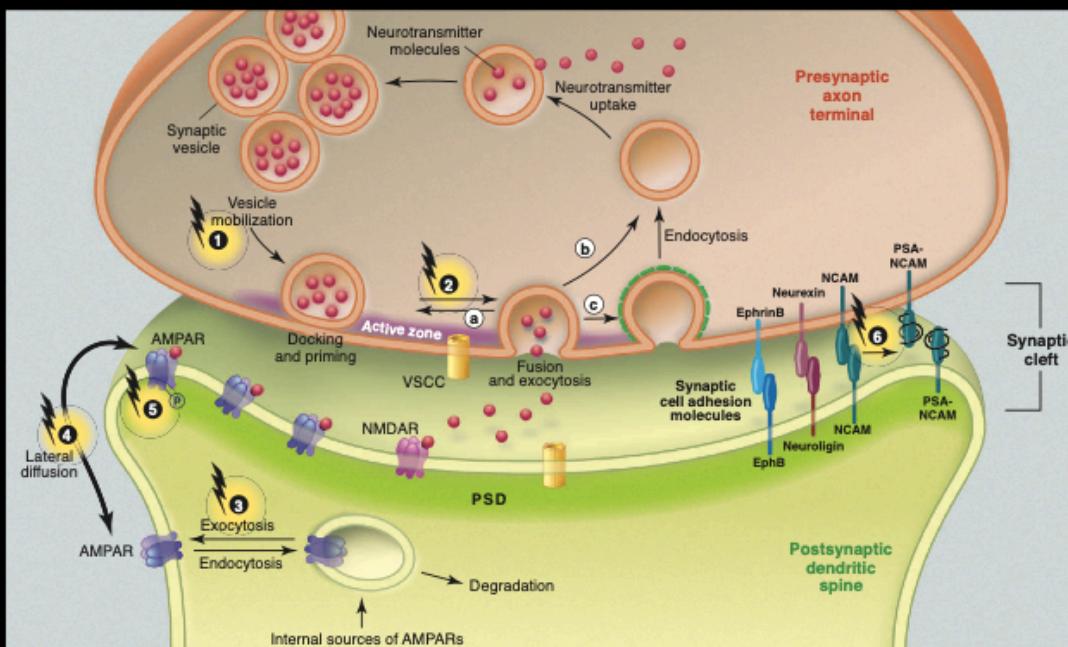
Notice this doesn't explain **Pavlovian Learning**. Because the time interval in the Pavlovian experiment is much longer than the STDP window.

And Long Term Plasticity could not explain "how do i learn something from childhood and remember it when i'm adult"

LTP can explain **rapid learning**

But what is the mechanism inside the synapse sensitive to the spike?

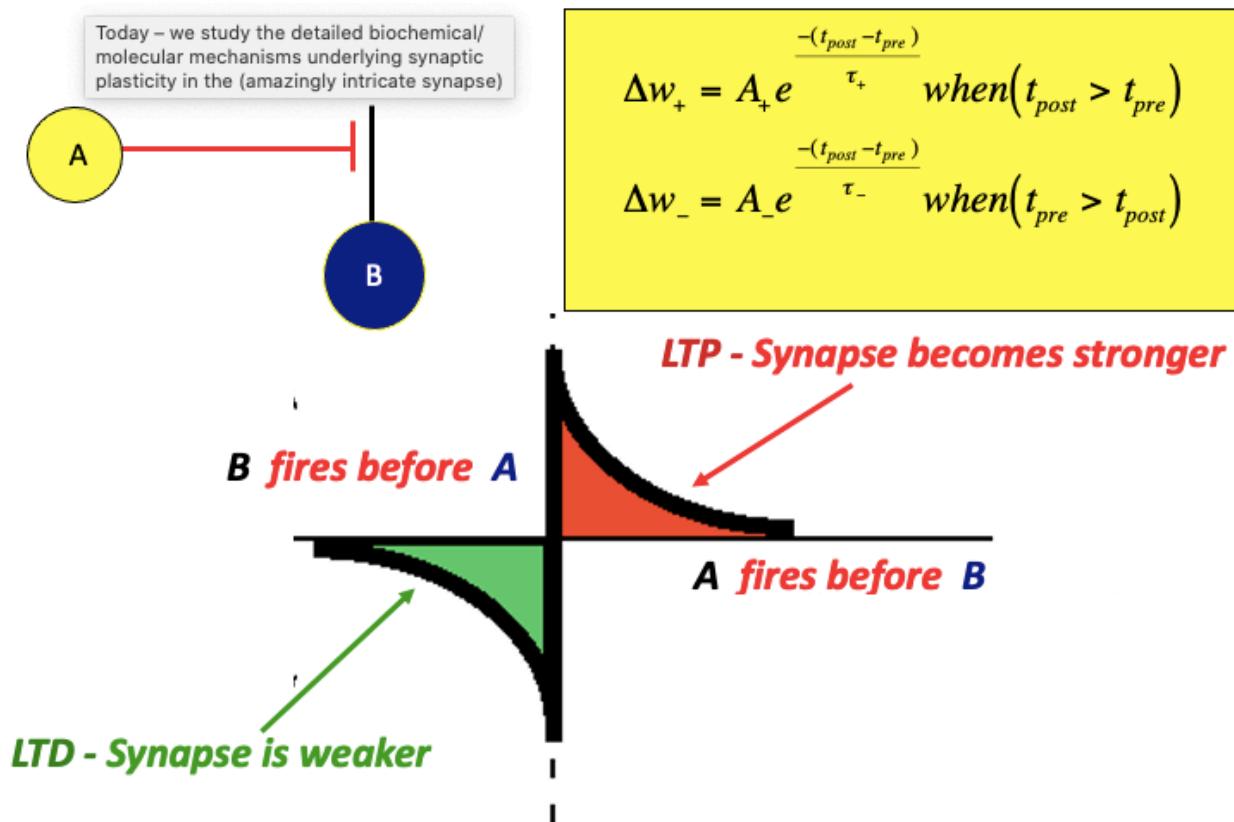
# Today – we study the detailed biochemical/molecular mechanisms underlying synaptic plasticity in the (amazingly intricate synapse)



Victoria M. Ho Ji-Ann Lee, Kelsey C. Martin, Science 2011

## Modeling STDP (Equations)

## Mathematical - "Hebbian" - Learning rule at the synapse



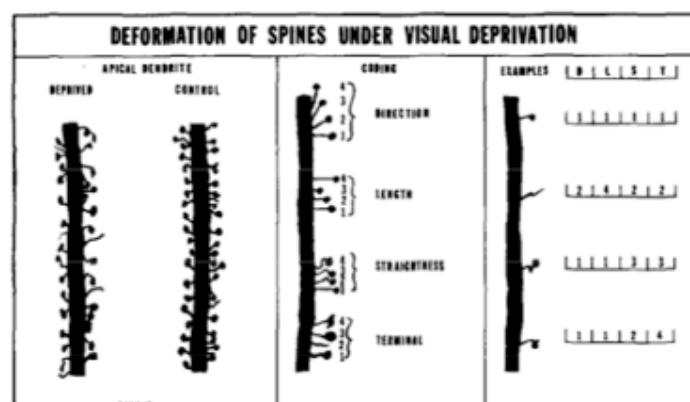
well equation and mathematical model are the first step to the machine learning

## Structural Plasticity

Morphological/anatomical changes that are correlated with learning

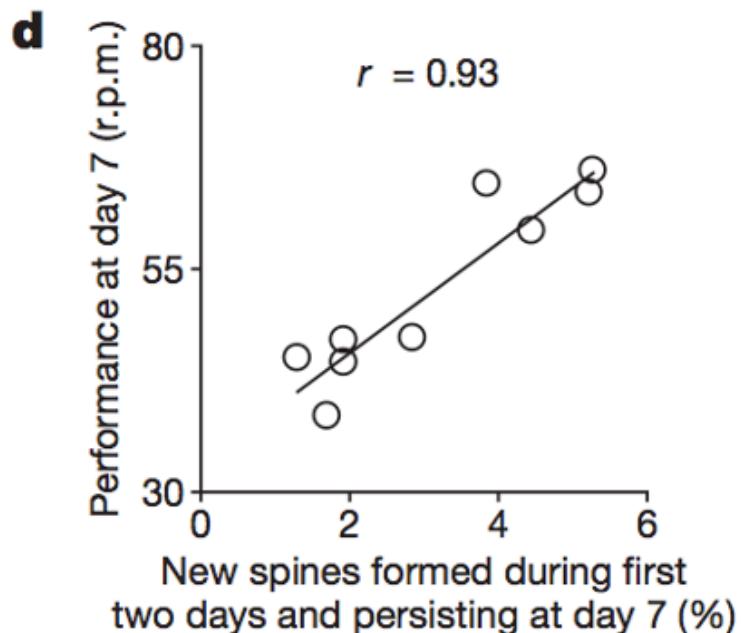
## 1967 – Globus & Scheibel

Sensory experience (visual deprivation) affects spine variation in rabbits



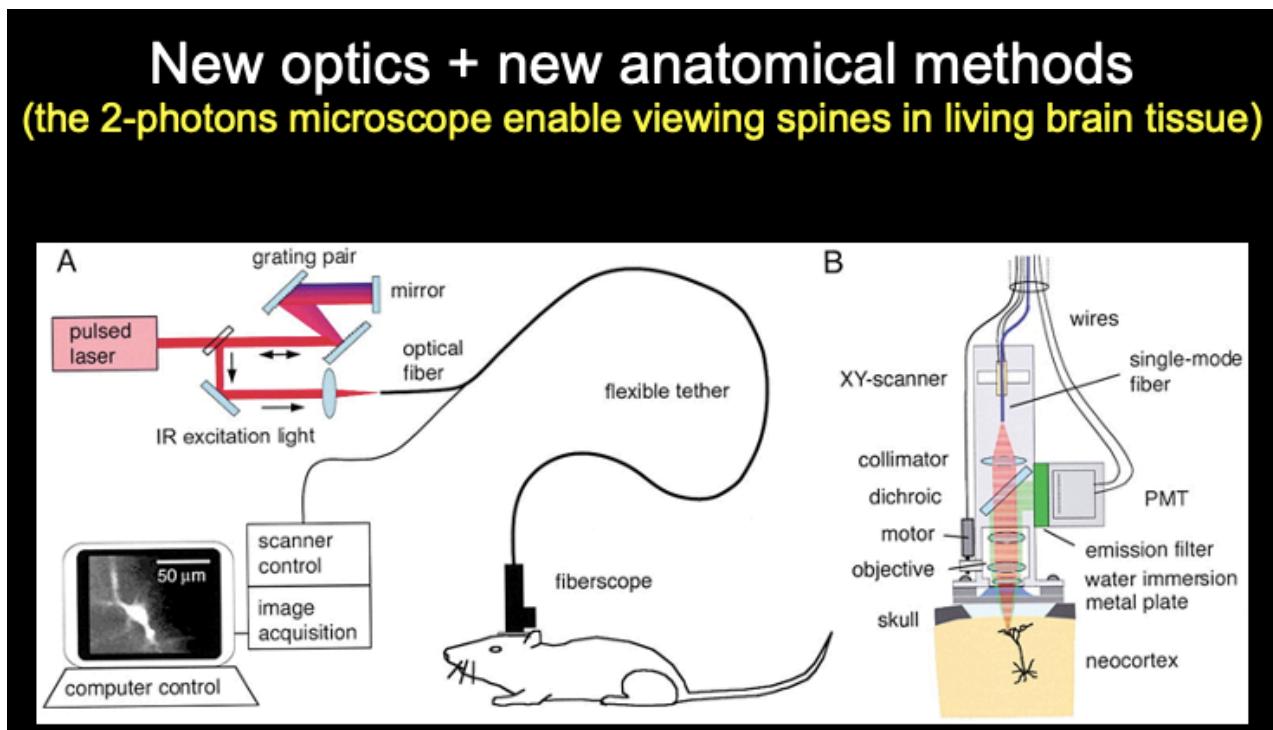
For example, to a kid, when you deprive the vision of one eye of a kid for enough time, early on, for example. Then you'll start to see **changes in the density of spines**.

# New spines correlate with behavioral improvement



(Yang et al. 2009)

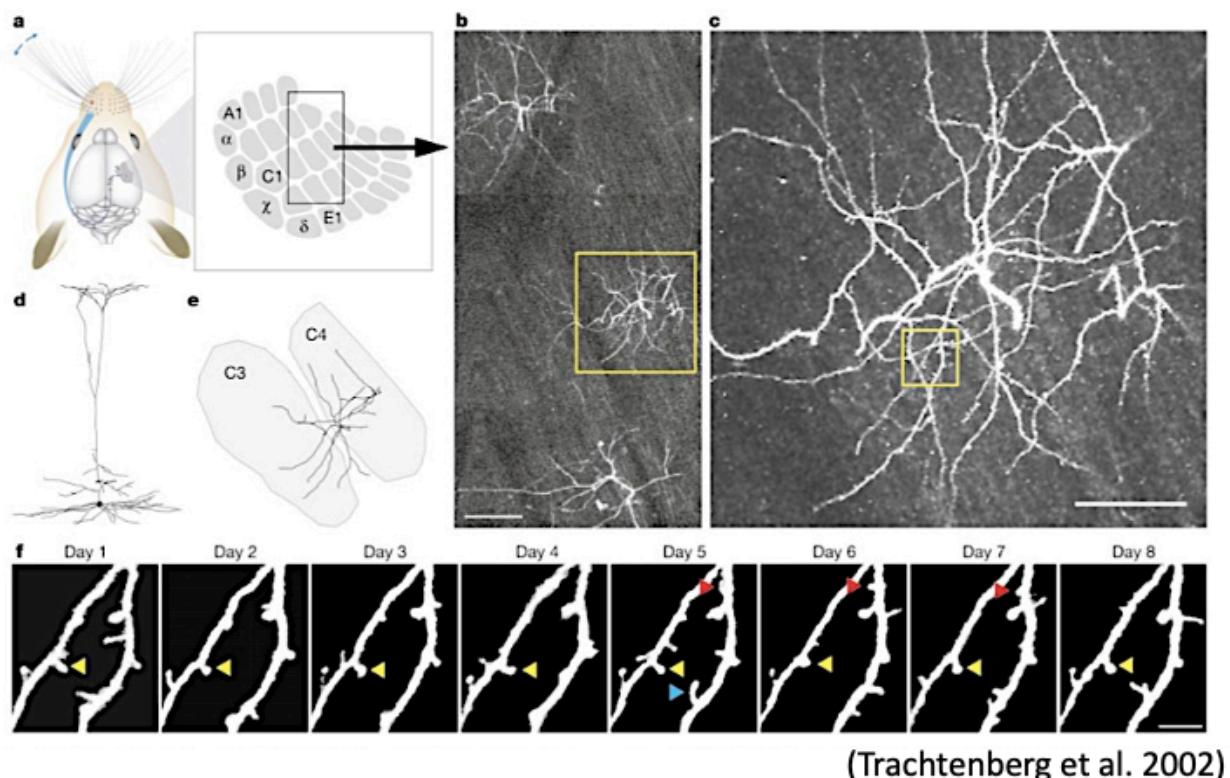
people show that there is an increase in number of stable new spines following a behavioral improvement of a mouse, of a rat.



2-photon microscope

the new microscope enables to view, in a very fine resolution, a particular region of the brain in the living behaving brain. Asking in real time while look at the cell what are changes that may underlie particular learning in this living brain.

## Spines appear and disappear frequently in the adult cortex



the 2-photon microscope can be used in zooming into the brain, the dendrite, the spine  
 the fig shows that there is a transient spine in day 5 (the blue arrow)  
 and a semi-transient spine (the red arrow)

**So there are spines that are stable probably through all your life.**

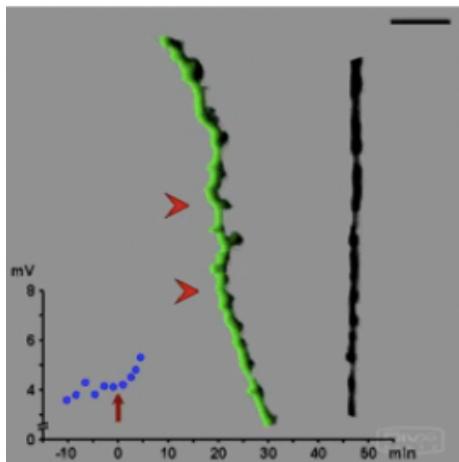
**There are spines that appear or disappear, they are trying to find a mate, a friend, a connection. Probably they don't. They dissolve. They disappear.**

We have not completely understand the rules of the structural plasticity, but we do know there is a change in the brain constantly all the time.

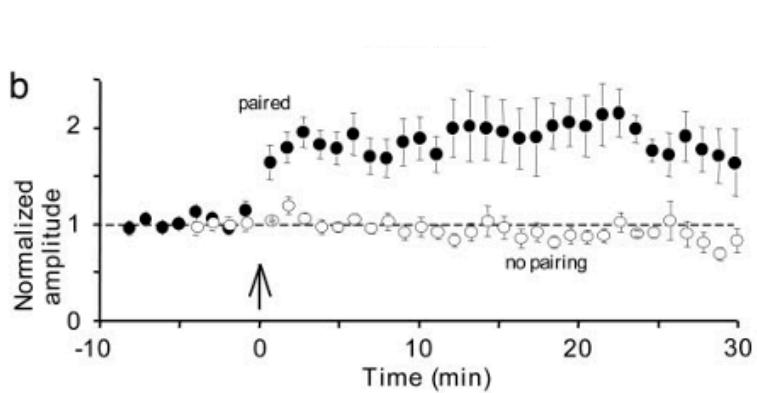
The question is does it relate or not to learning in plasticity?

The answer is yes.

# LTP lasting for minutes/hours/days?



Tobias Bonhoeffer, MPI, Munich)



So we have today a direct proof just by looking *in vivo* on the behaving brain using 2-photon microscope, that there are these new structure, spines. Growing disappearing, dissolving, popping up, again and again, and sometimes establishing a synapse.

And the outcome of this is that the synapse, the strength of the synapse, is becoming stronger when you have new spines, because there are new synapses or because existing synapses become stronger due to SDTP.

With this control normalized strength, these synapses become stronger. And when it becomes stronger, it persists longer.

And this happened relatively fast. After several stimulations, suddenly a new spine or existing synapse becomes stronger.

## Summary

1. **New dendritic spines** are "born" **constantly**

even now

2. More often so **during learning tasks/enriched environment**

learning challenging environment generates new, more spines, new synapses, new connections.

and these new synapses generate functional networks that together code for a new item

3. **New spines** are associated with **new synapses** - new functional networks (new memories?)

So clearly, the brain is using structural plasticity in addition to functional plasticity.

In this case, at the level of **dendritic spines**, not new cells, but dendritic spines to generate new functional networks.

And these **new functional networks** are related to challenging environment, to learning in plasticity.

## Neurogenesis and Learning

Are there new born cells (neurogenesis) in the adult brain?

We know that in some birds there is region in the brain whereby neurons are born in the adult male brain when there is a generation of the song.

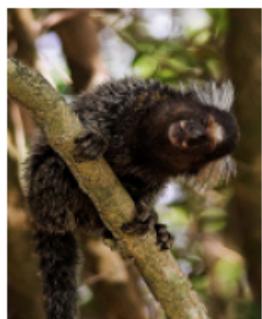
At first, we think that a mammalian is born with a given amount of cells, at least for a given period of time until you're mature and there are no newborn cells in your brain.

In the case of Rhesus macaque monkey, all neurons of the brain are generated during prenatal and early postnatal life.

Then Elizabeth Gould showed neurogenesis in tree shrews in 1997 and in marmoset monkeys in 1998.



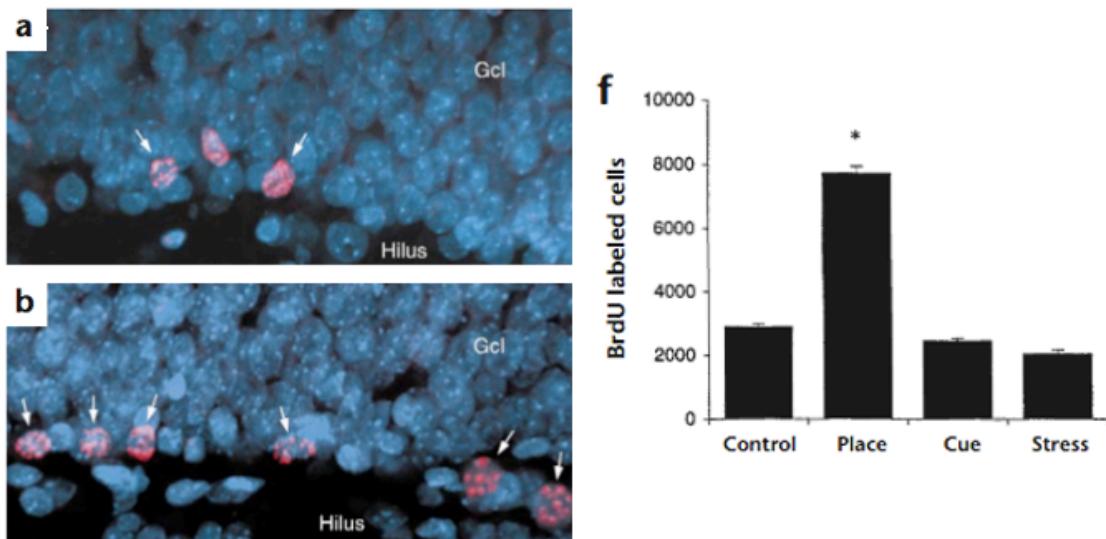
**1997 –Elizabeth Gould, assistant professor of neuroscience at Princeton, and colleagues, showed neurogenesis in tree shrews**



**1998 – neurogenesis in marmoset monkeys (primate)**

## In mature mouse hippocampus

1. New born (stem) cells
2. More new-born cells following memory task in Morris Water Maze



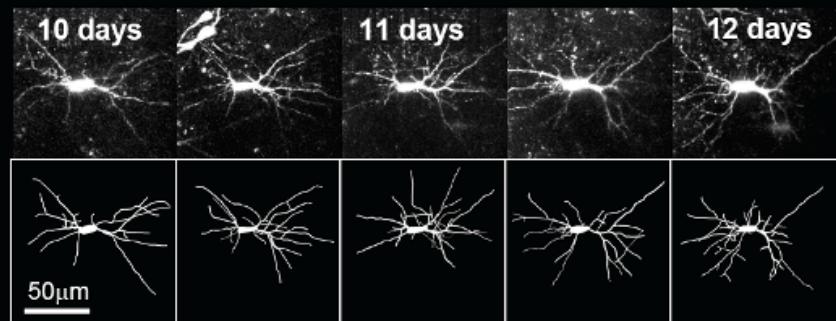
(Gould et al. 1999)

Now by using new techniques that enable us to mark **specifically stem cells**, newborn cells, in the adult brain of mouse and of human. And we know today That **there are at least 2 regions, maybe more, at least 2 regions in the brain that constantly generate new born cells, new stem cells in the adult brain.**

**Adi Mizrachi (Hebrew University) - with 2 the photon microscope**  
**An optical voyage into the living brain – detecting new born cells in the adult olfactory system (mouse)**

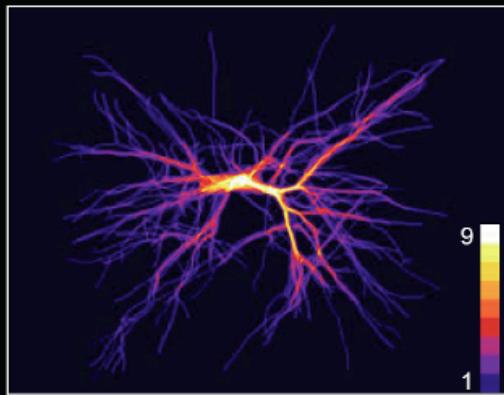
# Prof. Adi Mizrahi Lab

## Watching newborn (stem) cells growing in the adult brain



*Top: In vivo images of a newborn neuron developing in the mouse brain over 3 days.*

*Right: projection image of 9 consecutive imaging sessions showing the remarkable dynamics of newborn neurons.*



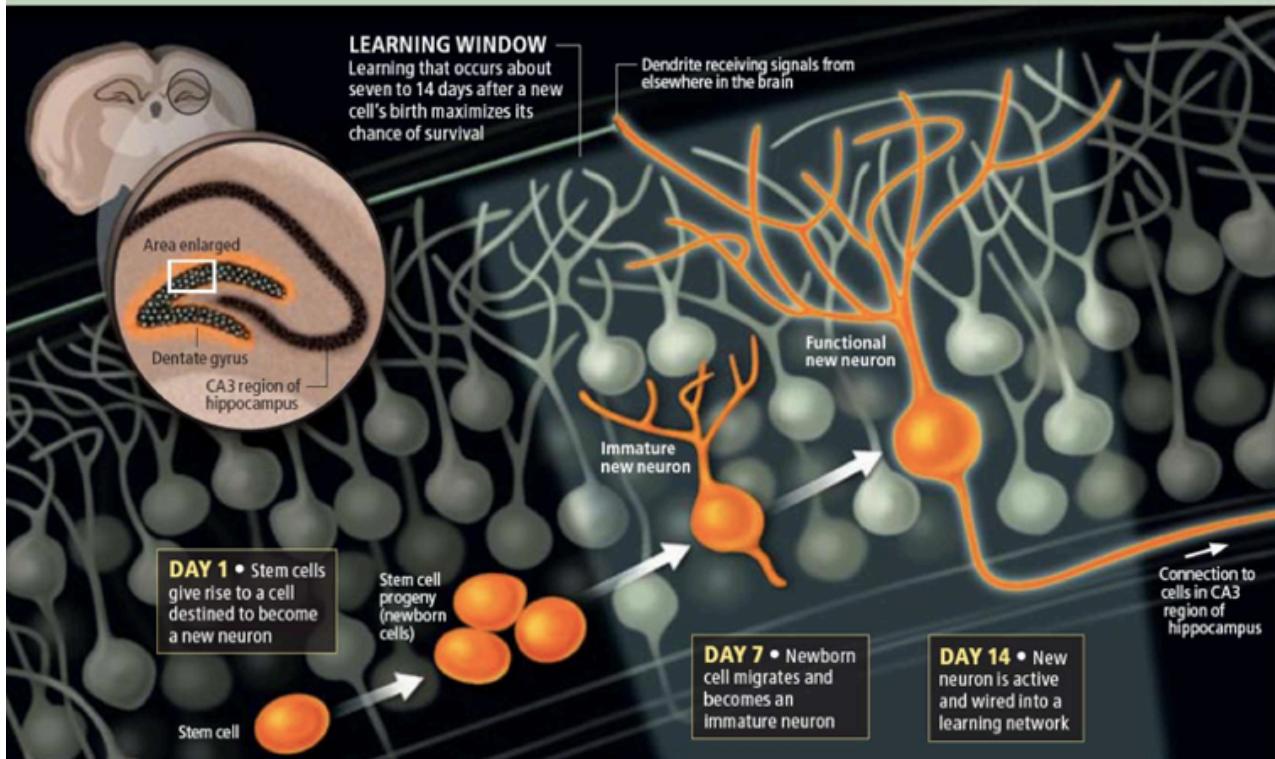
The Hippocampus and **the factory bar** where newborn cells constantly being born (thousands of them everyday)

Today we know that also human in the hippocampus generate newborn cells. And these newborn cells are associated with a certain type of behavior or improvement of behavior.

# HOW LEARNING HELPS TO SAVE NEW NEURONS

During their first week of life, newborn hippocampal cells migrate from the edge of the dentate gyrus in to a deeper area, where they mature and become wired into a network of neurons. Learning that occurs when the cells are between one to two weeks old enhances their

survival—perhaps exerting this effect by stimulating existing neurons, which in turn release signals that foster maturation of young cells. In the absence of learning during the maturation period, most new hippocampal cells will die.



These **newborn cells** are born as **stem cells** in a particular **niche of the hippocampus**, and they are migrated into a particular region of the hippocampus. And they become mature, involved, branched. They become part of the network.

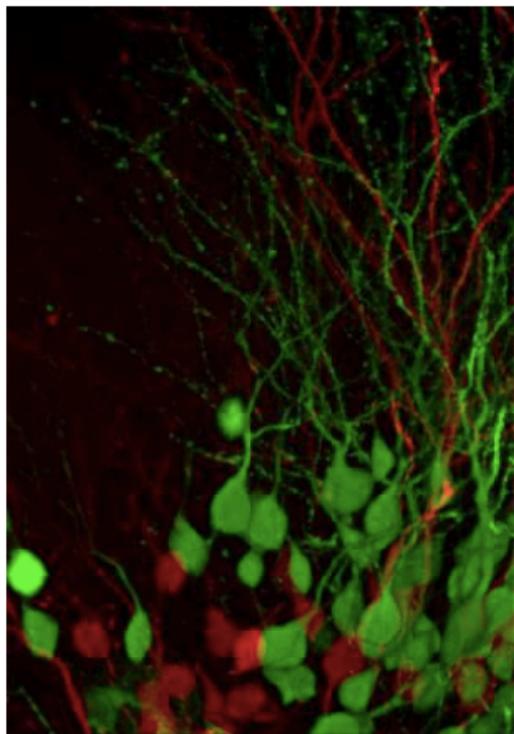
1. Some of them die out and this is an ongoing process.
2. Some of them remain functioning for the network (are integrated in the network).
3. And some of them remain alive for a longer time as a function of the challenges that the brain is facing.

So there is an association between the number of newborn cells and the capability to do new functions.

And the question is who are they integrated with? What makes them stable or not?

Now this finding has potential in applying the therapy:

## Implications: disease



Neurogenesis: provides hope for therapies for neurodegenerative diseases such as Parkinson's and Alzheimer's... as well as for rehabilitation from stroke and brain injury

How to generate more stem cells in Alzheimer patients?

Why stem cells stop being born sometimes after having a stroke?

Applying in learning:

# Implications: learning

**Learning new skills, thinking in novel ways, and cognitively challenging ourselves can influence our brain structure**

**Cognitive training programs can provide benefits (such as memory enhancement) for healthy adults and those with cognitive impairment**



You don't use it you lose it, is apparently correct.

The more you use the network, a challenging environment, an intellectual task, motor activity, the more you challenge the network, the more new connections you have, more spines.

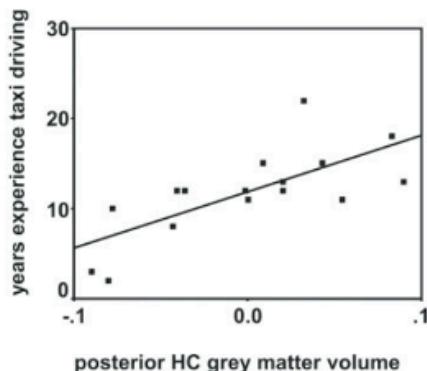
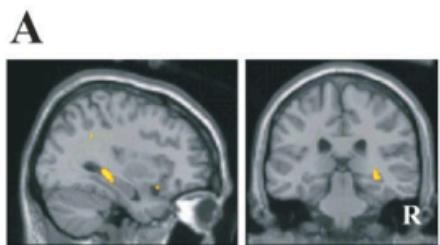
The more new cells you have in the hippocampus then you have to learn something new.

## A few comments and anecdotes about memory

There is an correlation between years of experience as a taxi driver learning the streets of London and the volume of the gray matter in the hippocampus.



## Hippocampus of London Taxi Drivers



(Maguire et al. 2006)

There are other studies, many studies, actually, showing that when you are an expert in something, for example, if you are a musician; you very, very good in playing the violin or the piano, then certain regions of your brain, the motor cortex, the auditory cortex, **region involved** **With this particular expertise Increasing volume, whether this increasing volume results from most spines or for most cells , not very clear.**

### The Future/Controversial Issues

1. Brain - inspired **learning machines** (machine learning)
2. How **trustworthy are our memories?**
3. Could we **read out** memories?

No

Because your memory is constructed on your whole neuron network in your brain. It is individually specific.

4. Could we embed new memories?

# QUIZ

1. In the Held and Hein experiment (the two kittens experiment) only the active kitten could functionally see. Why?

Vision is possible only when the brain successfully links between the movement it generates and the visual input it receives (the perception-action cycle)

Building an internal (brain) model of the visual world requires, early on, to generate visual predictions via self movement

✗ Being passively moved by someone else confuses (at any developmental stage) the visual system. Consequently, the visual system can not distinguish between self movement and external movement.

✗ Only the active cat developed operational motor system; a functional motor system is the foundation for the development of all other systems in their brain, including vision.

2. Sensory substitution implies that

Utilizing a healthy sense for a lost sense (e.g., the somatosensory/tactile sense for vision in Braille reading)

✗ Substitution of a lost sense with mechanical devices (e.g., artificial retina)

3. S. Ramon Y Cajal claimed that for the brain to learn:

Some structural change must take place in the nervous system

✗ That some metabolic change must occur between cells that are simultaneously and consistently active (functional plasticity)

✗ That intelligence is associated with larger brains

4. What is the Hebb hypothesis?

The connection between the cells will strengthen if cell A is repetitively involved as one of the cells that activate Cell B

✗ That some metabolic change is involved in learning

✗ That the synapse between cell A and B is strengthened if cell A is sufficiently active

5. The term synaptic plasticity describes:

That existing synapses change their efficacy

✗ The addition of new dendritic spines during learning and memory processes

✗ The ability of a synapse to switch from excitatory and inhibitory

6. Biophysical experiments show that excitatory synapses strengthens/weaken as a function of the timing of pre- vs. postsynaptic spikes (STDP). Mark the correct sentences.

In cortical/hippocampal pyramidal cells, when the pre synaptic cell fires a spike before the post synaptic cell – the excitatory synapses between these cells is strengthened (LTP) and vice versa for synaptic weakening (LTD)

When the postsynaptic spike fires before the pre-synaptic spike, the EPSP's amplitude (recorded at the post synaptic cell following presynaptic activation) is reduced.

7. What is the time-window for the spike-timing-dependent plasticity (STDP) mechanism?

Tens of milliseconds

8. What is the time-scale for long term potentiation (LTP) and depression (LTD)?

Hours (or even days)

9. The two-photon microscope enables one to

View newborn cells in the adult brain of the mouse

View anatomical changes in the living brain

X View new synapses forming during learning

10. The EPSP amplitude measured in the soma of the post synaptic cell is increased by a factor of 2. What could be the underlying mechanism?

Increasing the number of receptors in the post synaptic cell

Increasing the number of neurotransmitters molecules released from the pre synaptic cell

Increasing the number of synapses between the pre- and post- synaptic cells

11. What do we know about changes in the brain related to learning?

New dendritic spines with new synapse are created

New nerve cells (neurogenesis) are created in specific brain regions (hippocampus)

12. Is it feasible to copy memories from one brain to another ("disc on key")?

No as each of us stores/represents (codes for) memories in an individual way (different cells/different spike patterns in different brains).

No, because when forming a memory the particular activity in the respective neural network should be correlated with a particular physical item/event to be remembered.

13. Is it possible in principle to physically erase memories?

Yes, because eventually memories are stored in all brains using the same synaptic mechanisms; destroying these synapses will erase the memory embedded.

Yes, because when forming a memory the particular activity in the respective neural network could be monitored and then suppressed (memory will then be lost)

## WEEK 6: The Brain Computes

1. The brain compute (computational neuroscience)
2. computation at the level of single neurons
3. fundamentals cable theory for dendrites (W. All)
4. dendritic computation - the neuron as a computing device

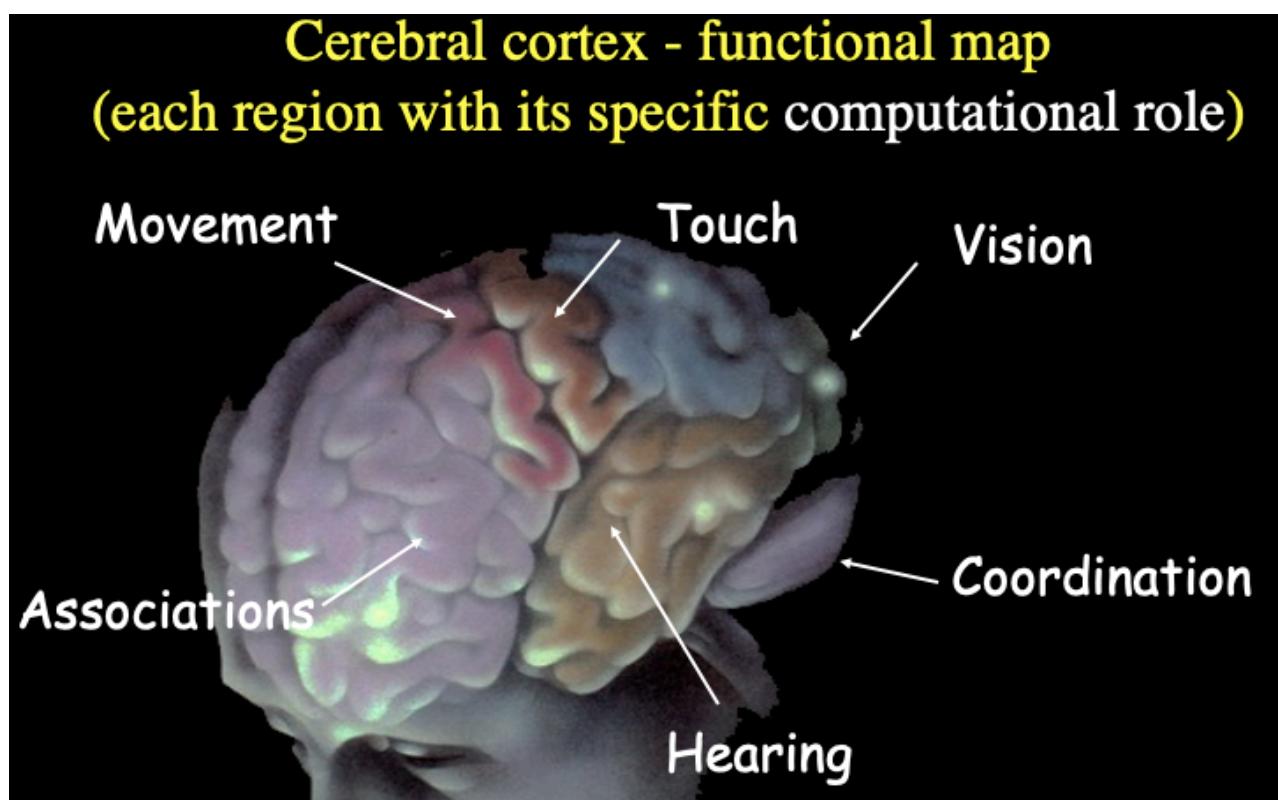
5. recent experiment breakthrough in understanding neurons as computing devices (the retina)

## The Brain Computes

How do the neuronal ingredients, synapses, neurons their electrical and chemical signals, and the distributed, interacting, networks that they form, represent and process information (compute)?

- 1.What are the problems needed to be solved by the brain?
- 2.What are the **algorithm** used to solve these problems?
- 3.And how do these algorithms implemented by the various brain regions?

**Each region in the brain has a particular problem to solve.** It has a computational role, a particular region.



Doing a single function needs the computation of the other elementary variables.

**The brain computes:**  
**During movement (crossing the street; reaching a cup) requires**  
**the computation of elementary variables**  
**(location of object, distance, movement direction and speed, etc.)**

### Figure-ground separation

The brain computes: Computing image correlation and binding different parts of the image (figure – ground separation) is essential for the organism

So one of the fundamental aspects of visual computation is to segment, to segregate, to bind certain dots that may be associated with some memory that you have.

Surly brain has an **algorithm** recognize faces and other subjects.

### Scan Algorithm

## The Brain Computes – active vision ("scanning algorithms")



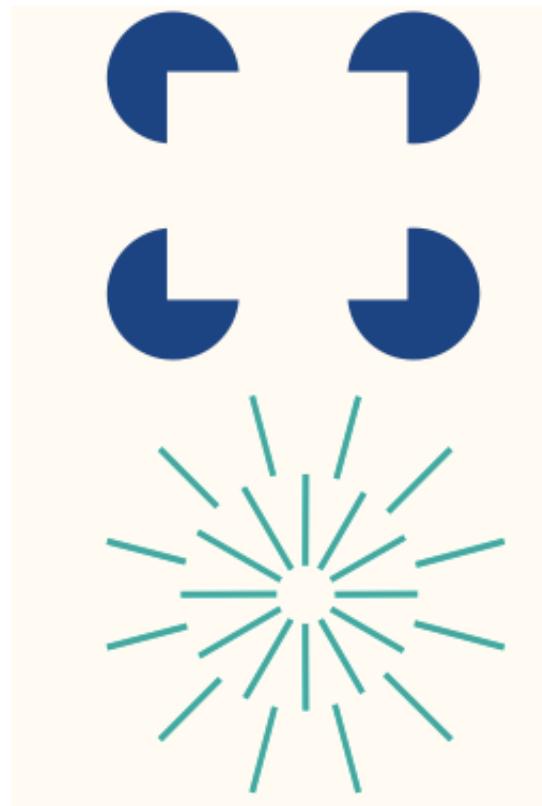
scanning mainly focuses on the eyes of the image you are looking at. Scanning moves between the eyes. Also, scanning stops a lot on the mouth.

it is not random scanning and not systematic point by point. There is some kind of algorithm that the brain developed in order to scan the figure/dace in the case and eventually come to a recognition.

eg. Age? Mood? Do you know the image or not?

### Illusion

# The brain computes



you may able to see a square and a circle which does not exist. The brain computes something, just because **it is connecting things using the experience of the brain from the past.**

This is some algorithm that are being implemented automatically, and the solution of the computation is that *there is a square/circle*. This is a result of a particular structure of your network.

## Motion

Another import aspect of the brain: to compute motion.

Motion is the very fundamental aspect of the nervous system, for any nervous system in any animal.

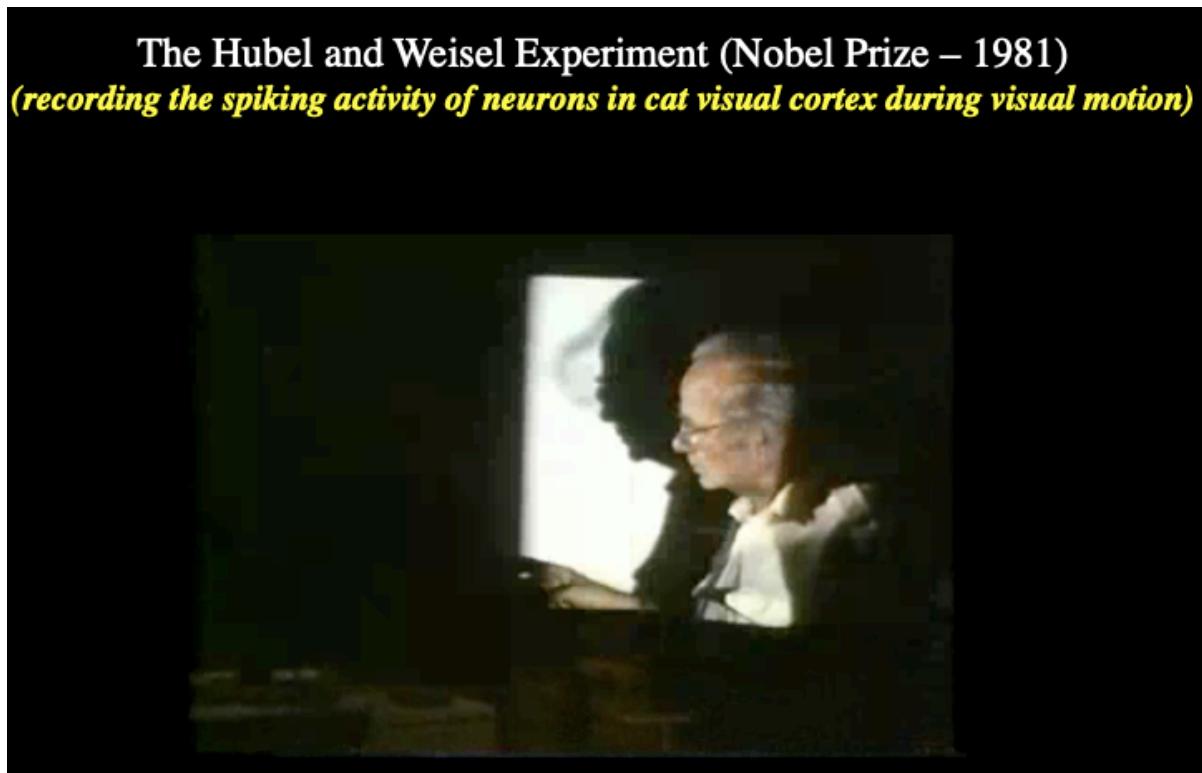
computing the motion, direction, speed

So this is basically what it means that the brain computes.

It has a mission. It has a problem to solve. It implements some algorithm using specific ingredients, synapses, dendrites, spikes and so forth. This is what I mean when I'm saying the brain computes. And in each module, auditory, somatosensory, vision, motion it is using the relevant network or networks in order to eventually, hopefully, come to a correct computation, using the input and then behaving appropriately.

## Computation at the Level of Single Neuron

The first evidence



The Hubel and Weisel Experiment (received a Nobel Prize in 1981)

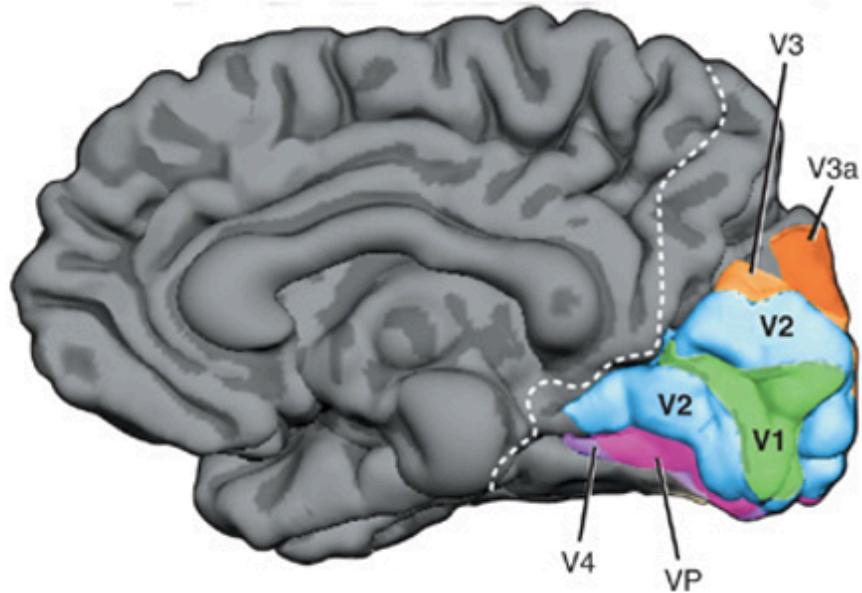
They recorded from the particular region of the visual cortex of the cat, v1. An electrode was implanted in the living seeing cat. They tried to find out what are the parameters being computed, represented by a single cell in the visual cortex of the cat.

What they found is that whenever there is a line, a line crossing the screen in a particular angle, the this particular cell started to fire.

They heared the tac tac tac sound from the cell firing

meaning that in the visual world the cell responds best when there is a line moving in some directions

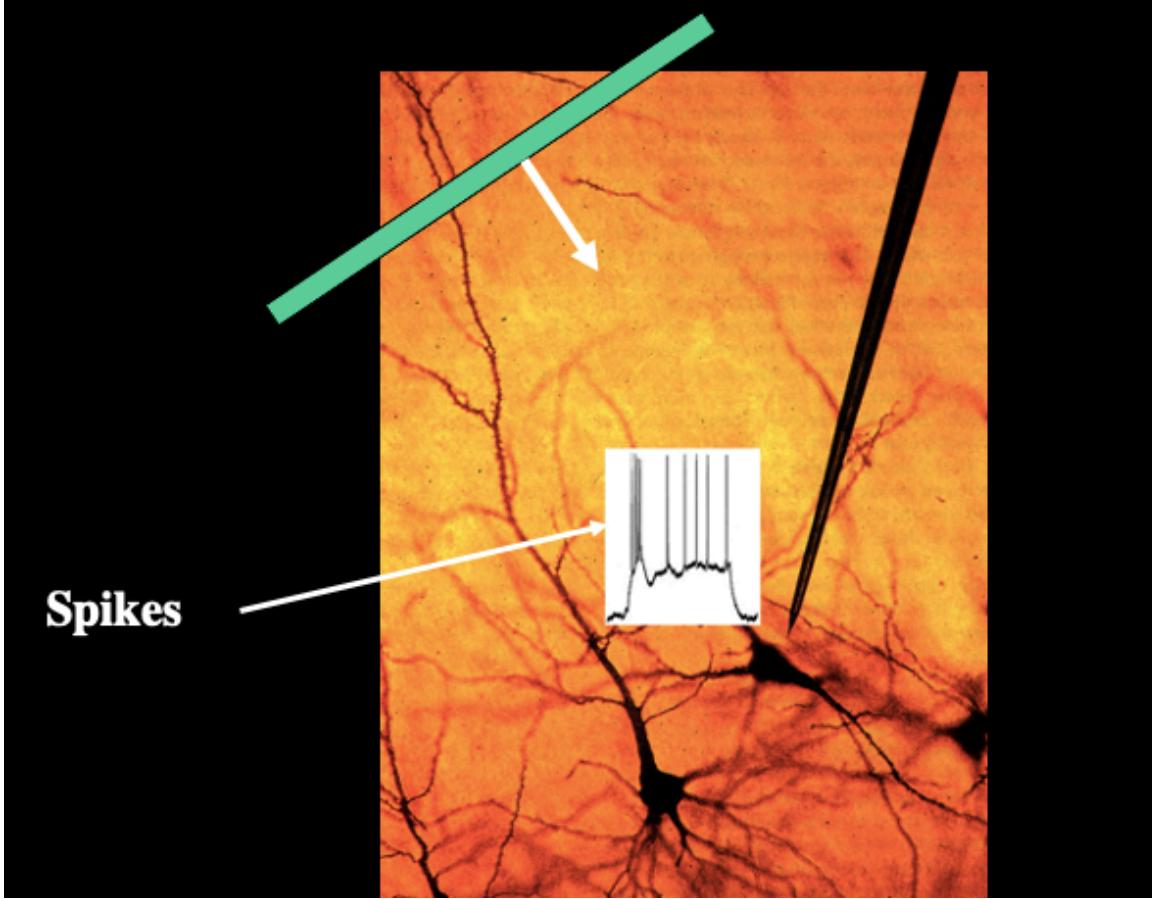
# Functional/anatomical subdivision of the visual cortex



v1 is the primary visual cortex (where Hubel and Weisel recorded)

they showed the cat looking at the screen with different angles of moving lines. And they found that when they recorded from this particular cell. They found that when there is a line crossing the screen, suddenly the cell starts to fire.

## Orientation selective neuron in the visual cortex

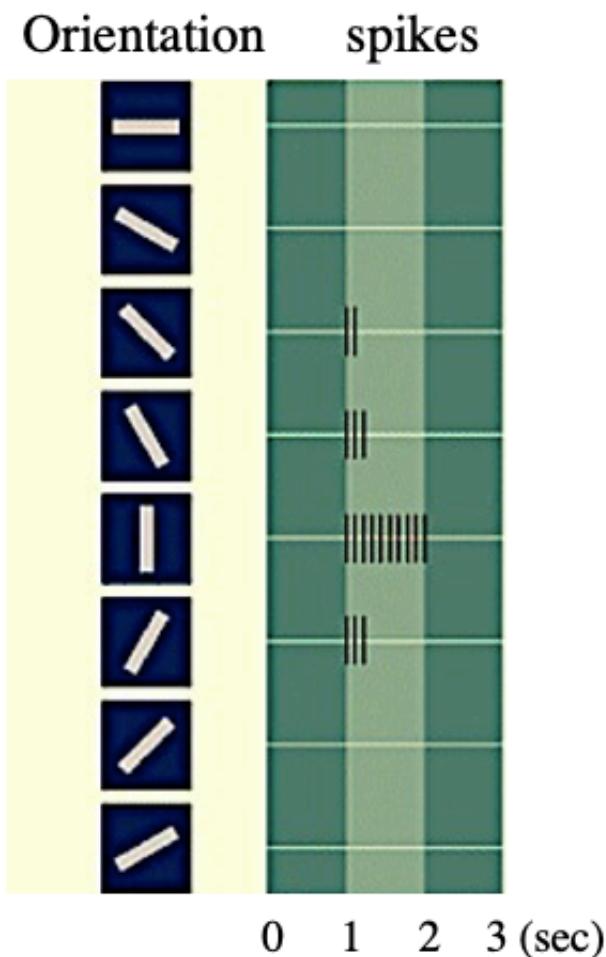


And when the angle changed a little, the cell doesn't fire.

So there are spikes responding, coding for this particular direction of line, in this particular cell.

We call this one cell an **orientation direction selective cell**.

## Orientation selective neuron in the visual cortex



What Hubel and Weisel found is that when you have an oriented line, 180 degrees or other orientations on the visual world, and you record from cells in V1 of the cat.

In some angle, for this particular cell, the cell fires more rigorously and strongly. In other angles, the cell does not fire.

This cell is tuned to respond to some specific angle.

This was a breakthrough. In retina, no cell responds to oriented lines. In the deeper region, the thalamus, no cell responds to the oriented lines. But in the next deeper into the brain suddenly there are these computation.

So this is a **orientation-selective**. And in this case also moving the direction of a cell that is responding to particular parameters in the word computes the parameters. (That is how you decompose the world.)

### Decompose the world into elements/parameters

We and the cats and the mouse and monkeys, decompose the world. **Early on in the visual system**, in the v1, early visual system, you decompose the world into lines.

And also to other parameters. movement, to color and so on. To edges and to other aspects you compute the aspects of the visual scenery scene. And you decompose it for its features, oriented lines, length Ending of lines, moving of lines, movement of lines and so on.

## Fundamentals of Dendritic Cable Theory

Early papers:

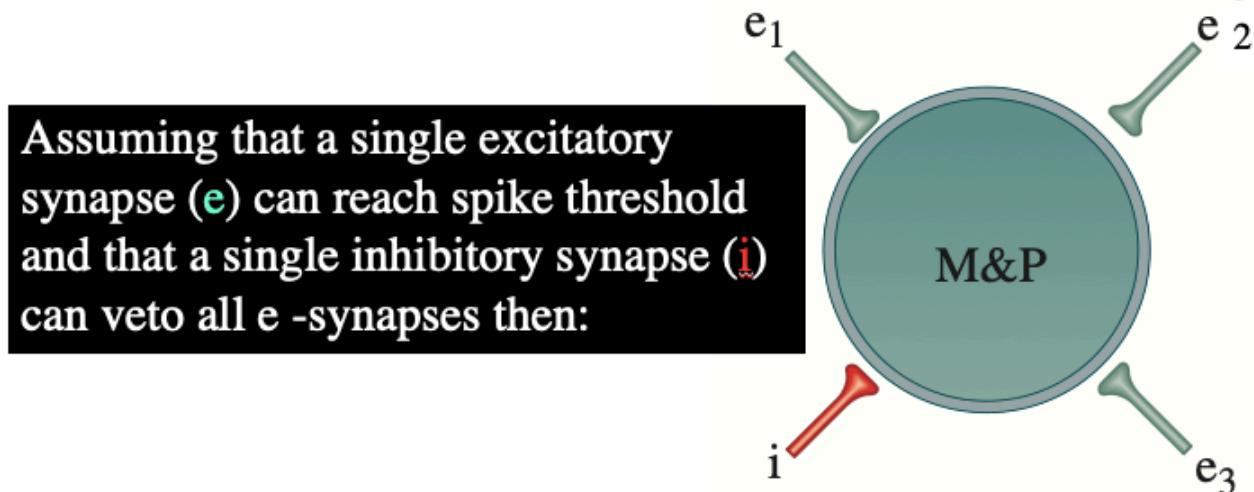
A neuron as a **microchip that computes** is a very influential work by McCulloch and Pitts. M&P, McCulloch and Pitts what we call today the **McCulloch and Pitts neuron**. (1943)

Has profound influence on the generation of the modern digital computer

This was inspired by 2 properties of the neuron:

1. one or none (either fire the spike or not)
2. neurons receive two types of synapses (E and I )

## The Neuron as a Logical (Computing) Device



OUTPUT ("1") is generated if:

(e<sub>1</sub> OR e<sub>2</sub> OR e<sub>3</sub>) AND NOT i

The logical statement (but they consider the neuron as a point neuron)

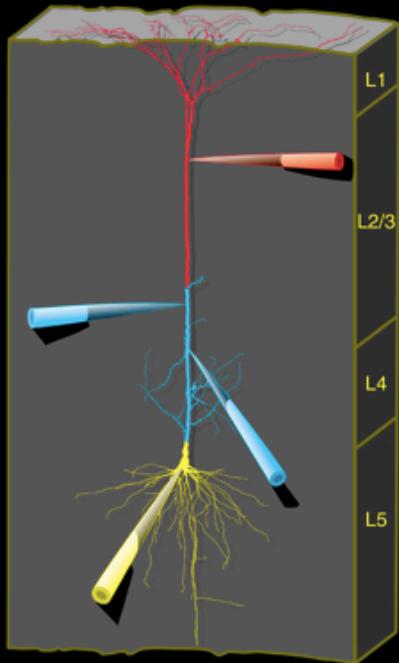
and output is generated only if this logical statement is implemented

This is how you can think neuron as a computational elements.

But neurons (dendrites) and their synapses are not “points” but rather a distributed electrical systems

What is the computational implications of it?

(this question requires a conceptual framework and rigorous theoretical approach)



*Matthew Larkum, Bern Univ.*

By a distributed electrical system can compute?

Does it add in principle, the fact that you have a distributed system like dendrites and axons?

Does it add to, at least in theory, does it add to the computational capability, capability of the nervous system or of a single neuron?

The mathematics is important.

Why model mathematically?

1. correct interpretation of experimental result (provide except prediction)

having interpretation of how the details explained the phenomena  
what kind of predictions can you do using the model that you build?

so the purpose of a good model is not only to replicate in the compact way the experiments, but also to provide some predictions .

2. Gain insights into **key biophysical parameters** (enables compact description of the physiological behavior studied capturing the essence e.g., HH model for the AP)
3. Suggest possible computational (functional) role for the modeled system (e.g., M&P neuron; Rall's ideas for dendritic computation – see next)

take a jump from biological field to the computational zone

## Rall Cable Theory for Dendrites

# Rall Cable Theory for Dendrites

Understanding (mathematically) the impact of  
(remote) dendritic synapses (the input)  
on the soma/axon (output) region

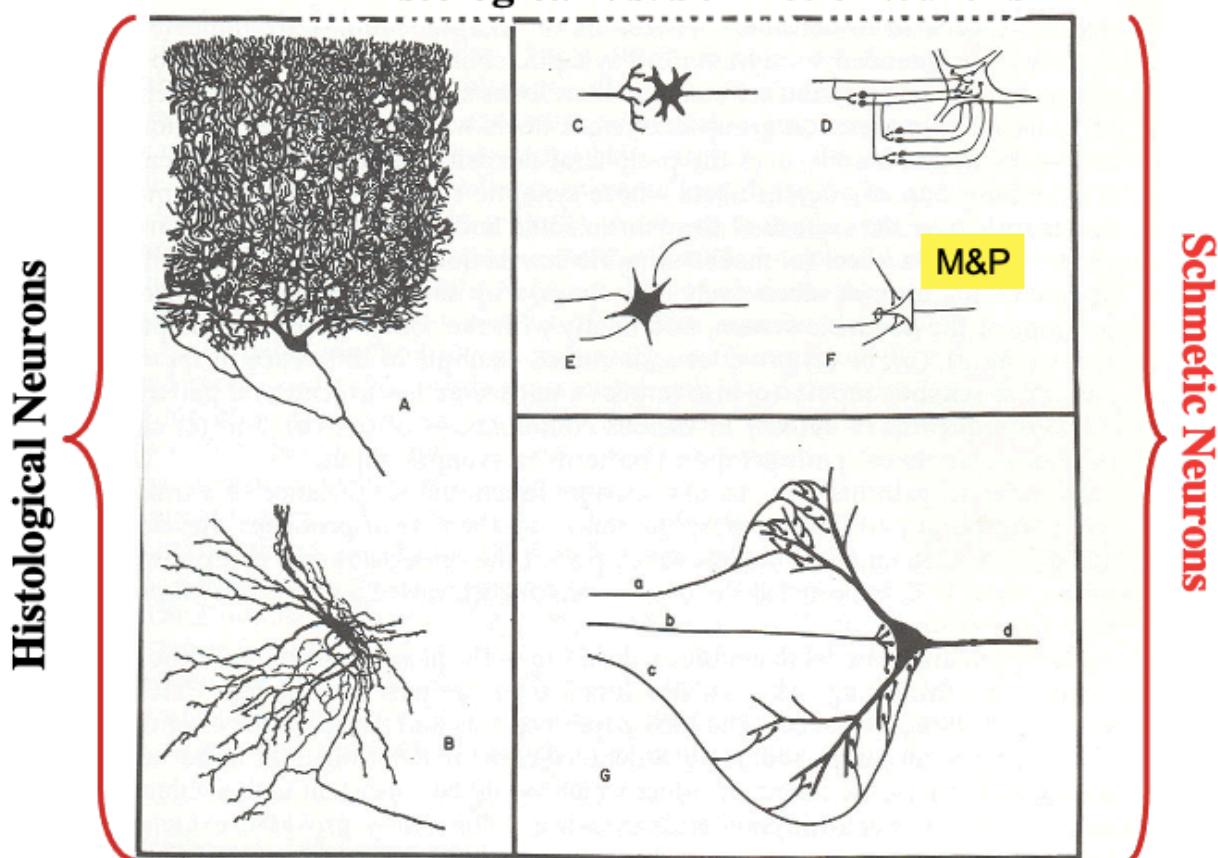


*Wilfrid Rall*

Rall tried to develop a mathematical theory to explain how remote dendritic synapse affect the output, the spike generation in the axon.

# Rall (1964)

## Histological Vs. Schmetric Neurons

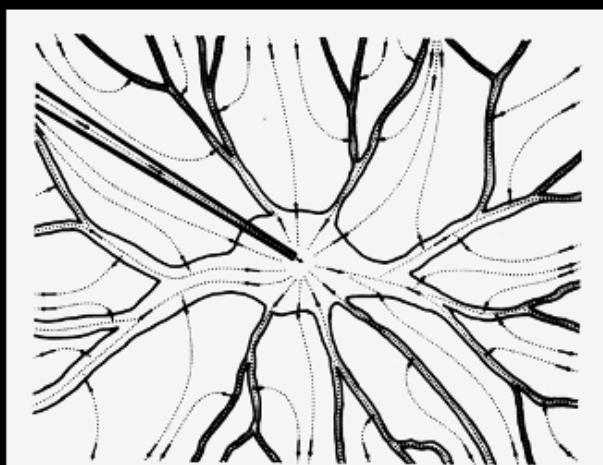


left: real neurons

Right: schematic neuron

### Rall's early motivation (1959)

Understand experimental synaptic potentials recorded at the soma



1. Most of the input current flows into the dendrites (not directly to soma)
2. Dendrites are non-isopotential electrical devices

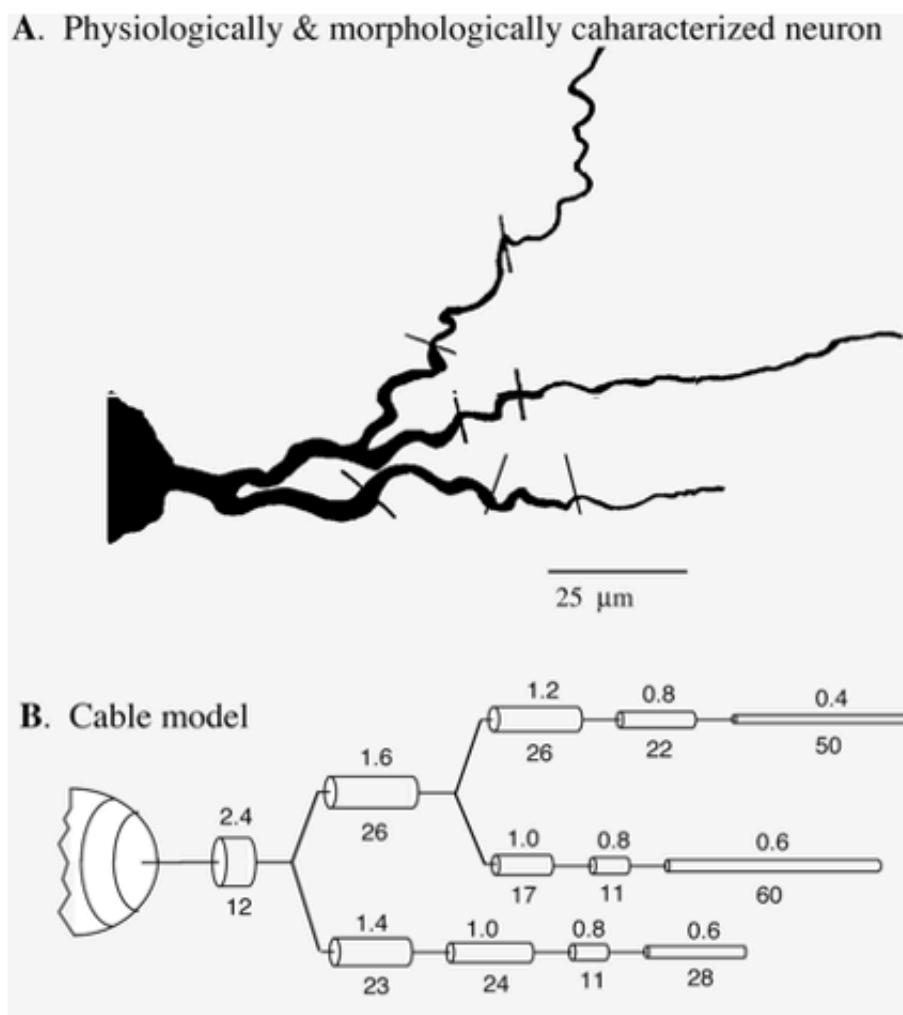
you can not think about the soma as an isopotential when it is located in a real neuron where so many dendrites pop out from the soma.

Because the dendrites and the soma and the whole system is not isopotential, there are some location with one potential and another location with another potential. So it's non-iso-potential.it is a **distributed electrical system**

- (i) voltage attenuates from synapse to soma;
- (ii) it takes time (delay) for the PSP to reach the soma;

Rall already understood that since it is a distributed system, there must be delay. It will take time from the synapse to reach the soma. It will take some time if we have a delay to see the effect of a synapse at the cell body.

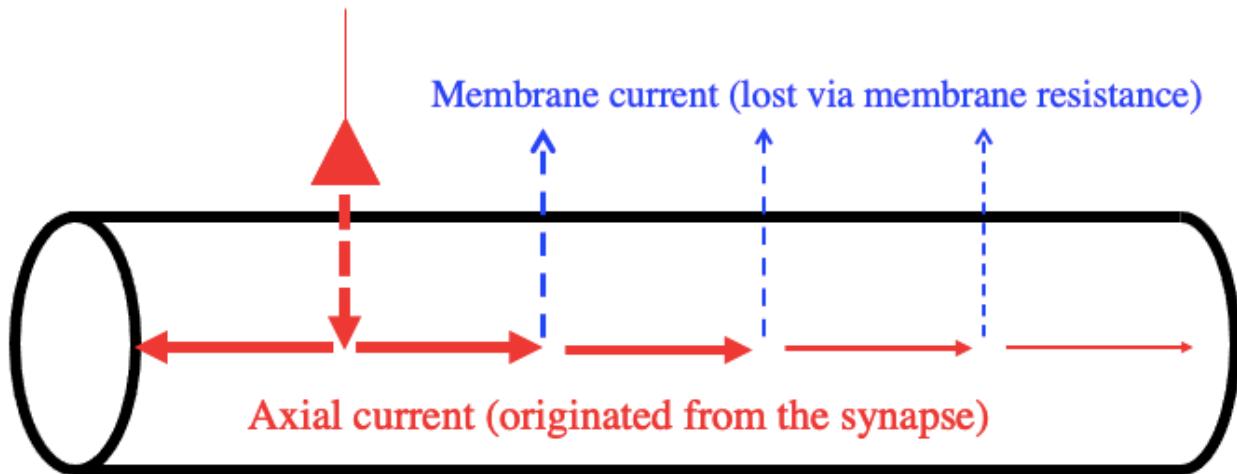
- (iii) somatic EPSP/IPSP shape is expected to change with synaptic location



### Rall's Cable Theory

## The origin of the passive (linear) cable equation

### synapse



imagine we inject current at the synapse location. the origin of currents flowing from the outside into the cell. It can either flow to right or it can flow to the left.

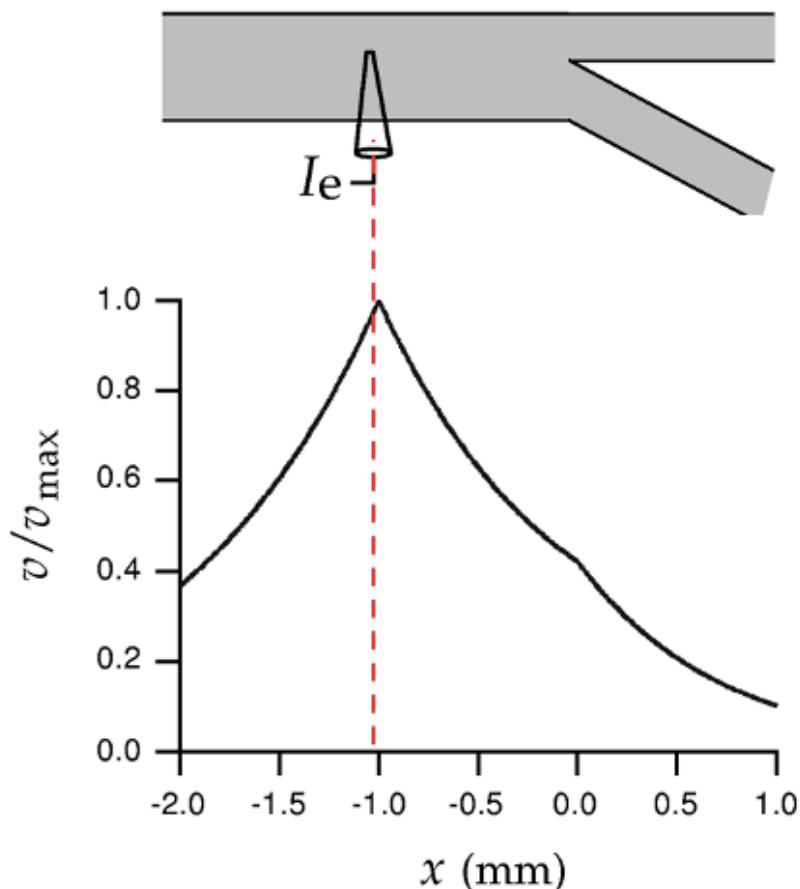
Because that membrane behaves like an RC circuit, so current can escape. Through the resistance, current can leak out through the membrane (charge the membrane capacitors). And because you lose current, the voltage here through the membrane will attenuate. There will be less and less voltage because you have less and less current charging the membrane as you go away from the synapse.

This is the origin of cable theory.

blue current: lost through the membrane

red current: axial current flowing axially

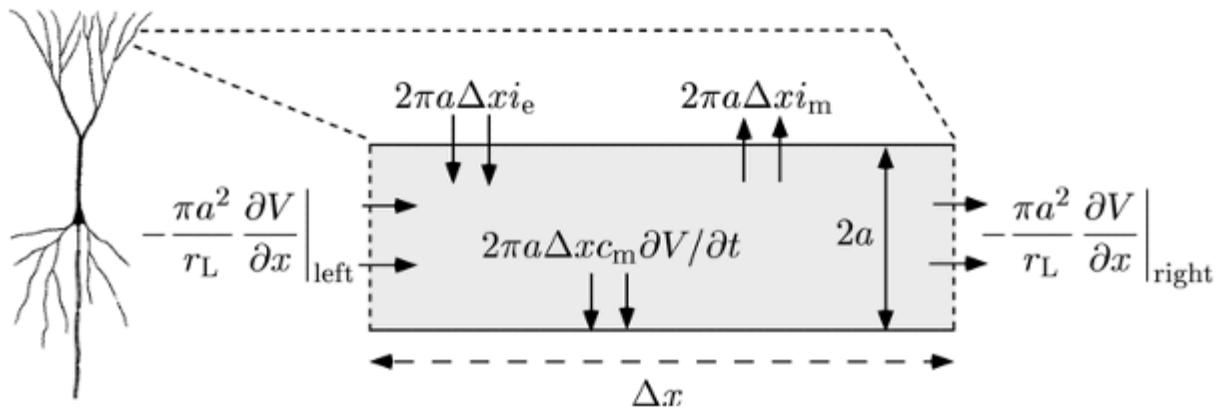
## Synaptic potentials attenuate from the synapse origin towards other regions of the dendrites



If you inject here a synapse or a current, you will get the maximum voltage here and the local voltage attenuate along the structure. It will continue to attenuate. Then it will encounter a bifurcating dendritic tree.

So how do you describe mathematically a cable, a passive cable?

# (1-D) Passive cable equation



$$\left(\frac{r_m}{r_i}\right) \frac{\partial^2 V(x,t)}{\partial x^2} - r_m c_m \frac{\partial V(x,t)}{\partial t} - V(x,t) = 0$$

$$\frac{\partial^2 V}{\partial X^2} = \frac{\partial V}{\partial T} + V(X,T) \quad X = x/\lambda \quad T = t/\tau_m$$

The first equation: (linear partial differential equation) you have **x (distance)** and **t (time)**, meaning that the voltage changes at each location with distance and time

the change in axial current (which is proportional to the second derivative of voltage with distance)= membrane current unless you injecting current from outside

This is a passive cable theory and the foundation for Rall's cable theory

Because all the parameter, the membrane resistivity, and the capacitance are passive, are static.

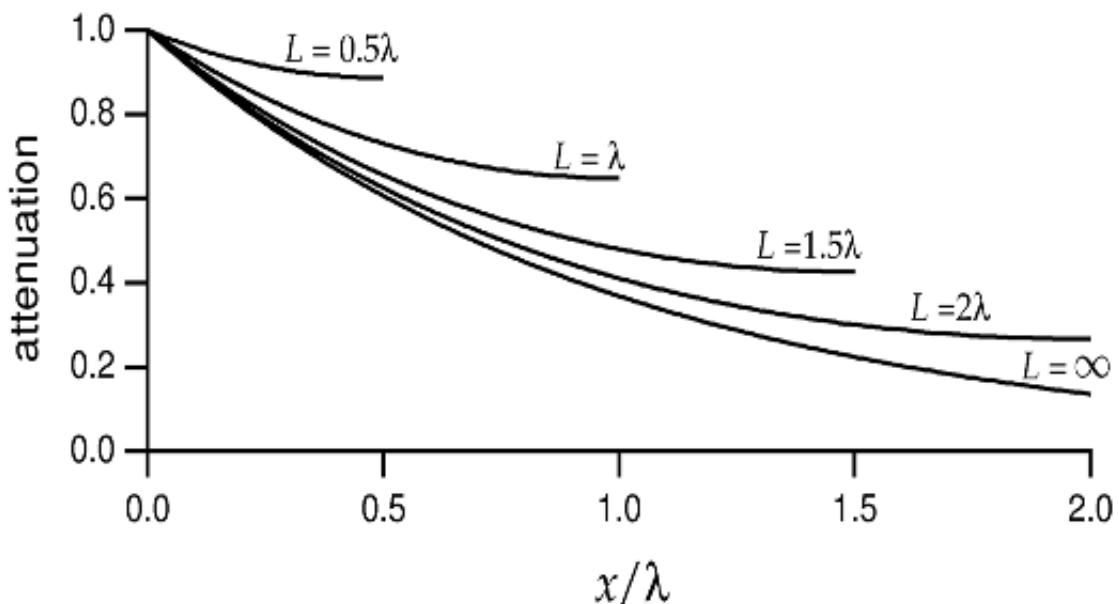
The second equation: dimensionless cable equation

Rall solved the differential equation for different boundary conditions

# Steady-state condition

(“Sealed-end” boundary)  $\frac{dV}{dX} = 0$ ;  $x=L$

$$\frac{\partial^2 V}{\partial X^2} = \cancel{\frac{\partial V}{\partial T}} + V(X, T)$$



the attenuation of the voltage depends on the property of the cable

when the cable is infinite, we can see the steepest slope.

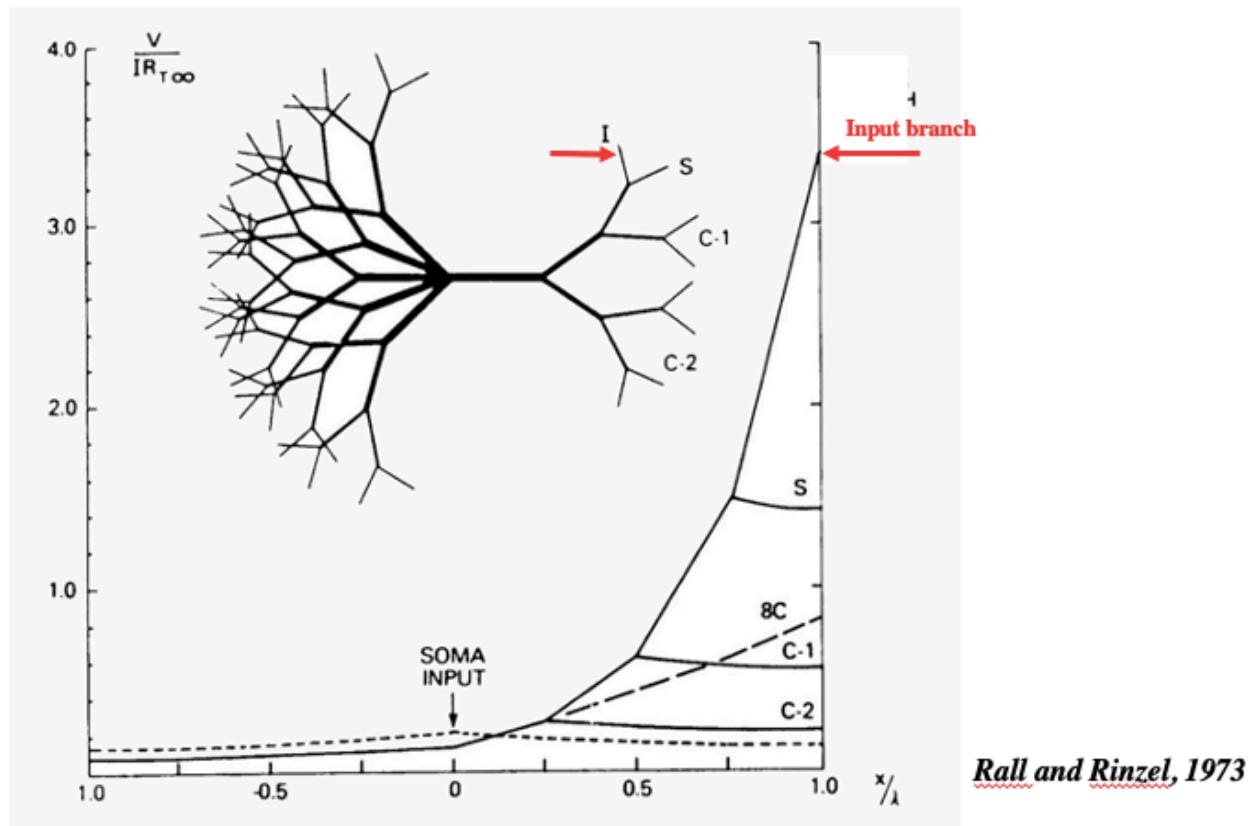
Sealed-end boundary:  $\frac{dV}{dX} = 0$  when  $x=L$

The slope of the attenuation also strongly depends on the boundary conditions at the end of the cable

For the infinite case, it attenuates exponentially with distance

For sealed-end short cylinders, like dendrites are, it will attenuate less steeply with distance

## Steep (asymmetrical) voltage attenuation from dendritic synapse to soma



we can see very steep attenuation at the input branch

locally, the injected synaptic current will enable to build up a large voltage especially if it is on the spine head

but from the input side, very fast and nearby, you will get a very steep attenuation (a lot of current flows into the increased diameter) (not sealed, it is a long cylinder)

But there is a leaky end (the twin-branch) and very little current flows through the side branch because the side branch is sealed (it is a short cylinder with sealed end) meaning there is almost no attenuation

Finally, some of the current will reach the soma

it is a very large non-isopotential system with large voltage near the synapse and low voltage eventually at the soma

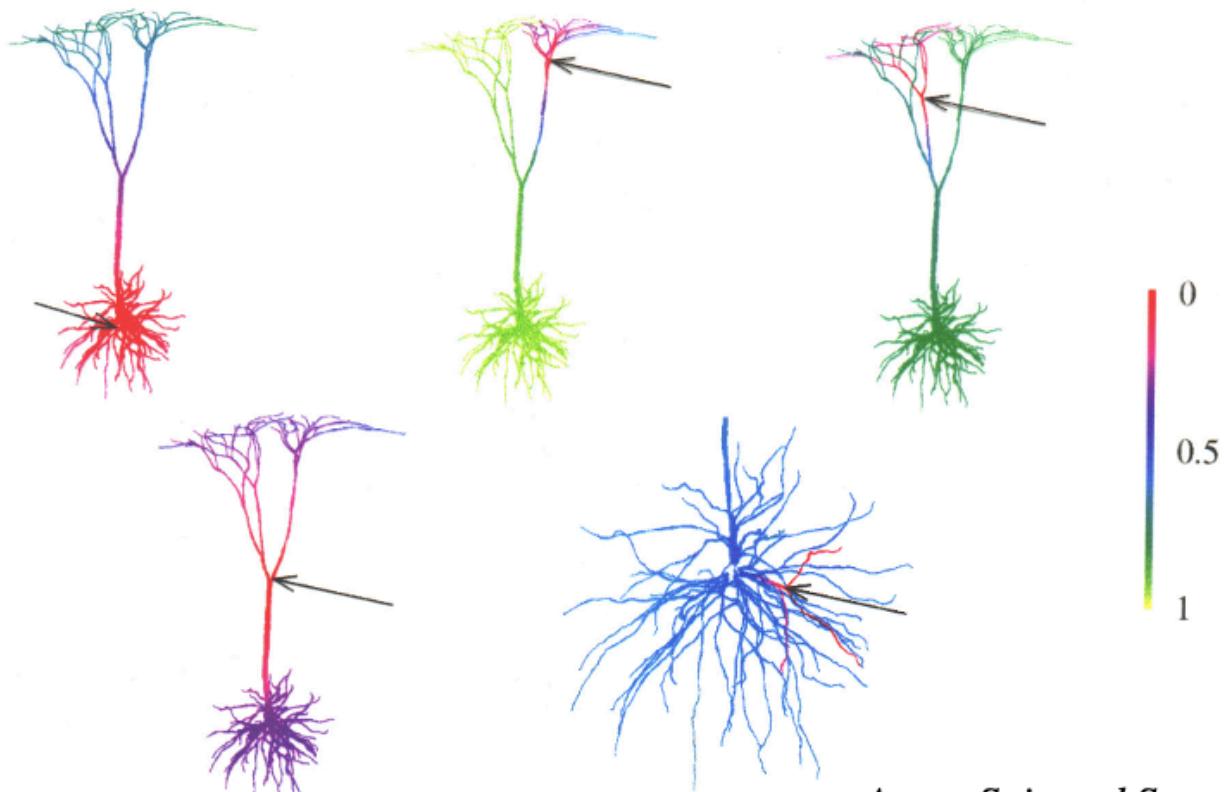
near the synapse, it could be 20, 30 maybe 40 millivolts (at the synapse post synaptically, big EPSP)

but at the soma, we will see a small EPSP maybe 1 millivolt

so in this case, 40 fold attenuation (in some case maybe hundred-folds attenuation from the input site to the soma) that is one property of dendrites

notice if you inject same current at the soma instead of the branch, you will not lose very much terms of voltage if you compare what you would gain at the soma now with direct attenuation to the soma compared to what remains of the soma from the distal input *but the difference is not so big*

## Dendritic “functional subunits” (“synaptic territory”)



Agom-Snir and Segev

So each synapse will have a neighborhood territory or a neighborhood like a unit or sub-region that is effected by this synapse very strongly, locally.

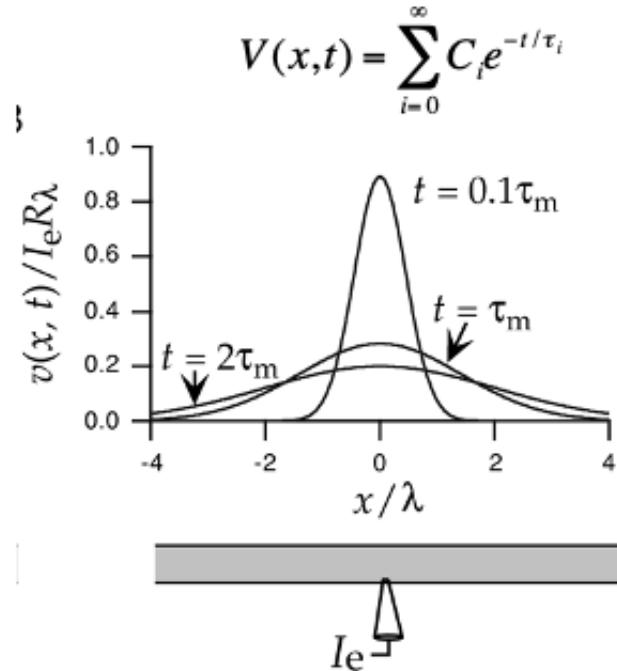
this is a figure with color-coded, red means that all local region will feel large voltage

Then the distal part is less affected by this synapse

These **notion of regional sub-units** can be used doing specific computations

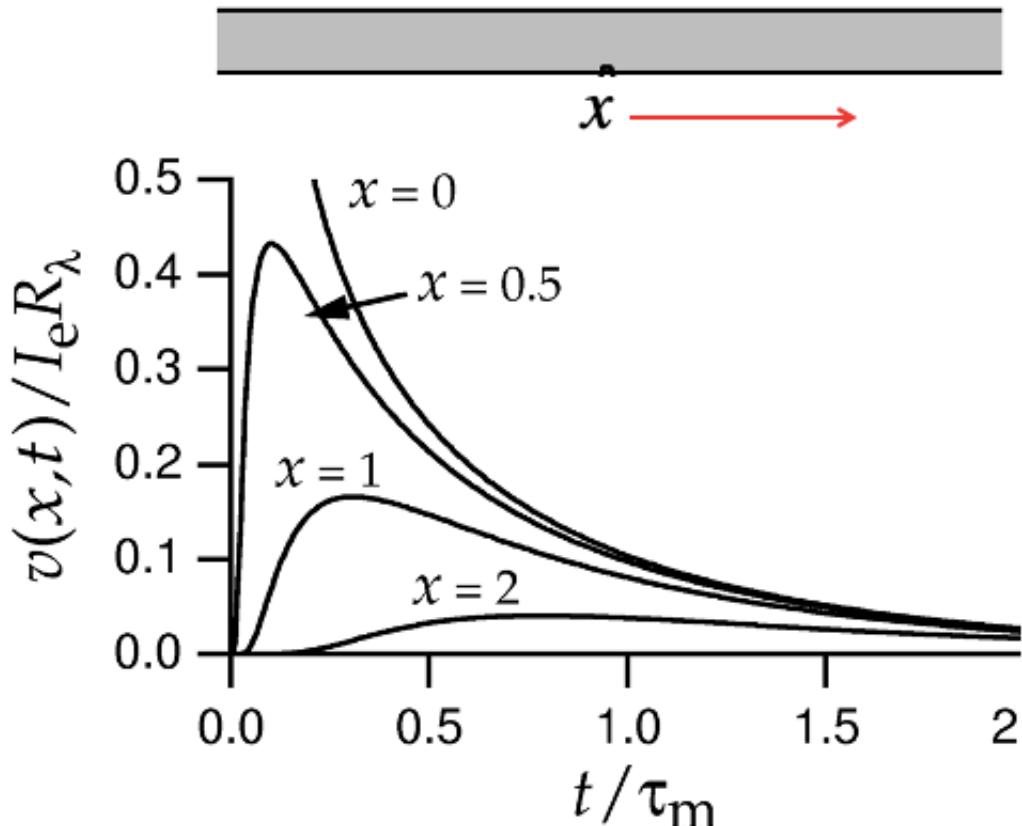
# Transient synapses

$$\frac{\partial^2 V}{\partial X^2} = \frac{\partial V}{\partial T} + V(X, T)$$



after enough time, everything will go down because current leaks out  
and eventually, you will go back to resting which is a iso-potential system at rest

## Transient synapse (attenuation, shape change, delay)

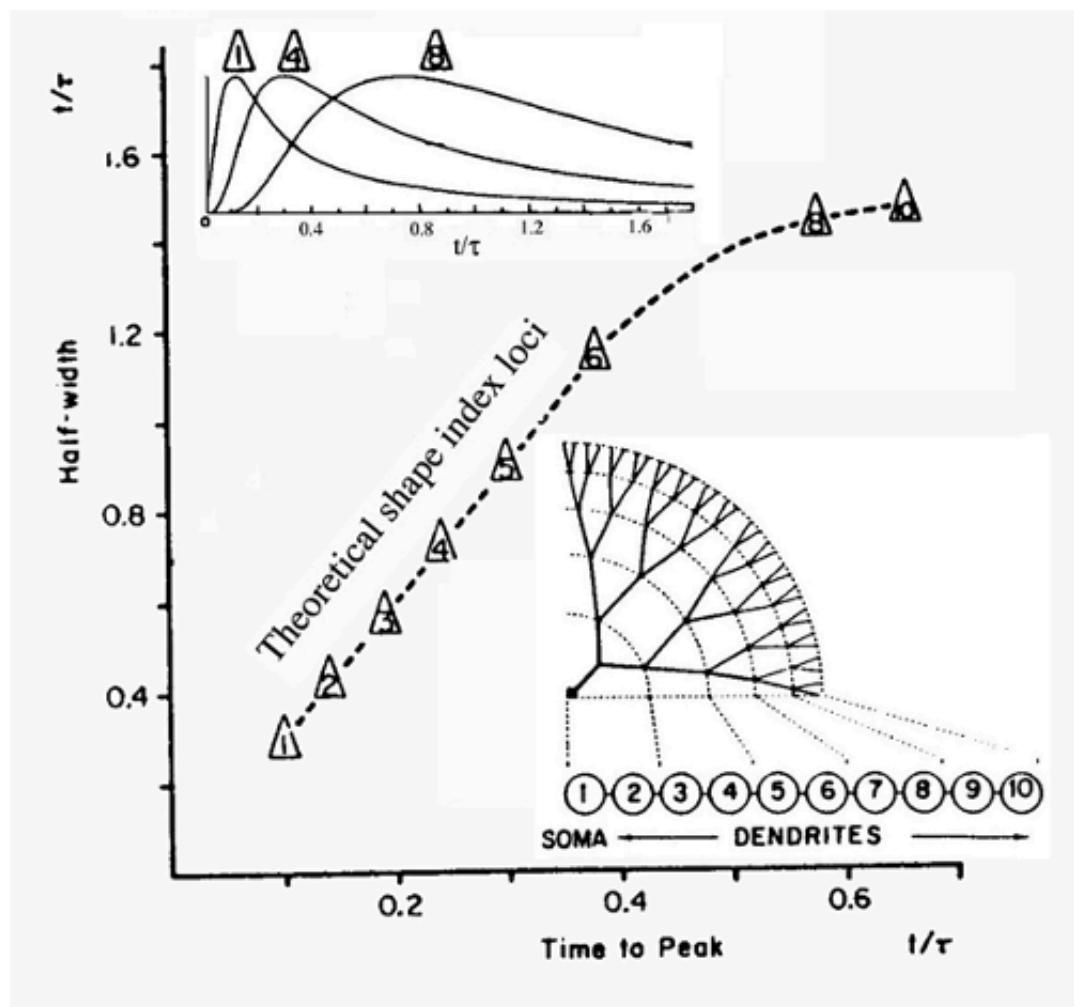


### The shape of EPSP

the change of EPSP shape (along with time) in each point

you will find that your EPSP shape will become broader when you go away from the synapse

## Experimental predictions distal synapses are broader and delayed



Compartment 1: soma

compartment 10: away from soma

(it is the simplification of the complicated dendritic tree)

inject at 1 or 4 or 8 and recorded at the soma

look at the shape of injecting at 8, we notice that **the distal synapse are delayed and broader**

and if injecting current at the soma, it will not be delayed. it will be immediately at the soma and it is less broad

from the distal synapse, the time to peak is delayed and the half-width is big

if the synapse is near the cell body, the time to peak is brief and half-width is small

**so if you get the record from the cell body, you can predict where is the synapse on the dendrite**

basically the theory will help you record the shape of EPSP at cell body and reconstruct the location of a synapse on the dendrites

## Dendritic Computation

a few theoretical ideas:

### 1. Dendrites enable neurons to act as multiple functional subunits

think of dendrites as computing first locally somewhere and then globally at the axon soma

### 2. Dendrites enable the classification of inputs

think of dendrites as classifiers

### 3. Neurons with dendrites can compute directional of motion (directional selective)

dendrites as implementing directional selectivity, computing the direction of motion of visual motion for example

### 4. Dendrites improve sound localization (in the auditory system)

### 5. Dendrites help to sharpens the tuning of cortical neurons

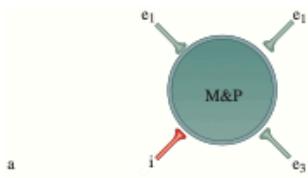
let's say in the visual system, are tuned to a particular orientation or a particular motion, direction, motion.

dendrites can tune, can sharpen, can make the neuron more accurate in its sensitivity to this angle and not to this angle.

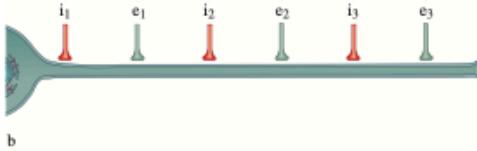
## Neuron as multiple functional subunits

## Neurons as multiple functional subunits:

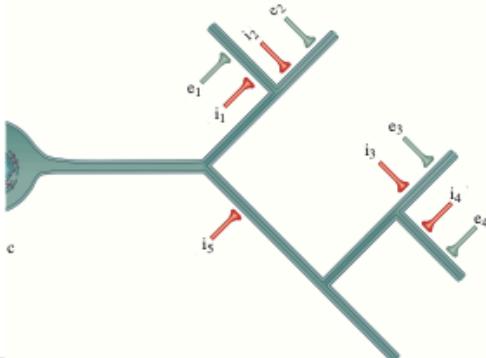
Dendrites endow the neurons with extended logical-like operation (extension of M&P idea by Koch and Poggio)



(e1 OR e2 OR e3) AND NOT i



e3 AND NOT (i1 OR i2 OR i3) OR (e2 AND NOT (i1 OR i2)) OR (e1 AND NOT i1)



*"On the path"* conditions

notice that there is an **inhibitory synapse (i1) near the soma**, meaning that this inhibition is more **global**, and **affects all the excitation that comes from more distant region**

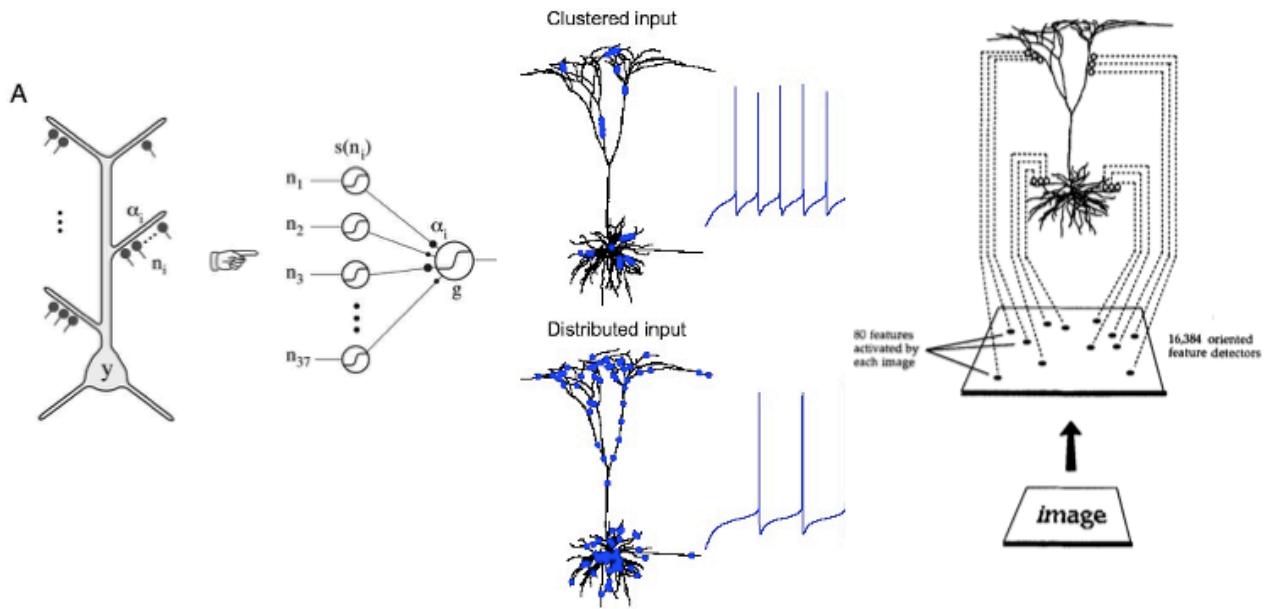
even e1 or e2 or e3 is active, the proximal to the soma inhibition can veto it

Logic statement:

e3 AND NOT (i1 OR i2 OR i3) OR (e2 AND NOT (i1 OR i2)) OR (e1 AND NOT i1)

## Input classification with dendritic neurons (Barlett Mel)

## Input classification with dendritic neurons (B. Mel)



the neuron is locally performing some kind of non-linear operation, non-linear summation of every local synapse, and then sum these local operations globally at the soma, what is called the **Pi Sigma Neuron**

So, the clustering of synapses into sub-regions whereby within each region.

Barlett Mel considers neurons as classifiers. For example, a picture of human face consists of different part, and each part will be projected into a cluster that performs non-linear operations locally. So the picture of human face is systematically, topographically, in nearby region here, is projected into nearby region.

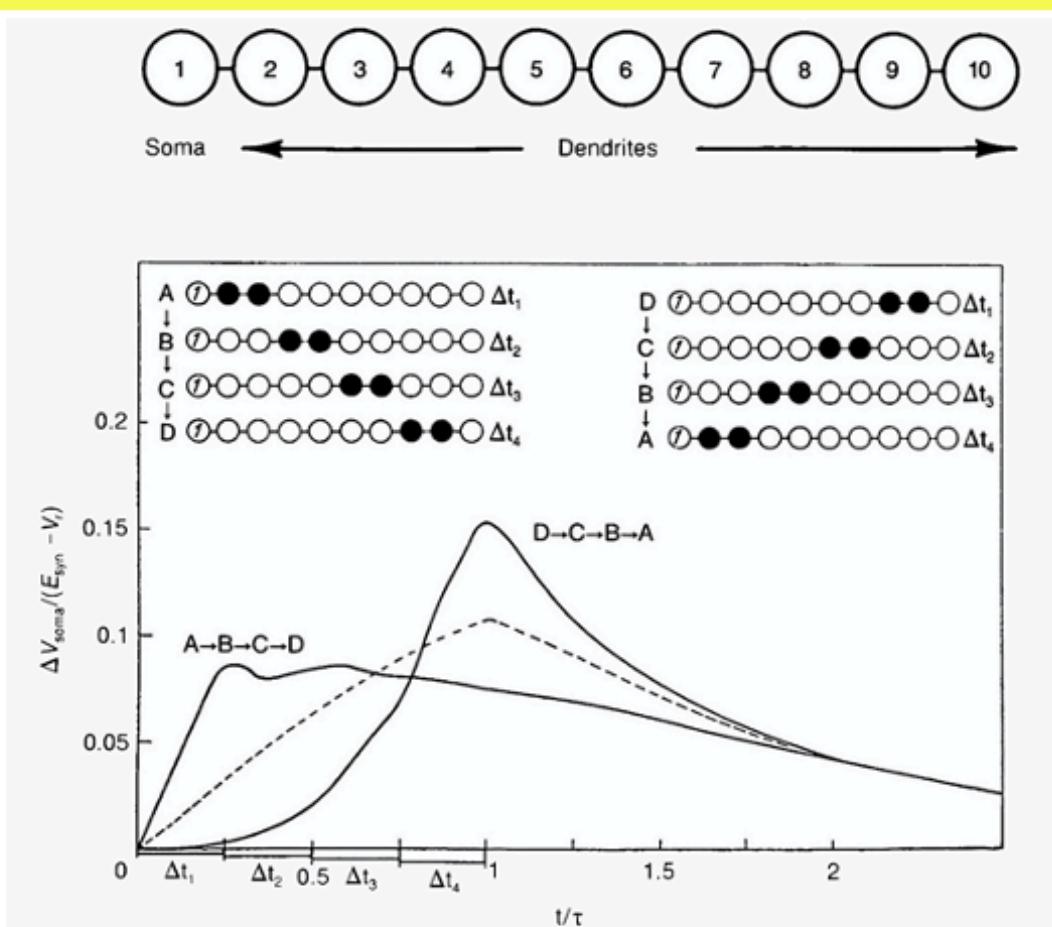
Then the output will be this is a human face or not. That means that the cell becomes a classifier.

**So, the dendrite distributed dendrite with these local synapses. Performing local non-linear operations, maybe have as a cluster on classifier.**

**Neuron as directional selective computational device**

# Neurons as directional selective computational device

Rall 1964



the direction of stimulation: ABCD-from proximal to distal

So A, B, C, D at the soma looks like this. You see immediately in **EPSP coming from the nearby synapses**.

And on the shoulder of this EPSP that would have attenuated, you have the second, more distant synapses summing up temporally. You will see a broad shoulder.

the direction of stimulation: DCBA-from distal to proximal

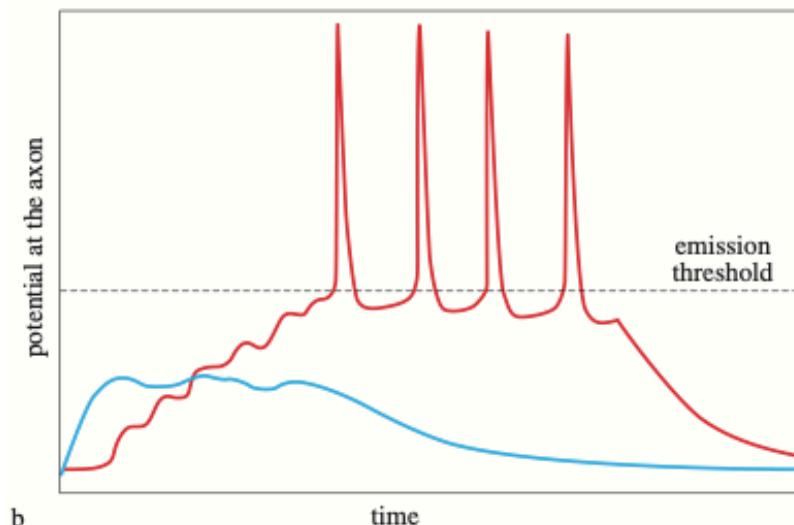
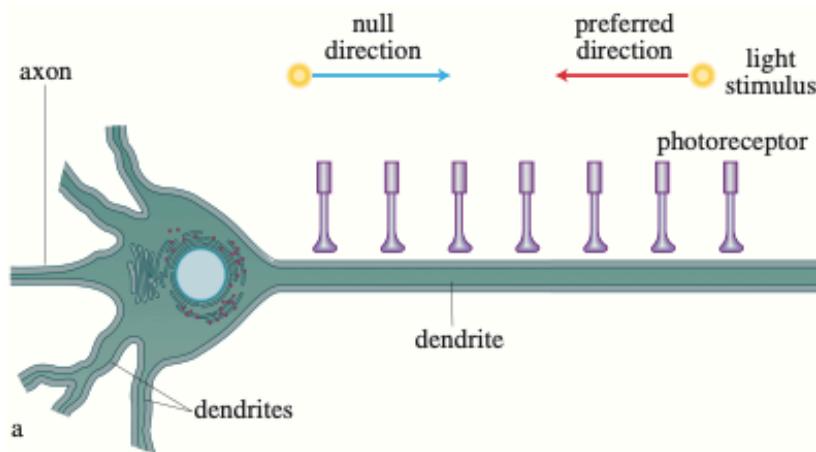
Because the distil one was the first, and it takes it time to reach the soma. You will see a delay. But on the way, it summates with a more proximal, with a more proximal, with a more proximal, they summate one on top of the other, building up a large voltage.

there is a **threshold** at the soma. To generate a spike you need to cross the threshold. there is only in one direction of synapses activation will get an output spike. And in the other direction, you will be sub-threshold and not cross the spike threshold so there will be no spike.

For example, in retina:

# Neurons as directional selective computational unit

Rall 1964



light moving from distal to proximal (right to left)

| in this direction of light moving. You will build up voltage which may cross threshold and generate a spike.

light moving from proximal to distal (left to right)

| broad shape EPSP and no enough to cross the threshold

This computation depends on the distribution of the synapses over the dendritic tree

| if the synapses all sit on the soma, you will lose the computation

something about the structure and its synapses generates a possible function

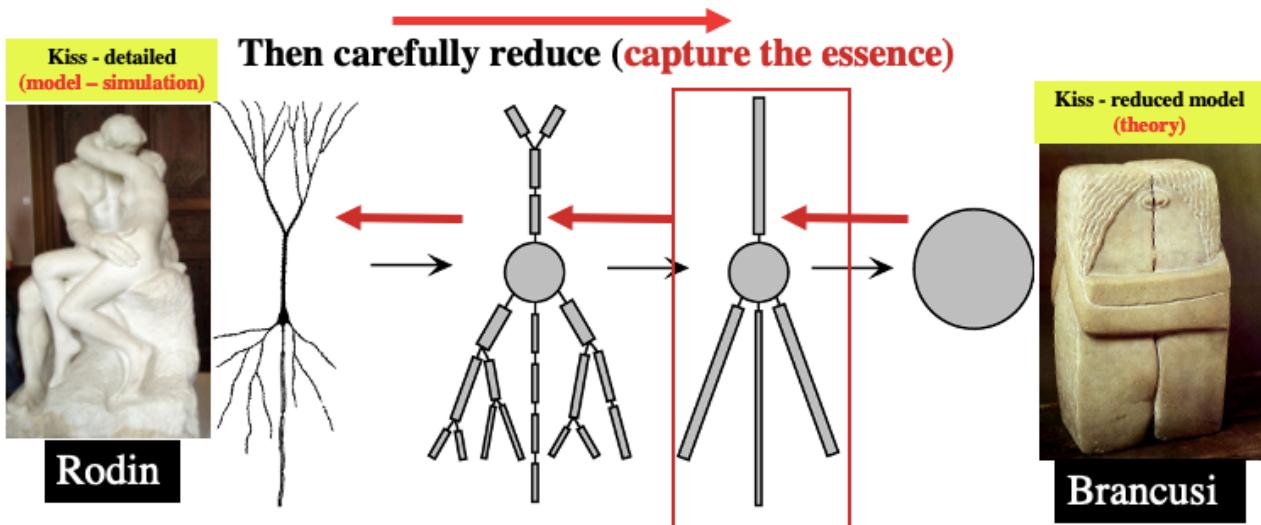
Wilfrid Rall suggested you must be careful to build a mathematical model

## A comment about “granularity of models” and their utility



Detailed “realistic) model  
“Psychic” cell

“Point Neuron”



you may look at a neuron and represent it with a point

but this point neuron cannot compute the direction of selectivity on its own because computation depends on some structure

The question is do you need all the complexity of neurons to perform this?

Rall suggested going to what level you feel is relevant in terms of modeling in order to understand the phenomenon you are trying to understand

you can lose some details depending on the problem your model trying to resolve

## Recent Breakthrough

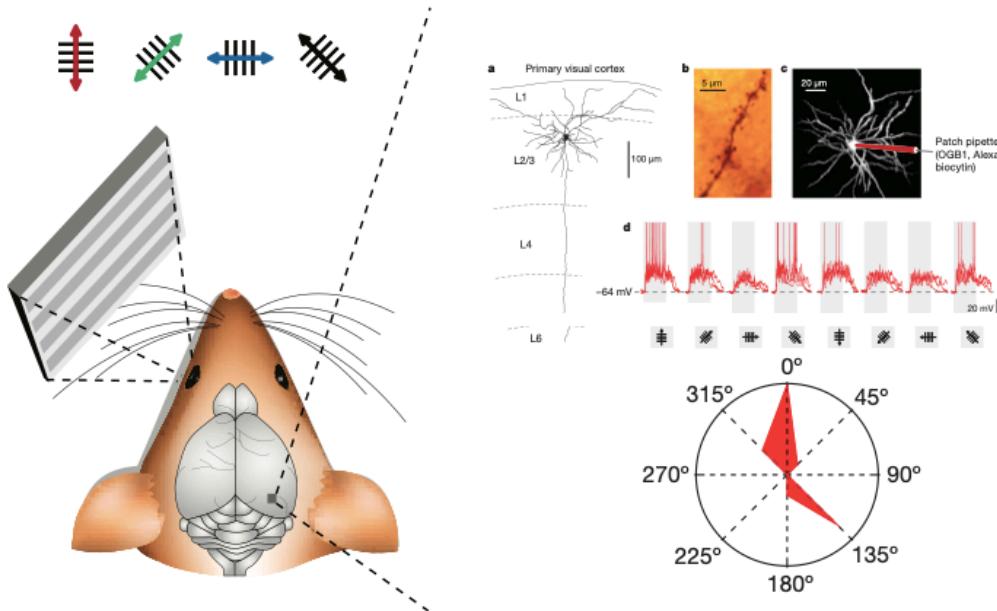
### 1. Arthur Konnerth's Lab in Munich

how does the neuron compute direction of motion

letting a mouse look at the screen with lines moving in different directions and recording from a particular cell with an electrode

this is the cell he was recording from in layer two, layer three of the cortex-the visual cortex of the mouse, V1

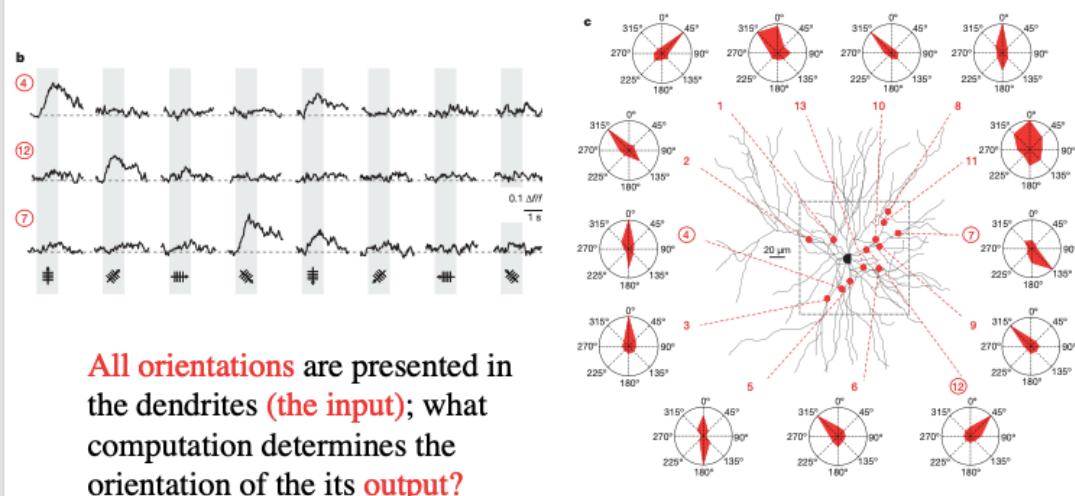
## 1. Orientation selectivity of L2/3 pyramidal cells (output) in V1 of the mouse neocortex



*Konnerth et al., Nature  
2010*

you can say that this particular cell is oriented, which is responds to the direction

## Orientation selectivity of dendritic synaptic inputs in L2/3 pyramidal cell in V1 of the mouse neocortex *in vivo* 2-photon Ca<sup>2+</sup> imaging



*Konnerth et al., Nature  
2010*

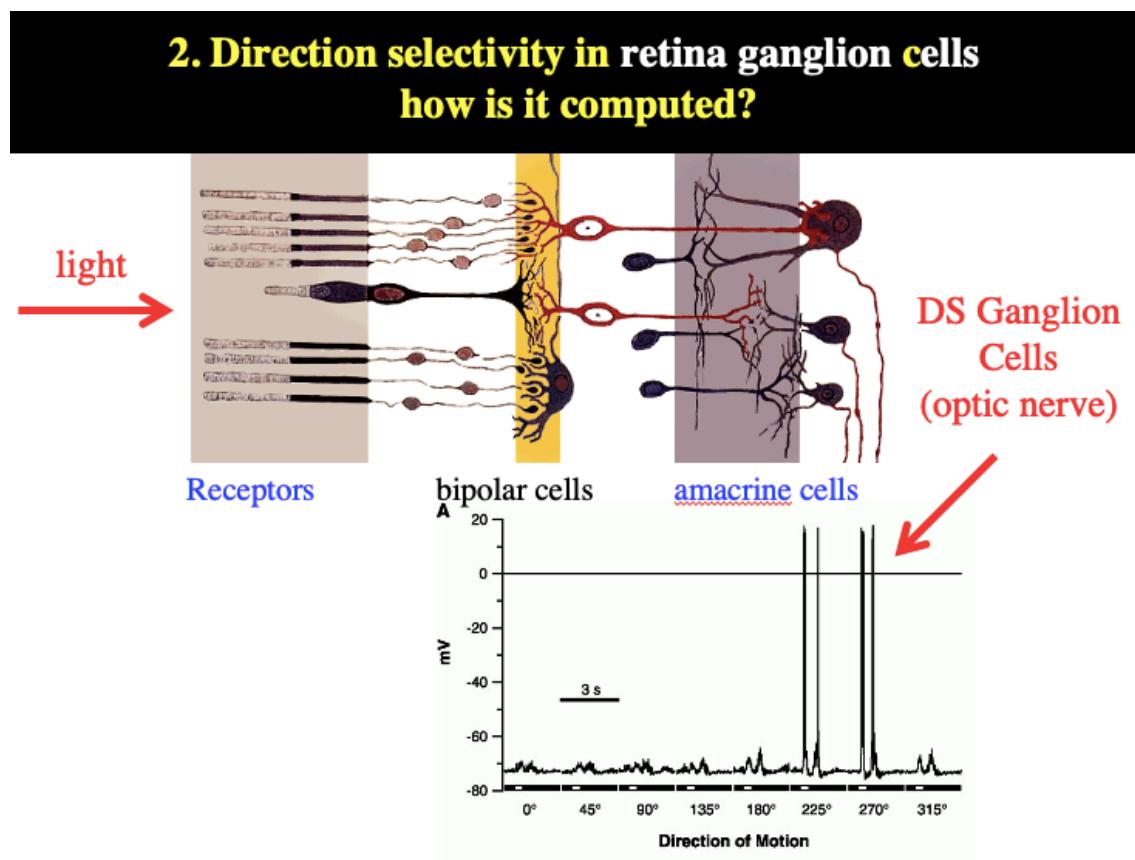
this particular cell, the layer two-three pyramidal cell in the mouse visual cortex V1, all orientation are presented on the dedrites. So, the dendrites experience as an input, all the orientation, all the synapses. The different synapses code for different orientation onto the dendritic tree, but the output is oriented to a particular orientation, like the input that is sensitive to particular orientation. Also the output

of this cell is sensitive to particular orientation. How does this dendritic tree transform the sensitivity of dendritic tree, so to speak? How does the output represent a particular orientation?

Maybe there are a lot of cells here. And all the cell just follow the majority of the direction detection. And they decide that the majority dictates the orientation.

That's one Interesting and important new technology. That enables us **not only to record the output of a cell, in VIVO**, in the behaving, in the full in VIVO situation. **But also the input to this cell and some computation is being performed by the dendrites generating a particular direction of selective output.**

## 2. Direction selectivity in retina ganglion cells



Input from left and output from right

notice that in some angles of direction there are spikes

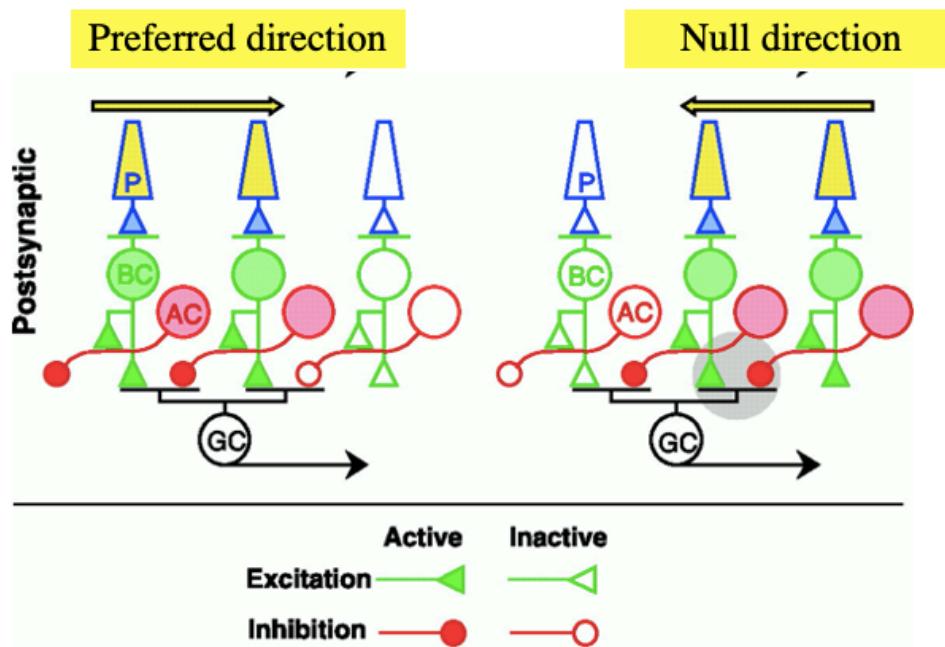
so this is a tuned cell that tends to fire only in the retina already, only when there are this direction of motion 225 degrees or 270 degrees and no others

so the tuned cells is already exist in the retina even before the cortex. **the computation is implemented at the level of this local network at the retina**

**the Reichardt detector**

## The “Reichard detector”

(possible connectivity that implements DS in retina ganglion cells)  
*Based on asymmetry of E + I connection onto the GCs*



in one direction there is more inhibition coming at some location than in the other direction. So, some asymmetry within the network causes the one direction to involve less inhibition compared to the other direction somehow.

This will explain that in the preferred direction you will get an output.

For example, if the light moves from right to left, then the inhibitory neuron will be activated first, then the whole circuit won't be activated

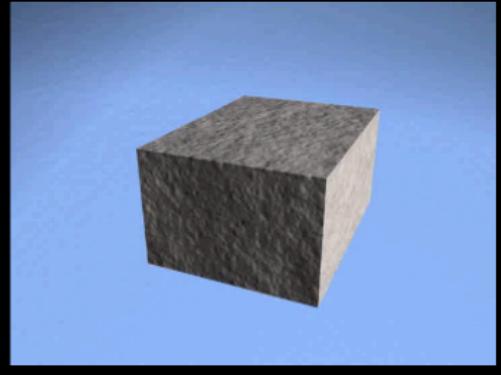
and if the light moves from left to right, then the excitatory neuron will be activated first, then the whole circuit will be activated

the question is: whether the structure exists or not?

Do synapses impinging on retina ganglion cells asymmetrically?

The era of “connectomics” – connecting structure (at the synaptic level) to function

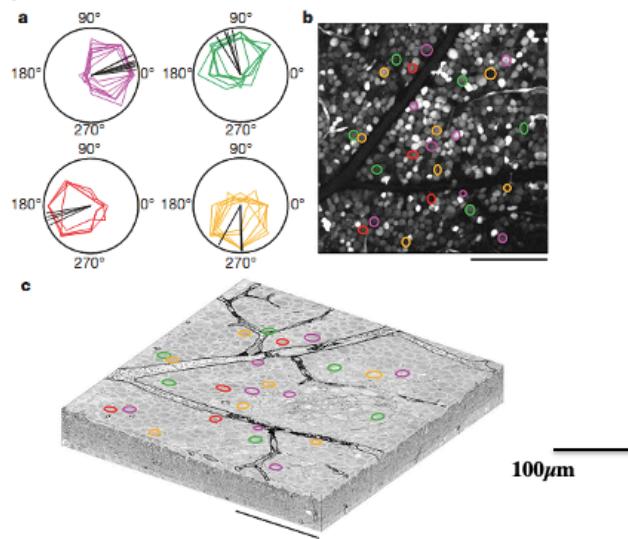
Kevan Martin – Zurich  
Winfried Denk – Heidelberg  
Jeff Lichtman - Harvard  
Sebastian Seung - MIT  
Mitya Chklovskii - Janelia Farm  
Clay Reid – Allen Inst.



a breakthrough

## Direction Selectivity in the Retina

- Combining Functional and Structural imaging

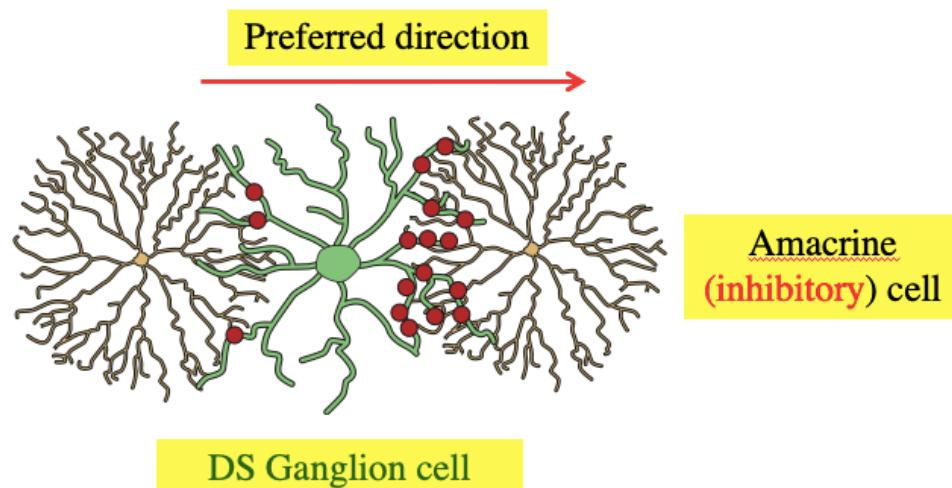


### Structural tracing using Serial Block-Face Electron Microscopy (SBEM)

reconstruct both the orientation selectivity of a particular cell

then reconstructing anatomy surrounding the cell (the environment of the cell in the level of synapse)

**Inhibition connects asymmetrically onto dendrites of DS retina ganglion cells**



there are more inhibitory synaptic inputs on the right than on the left

That is the source of the **selectivity**

That this point of light is moving in this direction, from left to right, it will first activate less inhibition onto this cell, then excitation will come to the cell and will tend to activate it.

If the input is coming from right to left, you will activate more inhibition, then the excitation will be vetoed by this inhibition.

#### Personal Comments

**The brain differs from other large physical systems**, in which the elementary units are simple and uniform (and their effect over the system is negligible). It is composed of neurons which are **inherently complex, dynamic and plastic units**, which form connected networks that exploit the impact of the individual neuron.

As with humans, the **complexity of the individual enriches the dynamics of the society (of neurons)** and enables it to learn, to successfully function in an unpredictable environment, and to create anew.

We need to **develop (conceptual/theoretical) tools** for connecting the “**low level**” **computations and learning capabilities performed by single neurons (and their synapses)** to the global **computational functions** of the nervous system- this is the central role of the new field of “computational neuroscience”

Only a very tight interaction between **theory/modeling and simulation**, and experiments will provide the (so very) missing breakthrough

# QUIZ

1. Which of the following (there can be more than one answer) are basic computations that brains perform:

- Figure-ground separation
- Classification of odors into types
- Calculating the number of elements in a group
- Calculating the exact velocity of a moving object

2. The Hubel and Weisel experiment about the response properties of cells in area V1 of the cat cortex showed:

- Neurons respond strongly (fire many spikes) to an oriented line moving in a specific direction.

3. Mark the correct answers about McCulloch and Pitts (M&P) model:

M&P model considers the neuron as a logical device with '0" and "1" (output) state and with E (excitatory) and I (inhibitory) input synapses.

In M&P model E (excitatory) synapses implement OR operation and I (inhibitory) synapses AND NOT operation

M&P model considers the spatial extent of the dendritic tree

M&P neuron makes use of the refractoriness of spike firing

4. Rall argued against the "point neuron" model because

Dendrites are non iso-potential electrical distributed devices

A significant portion of the current injected to the soma flows to the dendrites and do not remain in the soma

5. A Current injected in the middle of a dendrite

Will flow in both directions (centripetally to the soma and centrifugally away from the soma)

Will generate local voltage change which will attenuate with distance from the injection site

6. According to cable theory – mark all the correct sentences.

In short sealed-ended cylinders, voltage attenuates less steeply with distance compared to an infinitely long cylinder of same membrane properties and diameter.

In passive dendritic trees, the shape of the transient synaptic potential will change with distance from the synaptic site

At any location X, the change in axial current, is equal to the membrane current

Although the voltage change attenuates with distance from the dendritic input site to the soma, a significant portion of the synaptic current does reach the soma.

**X**The briefer the somatic EPSP, the more likely is that its origin is at distal location from the soma.

7. Comparing excitatory synaptic input triggered distally with identical synapse triggered directly in the soma

At the soma the EPSP from the distal synapse will be broader.

At the soma, the amplitude of the EPSP from the distal synapse will be smaller.

**X**At the soma, the time-to-peak is shorter for the distal synapse.

**X**At the soma, the EPSP from the distal synapse will be narrower.

8. Mark the correct sentences

Proximal inhibitory synapses are more global in their inhibitory effect (over excitatory synapses) than do more distal inhibitory synapses

Electrically distributed dendrites enable the neuron to perform local nonlinear operations (e.g., non-linear summation of synaptic inputs)

**X**The only computation that a neuron could perform is AND, OR and AND NOT logical operations

9. Rall showed that:

Activation of excitatory synapses in the distal-to-proximal temporal order results with a larger voltage change in the soma

One could build a direction selective neuron using only passive dendrites and orderly activated excitatory synapses

**X**Activation of inhibitory synapses in the proximal-to-distal order will result with large depolarization in the soma

**X**Activation of excitatory synapses in the proximal-to-distal temporal order results in a delayed and briefer EPSP in the soma

**X**Activation of excitatory synapses in the proximal-to-distal temporal order results in a delayed and broad EPSP at the soma

10. Enhanced optical resolution using two photon Ca<sup>+2</sup>-imaging (the work of Arthur Konnerth and team) has shown that:

The synaptic inputs to an orientation selective cell in mouse V1 are orientation selective, with a variety of different orientation selective cells impinging on the post-synaptic L2/3 dendrites

In V1 of the mouse, L2/3 cell are orientation selective

**X**That the orientation selectivity of an L2/3 cell may plastically change

**X**A particular layer 2/3 pyramidal cell in mouse V1 interact synaptically only with cells having the same orientation selectivity

11. Using the “connectomics” technique for direction selective ganglion cell (DSGC) in the retina, it was found that

That more inhibitory contacts are formed on the dendritic side of the DSGs that is in the null direction of this DSGC