Pre-Meeting Course: **Engineering principles of DBS and SCS in clinical practice: General introduction and emerging concepts**, Jan 12, 2023
Course Directors: Marom Bikson and Scott Lempka

Lecture 1: **Neurostimulation fundamentals: Dose, current flow, and neural activation**

Marom Bikson

Disclosure

The City University of New York: Patents on brain stimulation.
Soterix Medical: Produces tDCS and High-Definition tDCS.
Grants, assigned inventions, and/or serves SAB for SafeToddles, Boston Scientific, GlaxoSmithKline, Biovisics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple

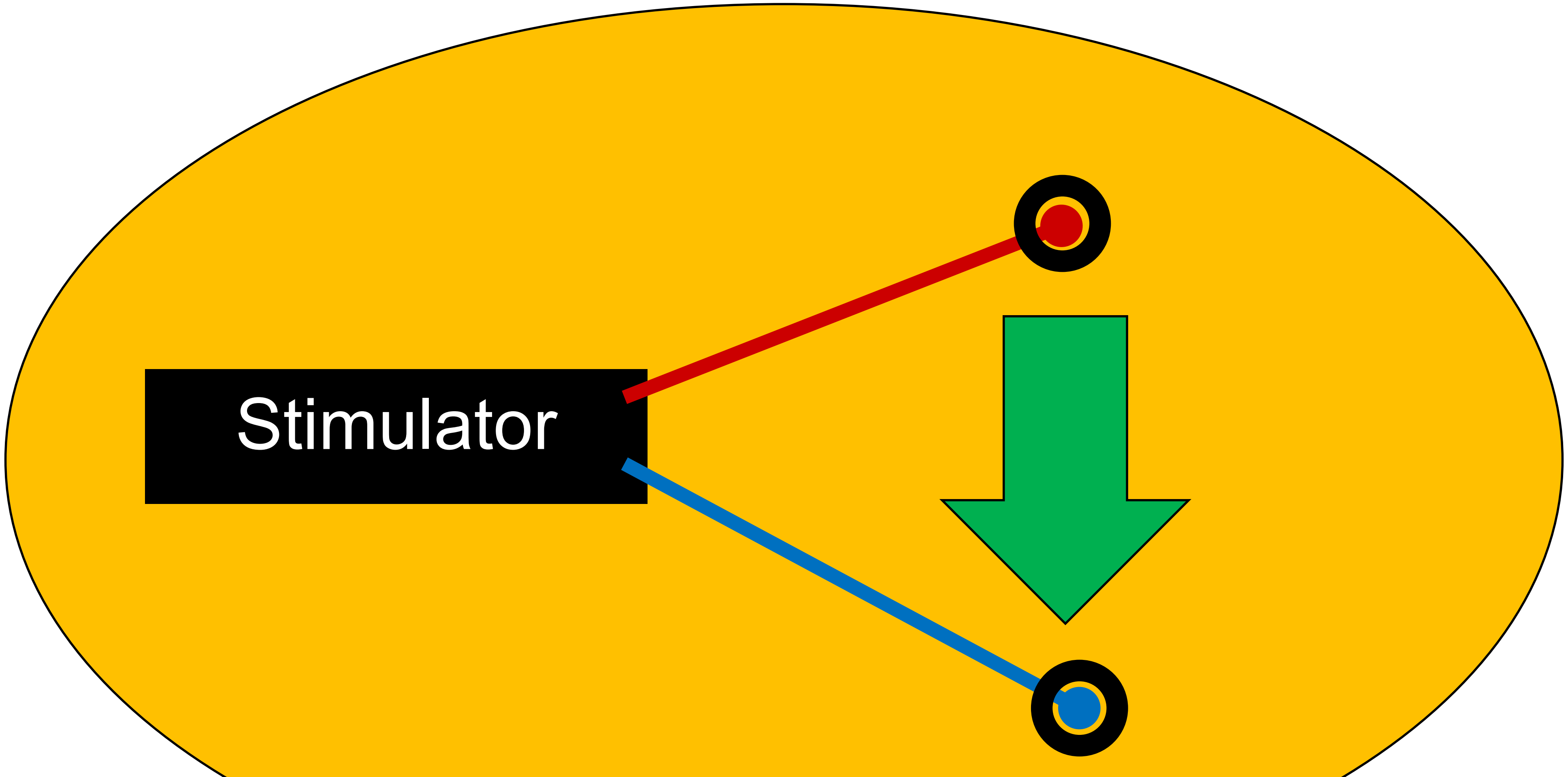
Support

NYS DOH, NIH (NIMH, NINDS) – *BRAIN Initiative*, NSF, Grove Foundation, Harold Shames, CCNY Fund, 21st Century Fund

Slides @MaromBikson

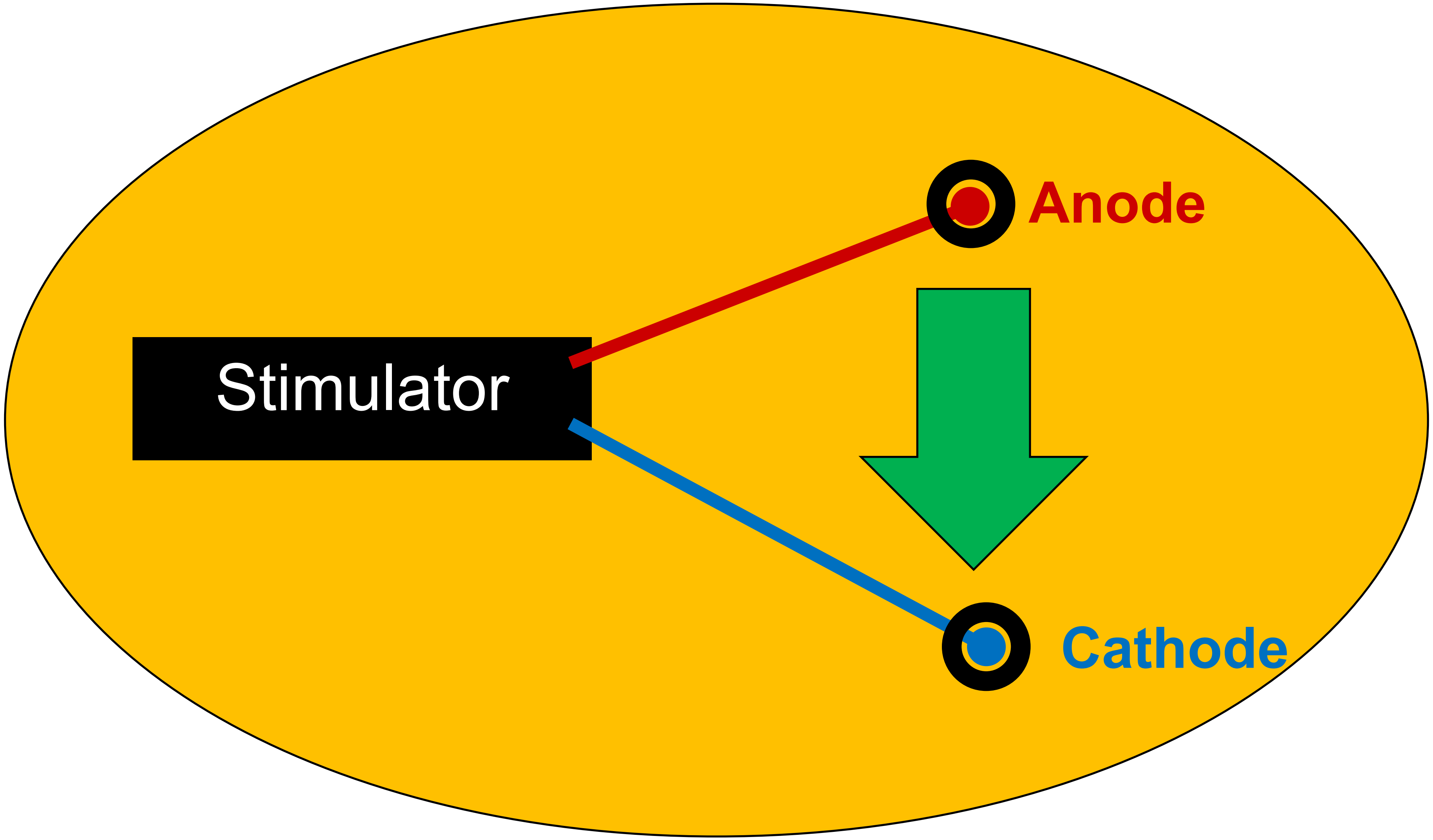
Part 1: Electrodes, current flow patterns, current density, electric field, tissue resistivity and impedance

Connecting an electrical stimulator to the body produces current flow through the body

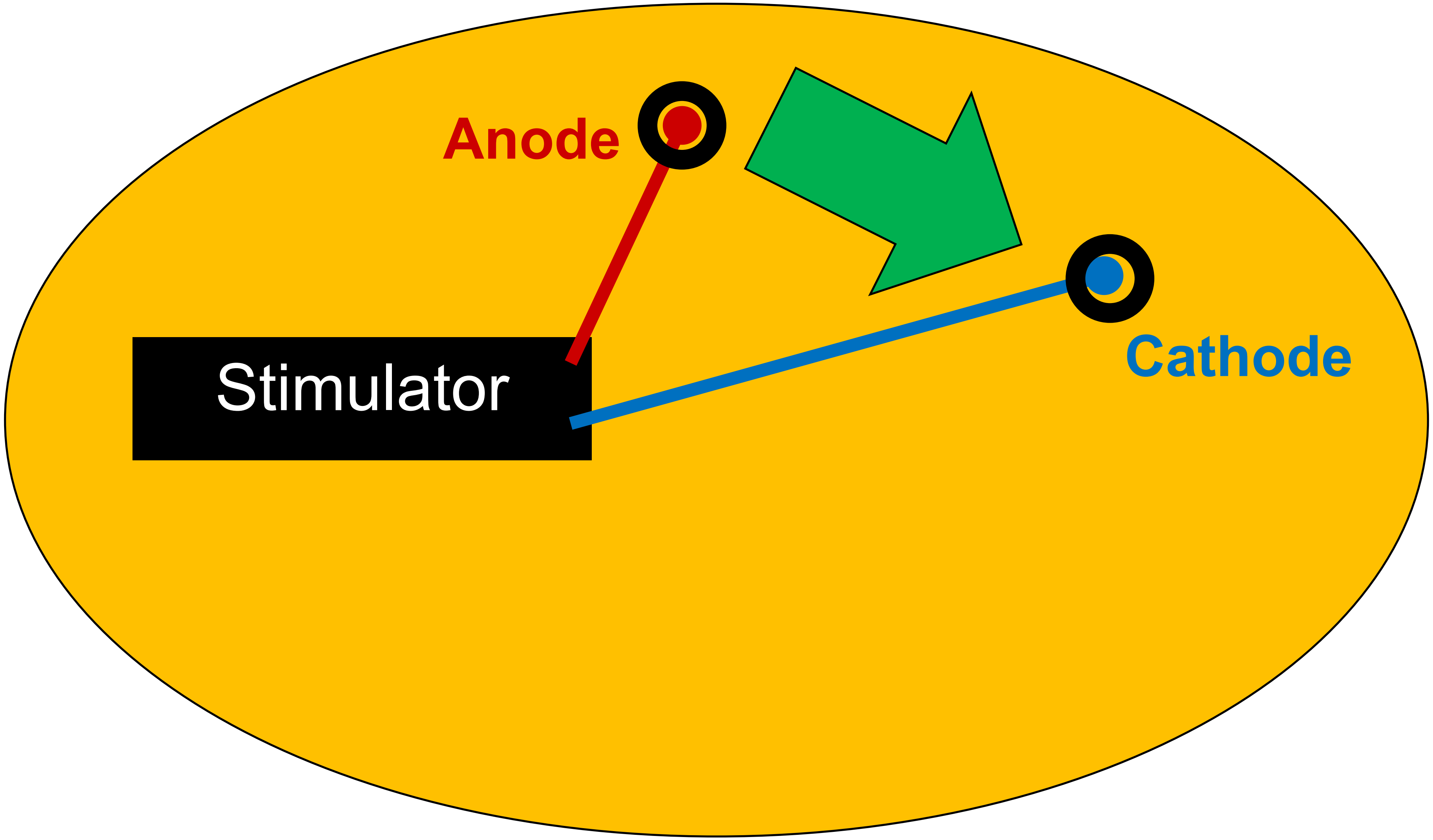


Current flows from the stimulator, through the wires (leads) and to exposed metal contacts (**Electrodes**)

Current flows from the positive Electrode (Anode) to the negative Electrode (Cathode)



The position of the electrodes determines which parts of the body are exposed to current flow



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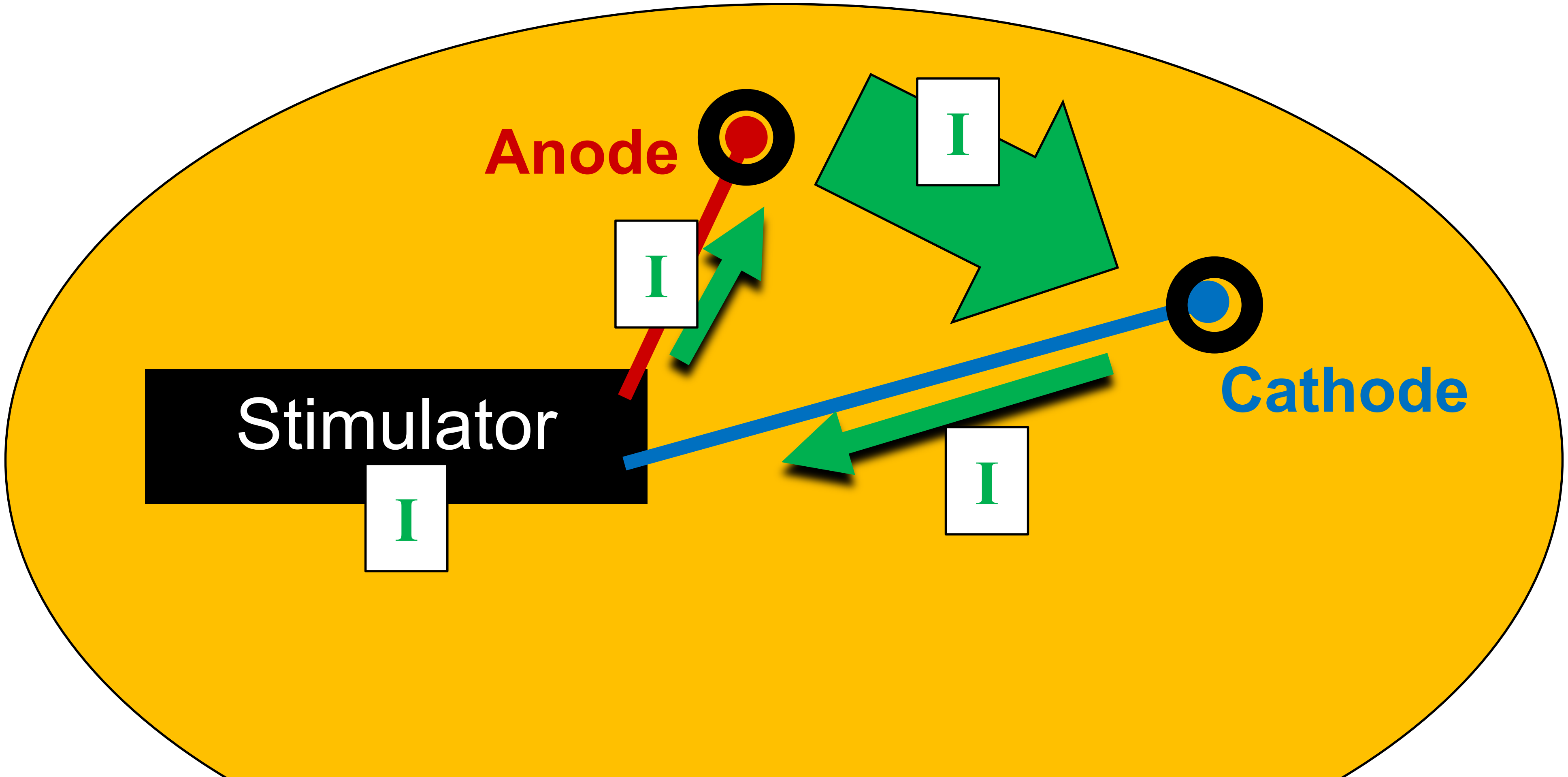
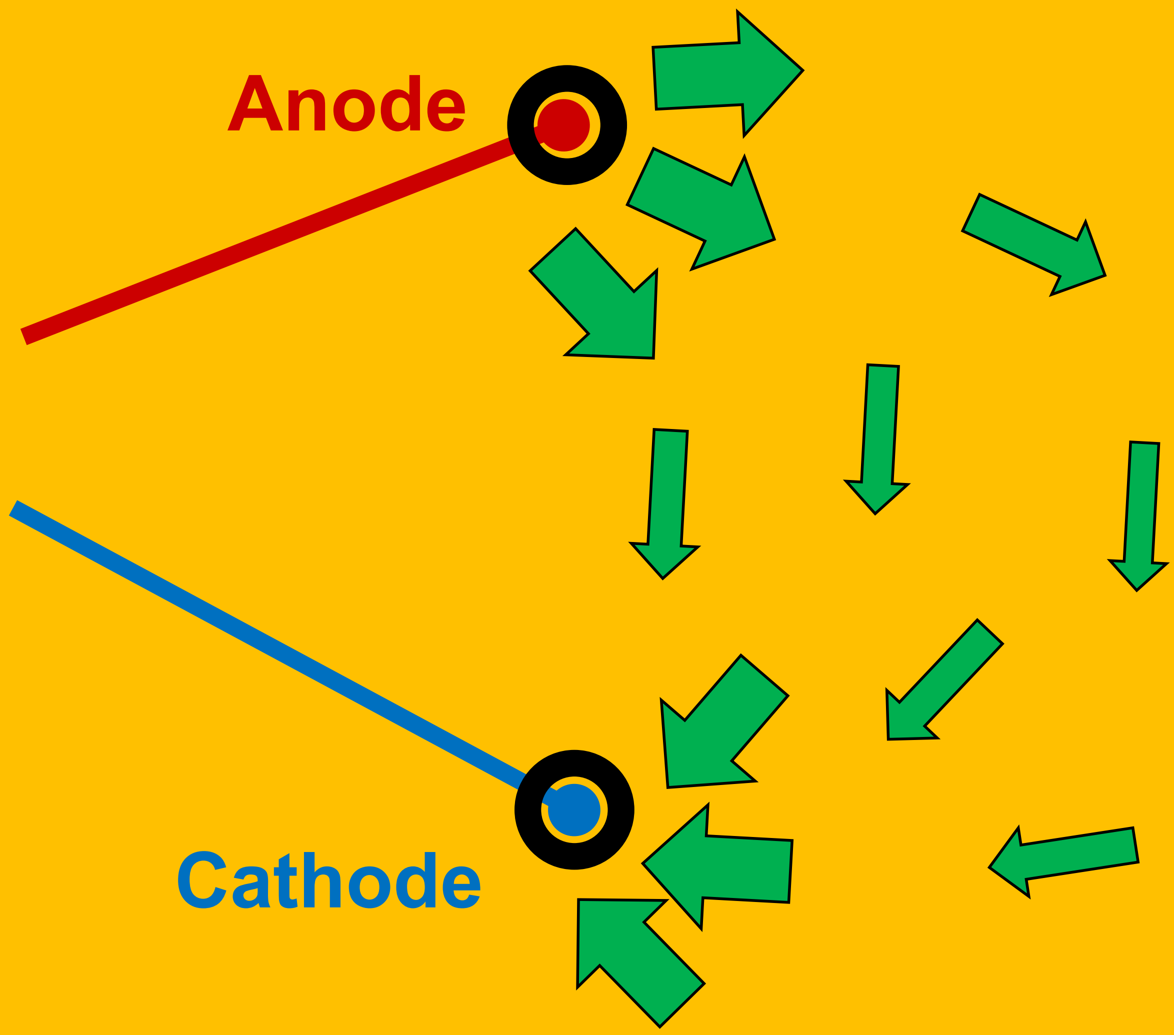


The total current produced by the stimulator (I in mA) is passed through the body

But the current flow through the body is not even, some part get more **Current Density** then others



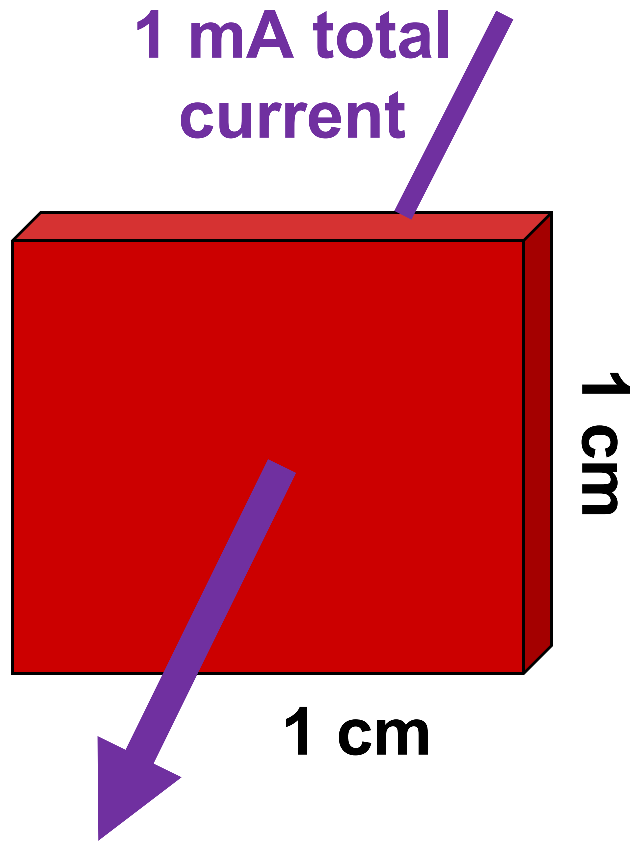
Current does not flow in a straight thin line between electrodes, but is **diffused** through the tissue.

The parts of the body near the electrodes get (much) more **Current Density.**

Current Density is current per area (unit of mA per cm^2)

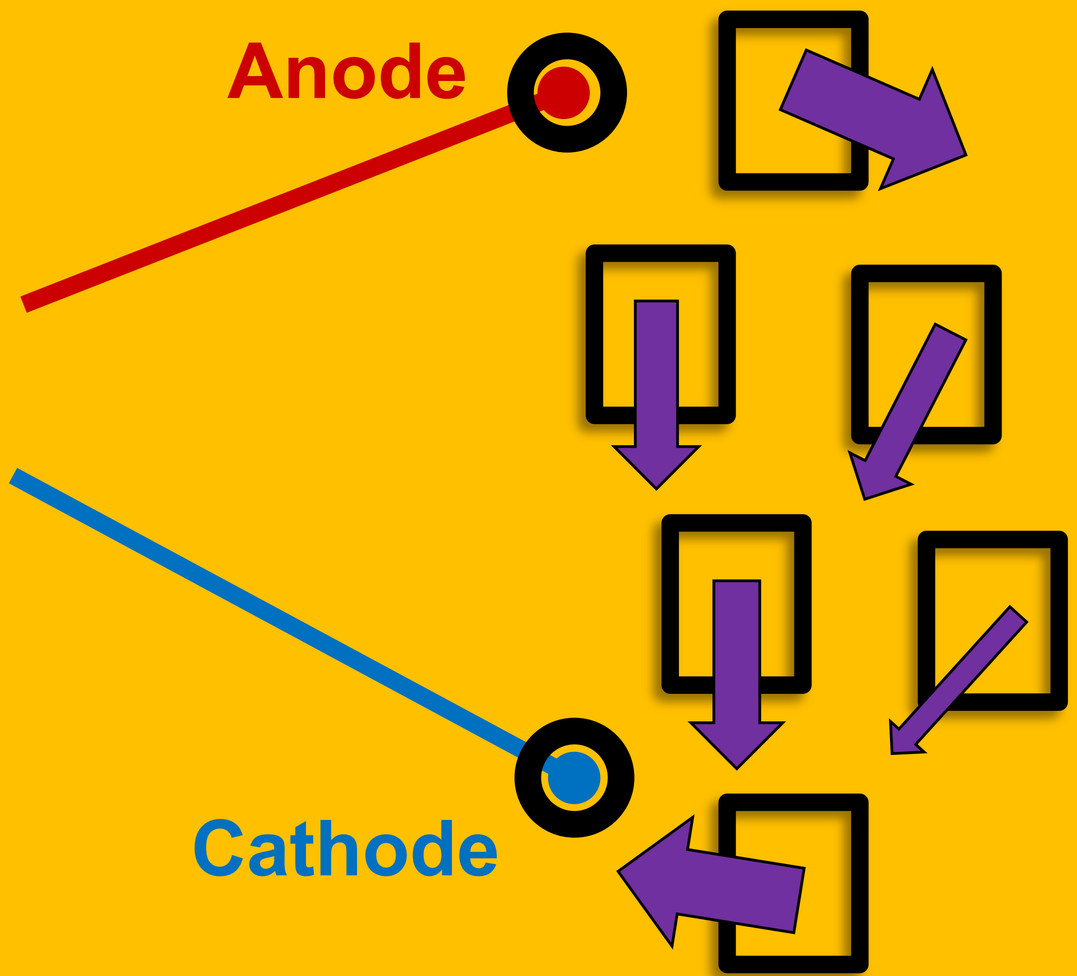
For example, an electrode has an area of 1 cm^2 with 1 mA of current passed through it.
What is the electrode Current Density*?

1 mA current / 1 cm^2 area = 1 mA / cm^2



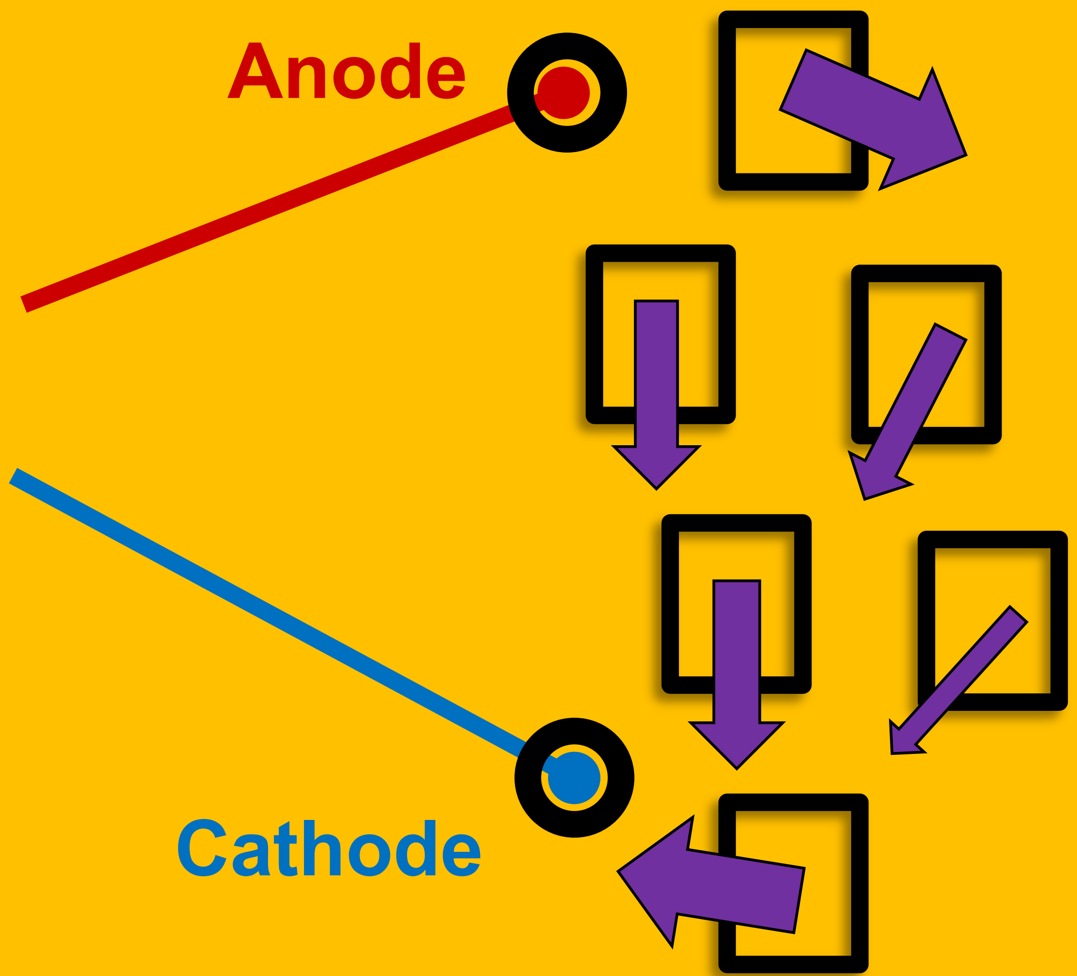
*Assume uniform current density on the electrode surface (no hot spots)

But the current flow through the body is not even, some part get more **Current Density** then others



In each part of the tissue we can describe the local **Current Density**

The arrow size illustrates variation in current density at each location



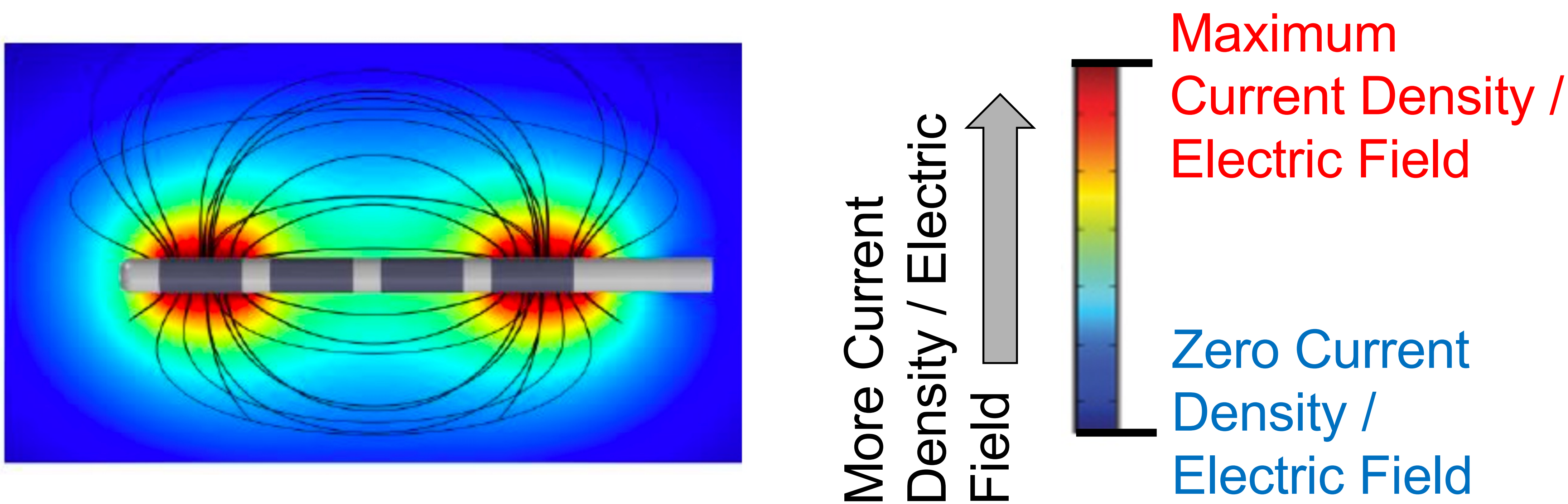
Current Density has a magnitude in each location, but it also has a direction

Current Density is related to Electric Field by a simple equation.

Current Density * **Resistivity** of Tissue = **Electric Field**

Current Density or **Electric Field** is graphed using a false color map that shows the magnitude at each location.

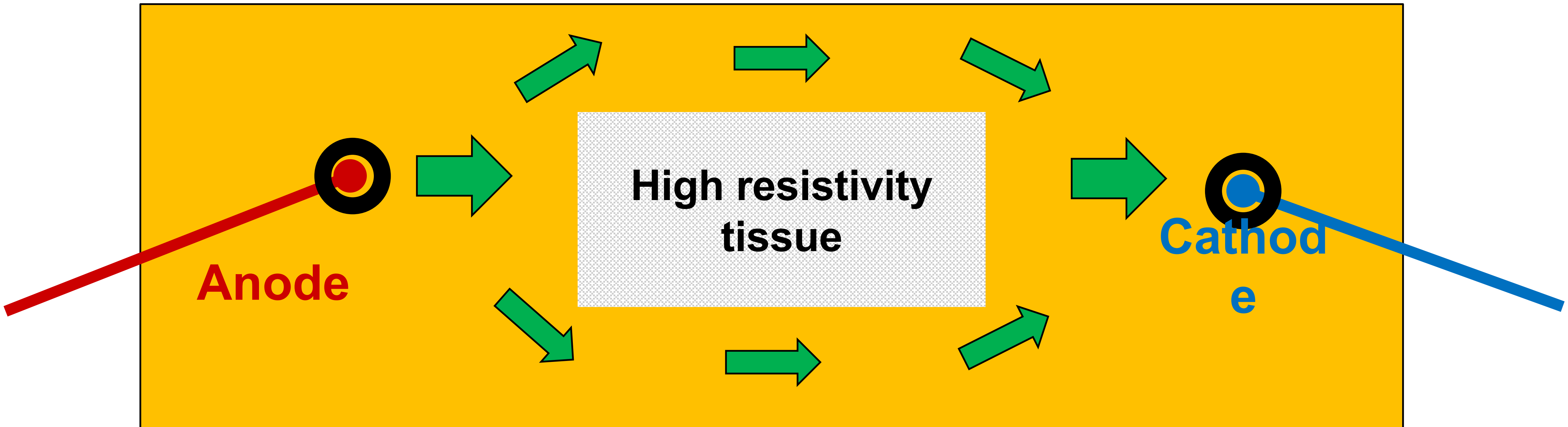
Sometimes **Arrows** (or lines) are added to show direction.



Resistivity is a property of tissue.

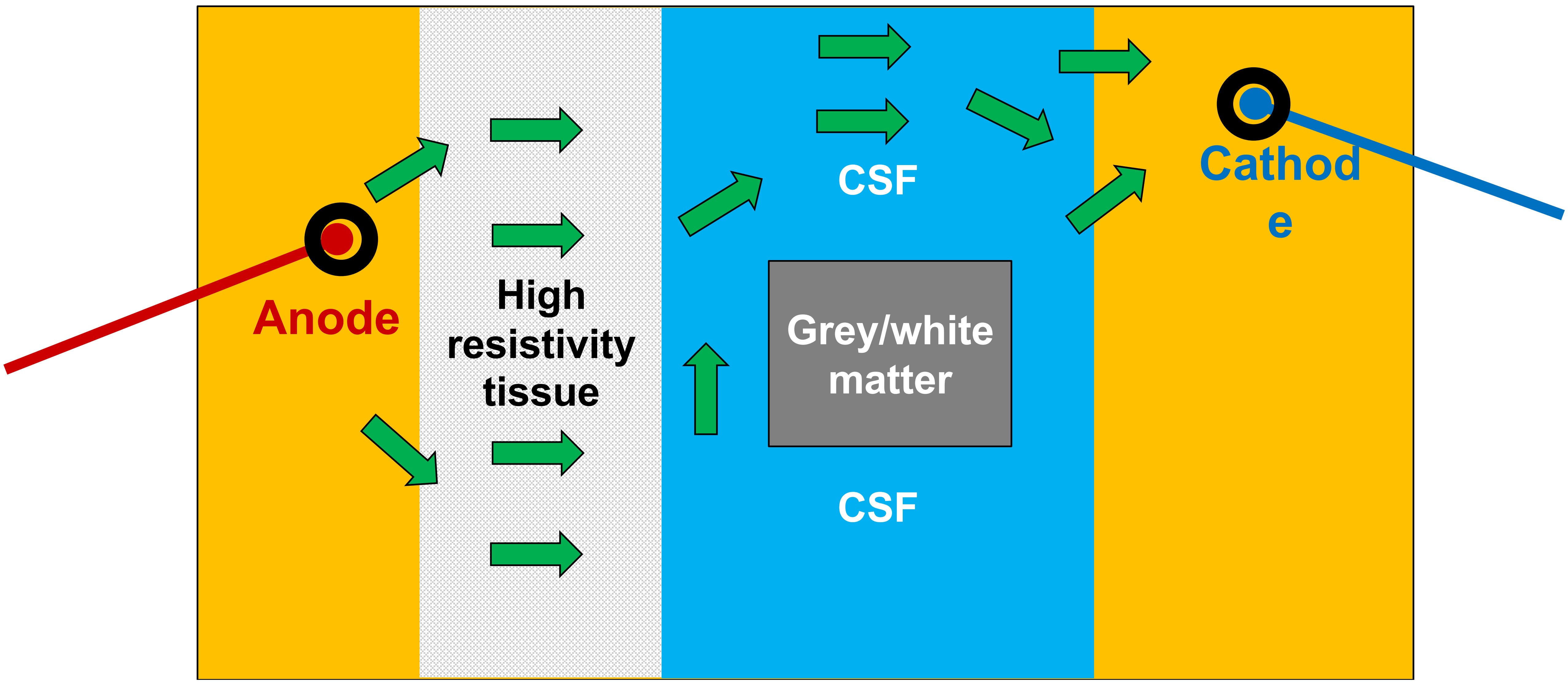
(units of ohm meter)

Some tissue has high resistivity like bone or fat. Some tissue has low resistivity like CSF. Grey and white brain matter has intermediate resistivity.



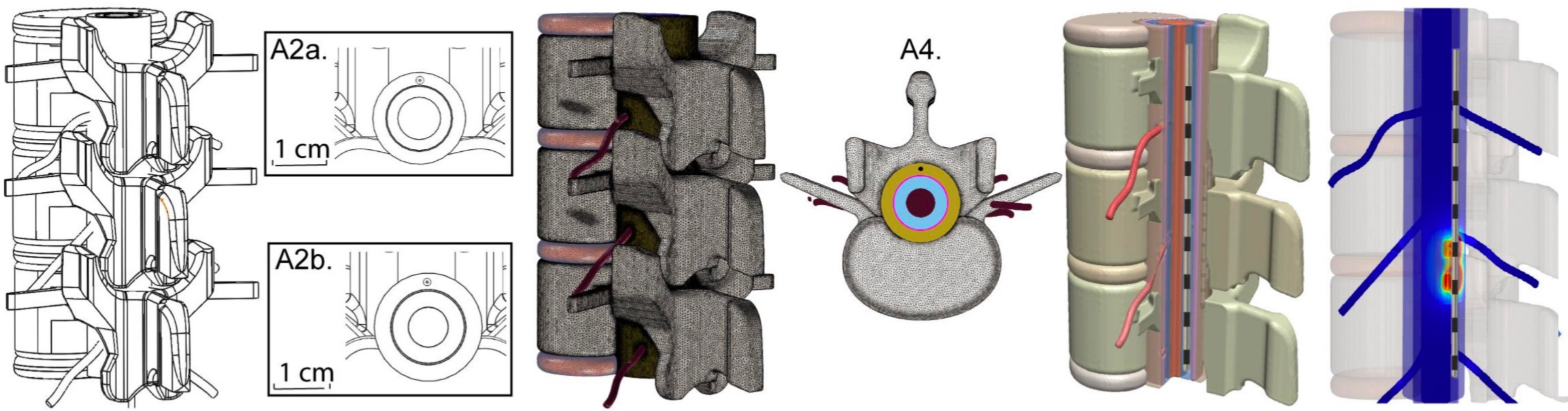
When current flows from one electrode to the other through the body, the pattern of current flow favors going through tissues with low resistivity.

Details of body anatomy and associated tissue **resistivity** can lead to **current patterns** that are hard to guess.



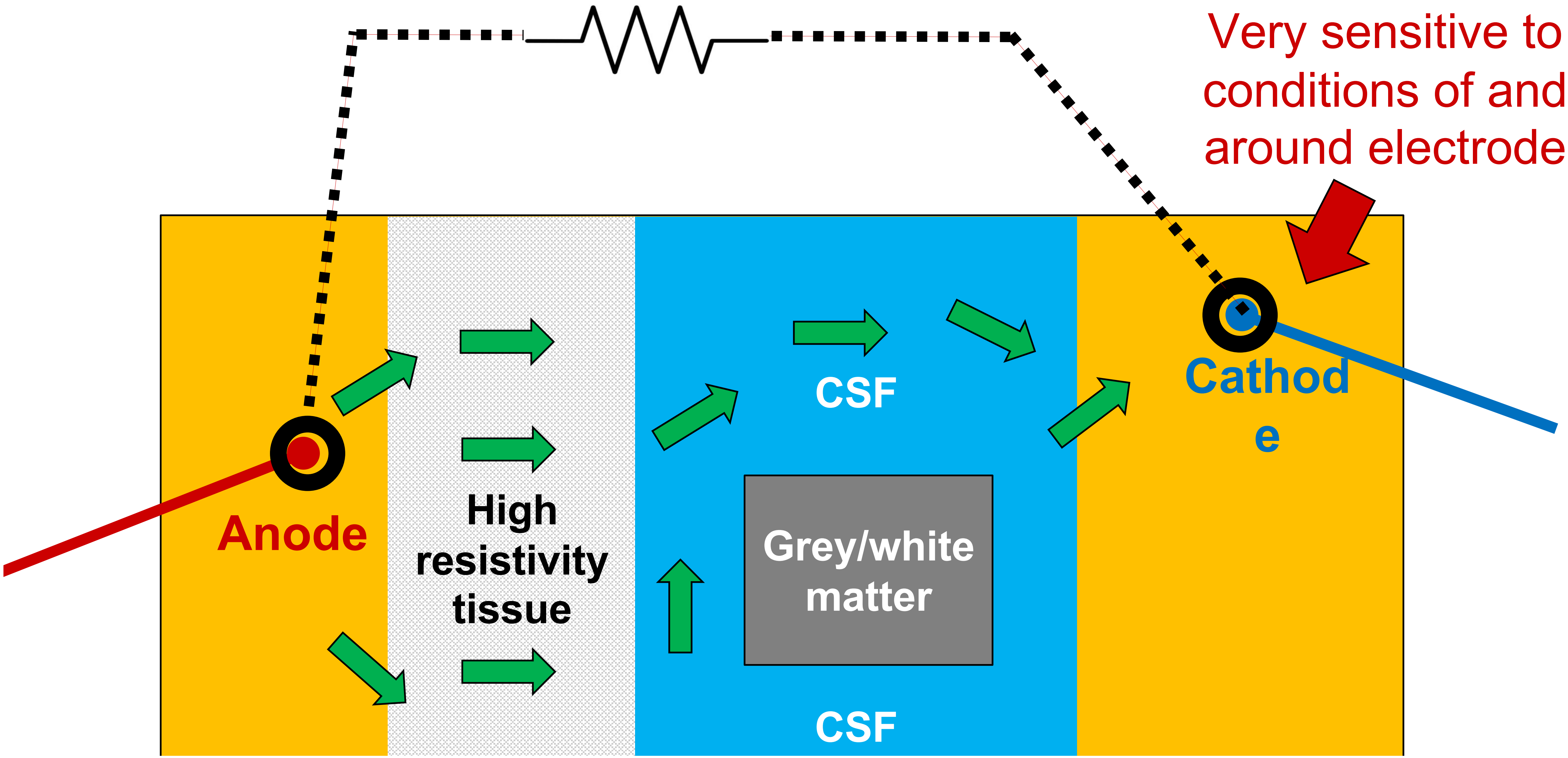
Computational models (and programming software) predict the complex pattern of current flow through tissue.

Models need to know tissue anatomy, the resistivity of each tissue, and the position of electrodes



Model anatomy may be geometric (using CAD software) or image-derived (segmented from scans of anatomy). The method to compute current flow used Finite Element Methods (FEM).

Resistance / Impedance (Ohms) is a single number (between a pair of electrodes) that reflects all tissues.



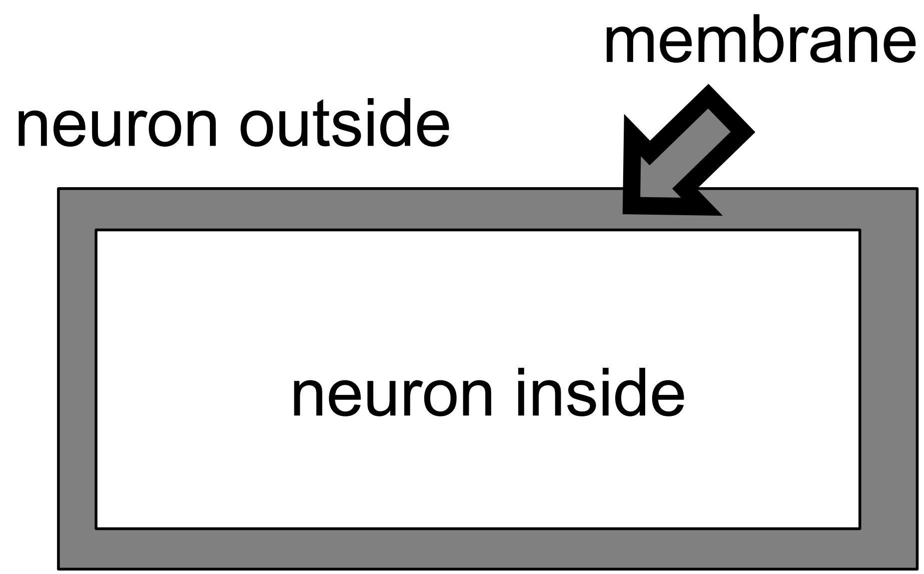
Part 2: Membrane polarization, action potential threshold, Volume of Tissue Activated

All cells (neurons) have a resistive outer **membrane**.
The shape of the membrane is the shape of the neuron.

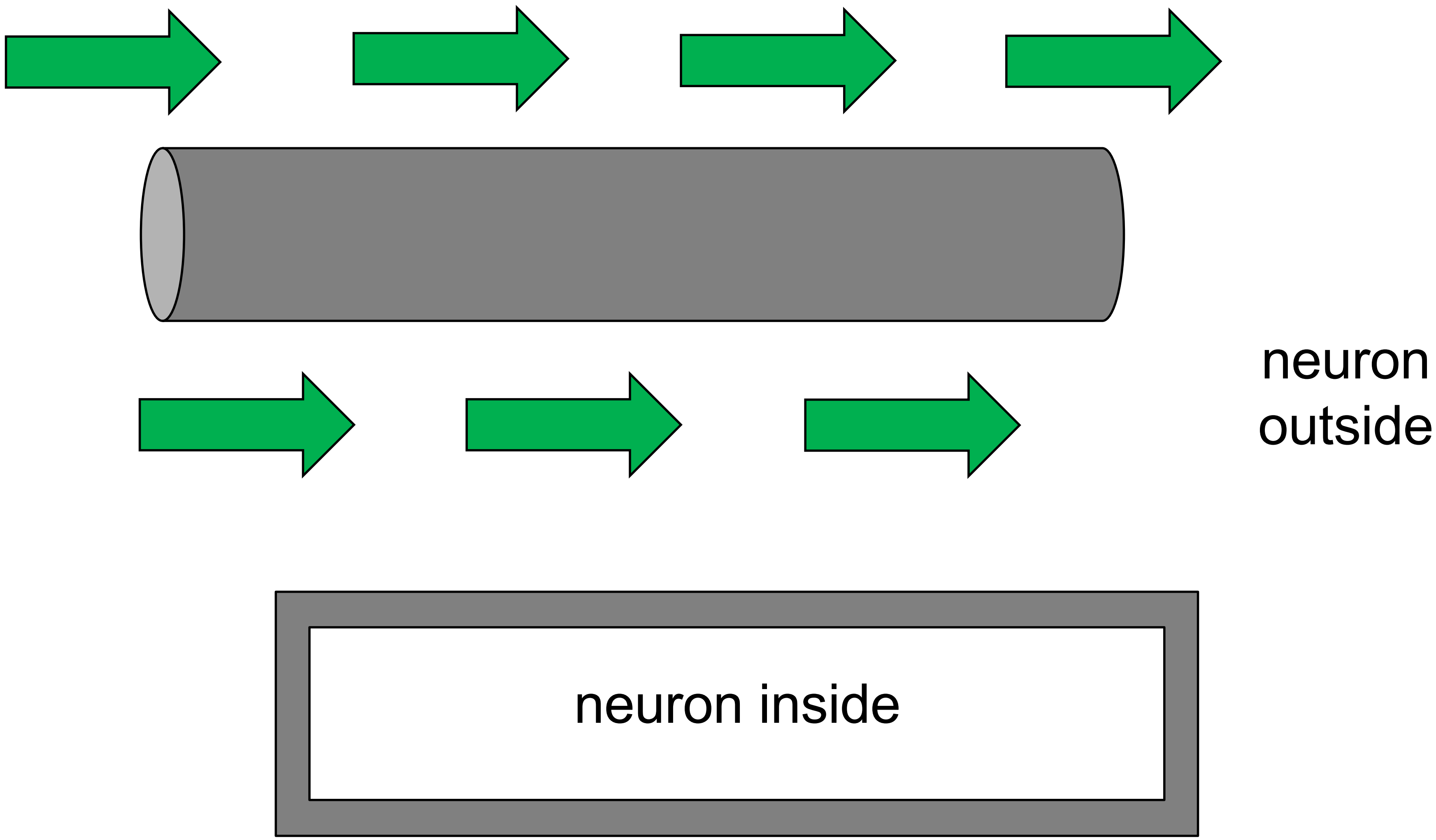
All cells (neurons) have a resistive outer **membrane**. The shape of the membrane is the shape of the neuron.

Lets assume our neuron is a tube. The tube has a shell which is the membrane.

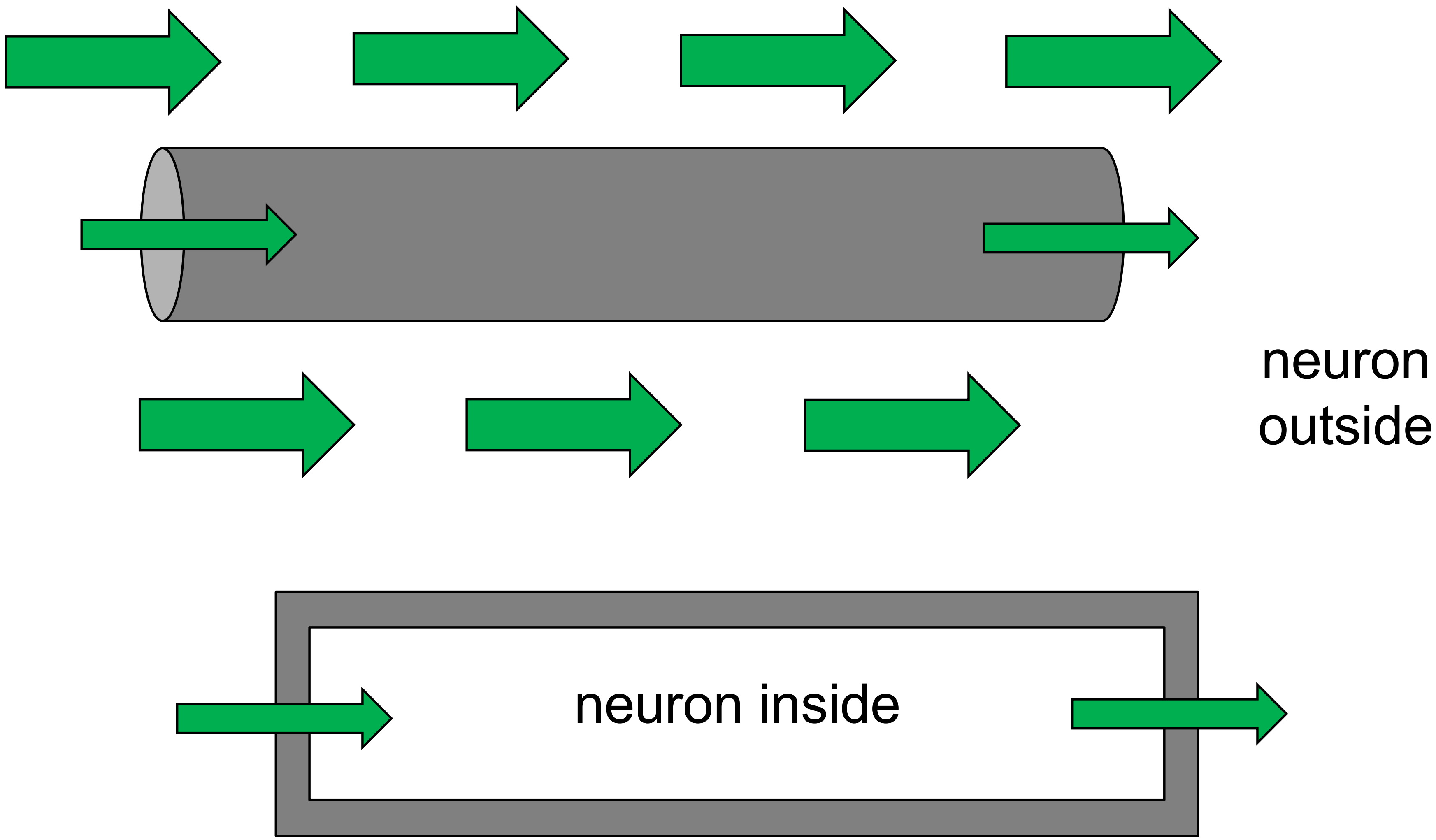
Cross section of tube neurons:



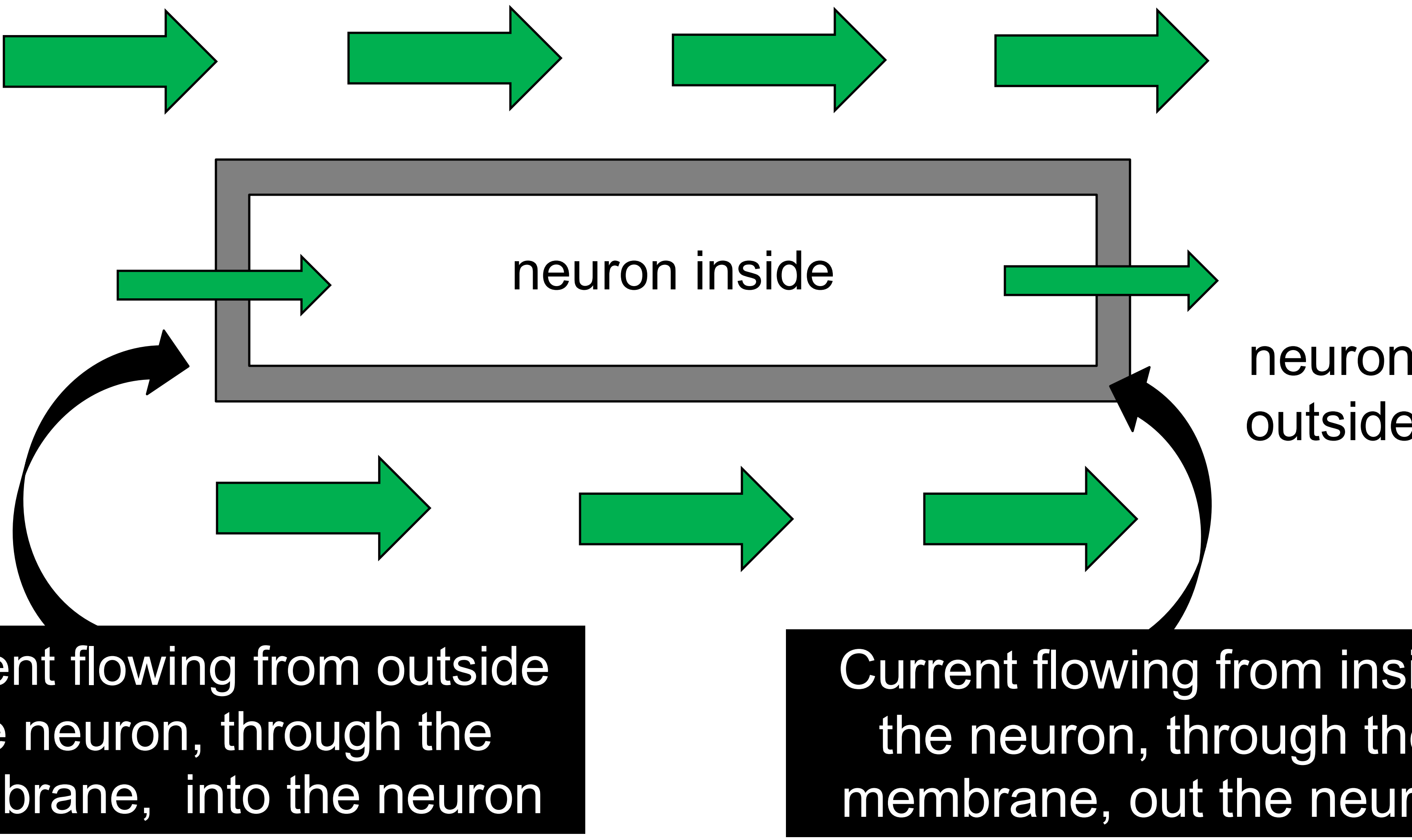
Current flow is generated around the neuron. There is a current density (or electric field) in the extracellular space around the neuron.



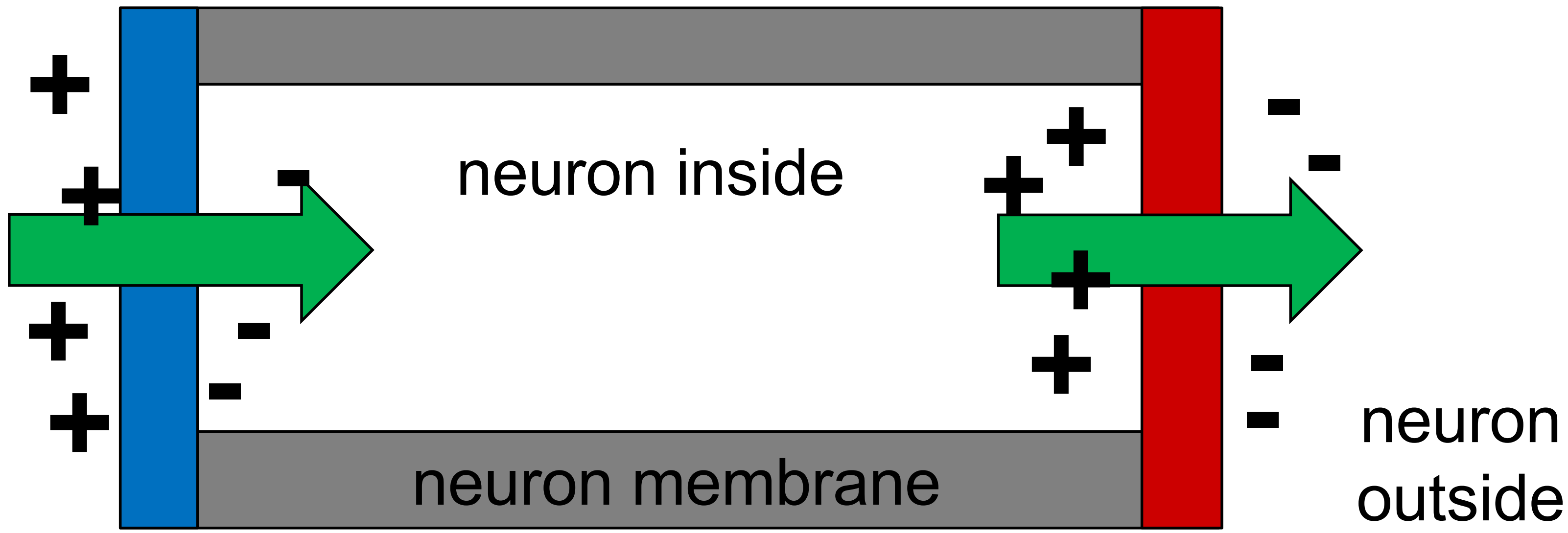
Most of the current generated outside the neuron flows around the neuron.
But some crosses through the neuron.



One part of the neuron membrane will have **current flowing in**, another part of the neuron membrane will have **current flowing out**



Current flowing into the neurons **hyperpolarizes**.
Current flowing out of the membrane **depolarizes**.



Current flowing into the neurons **hyperpolarizes**.
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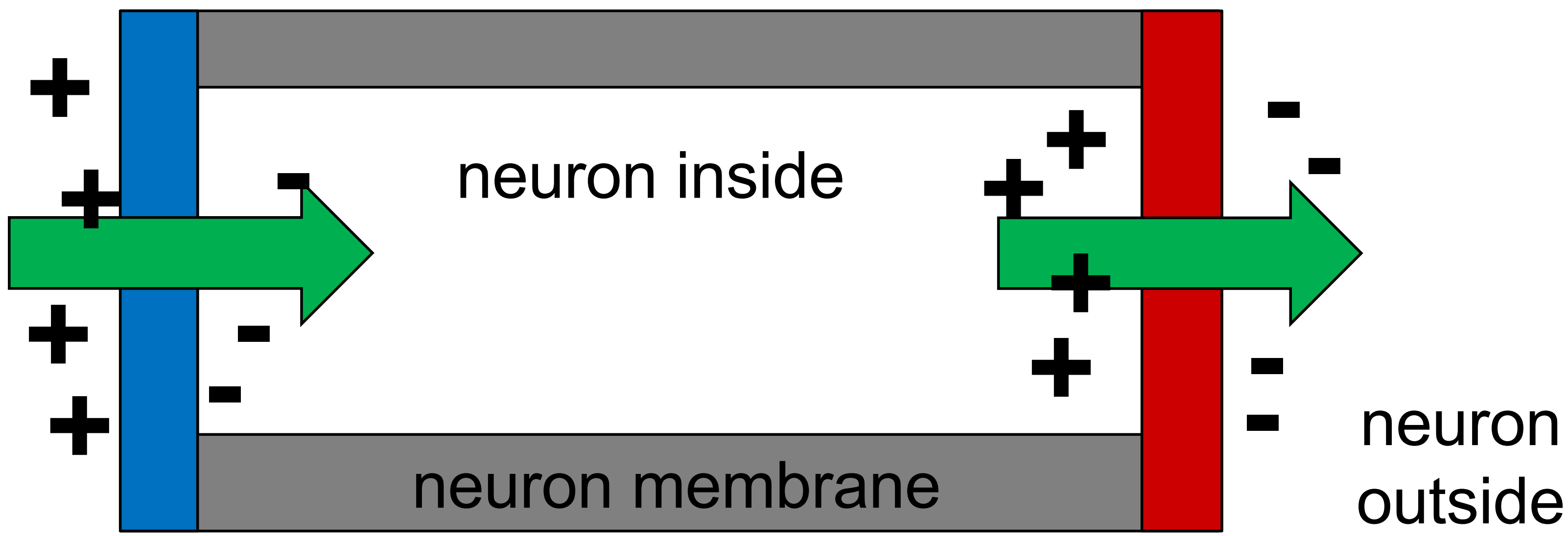
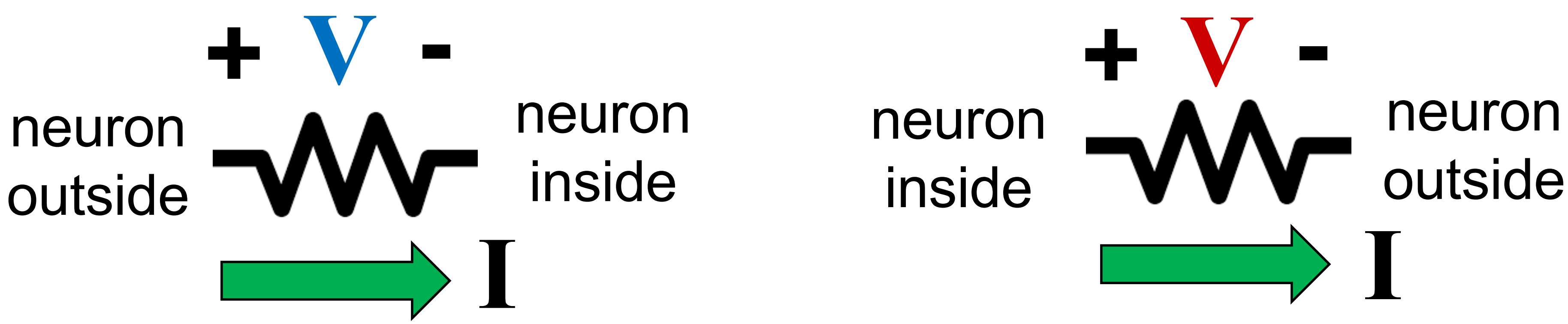
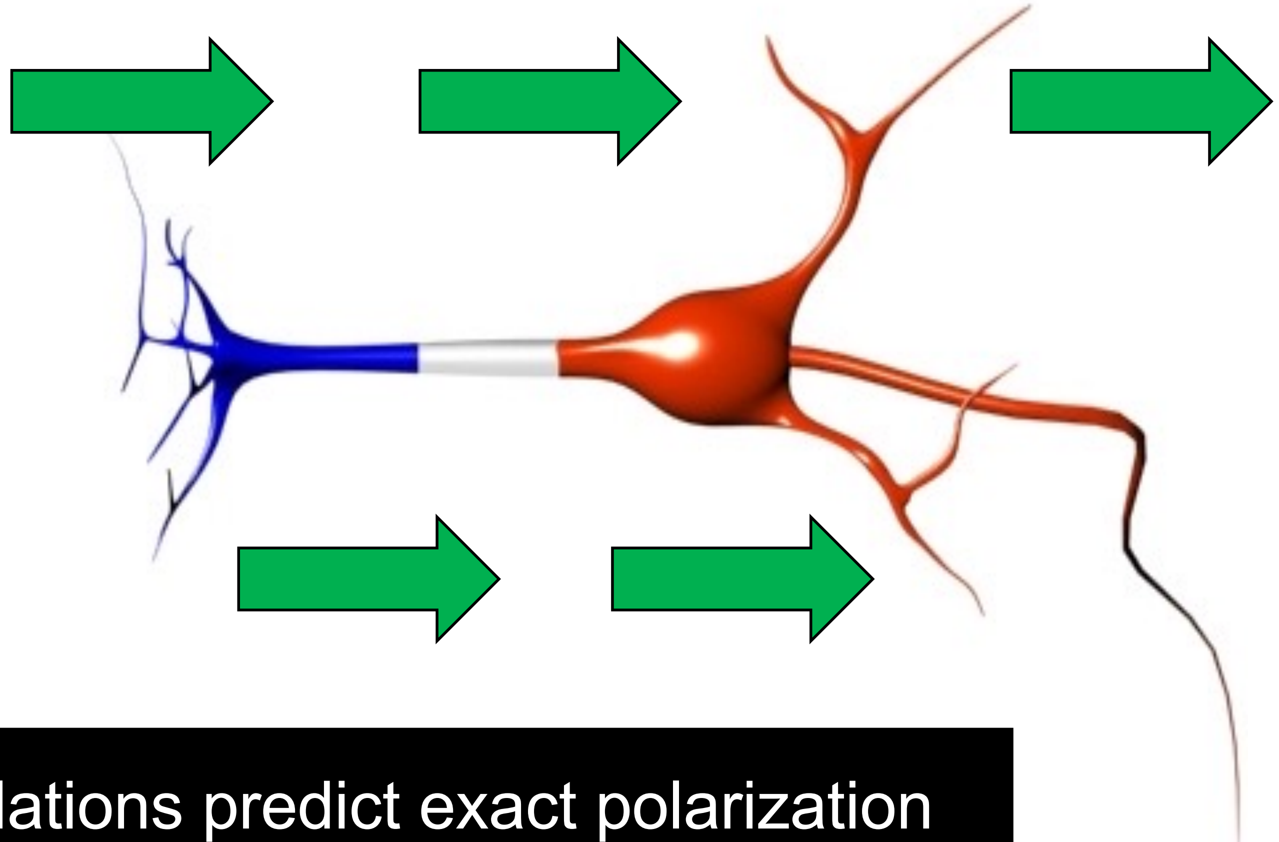


The direction of polarization is consistent with Ohms law

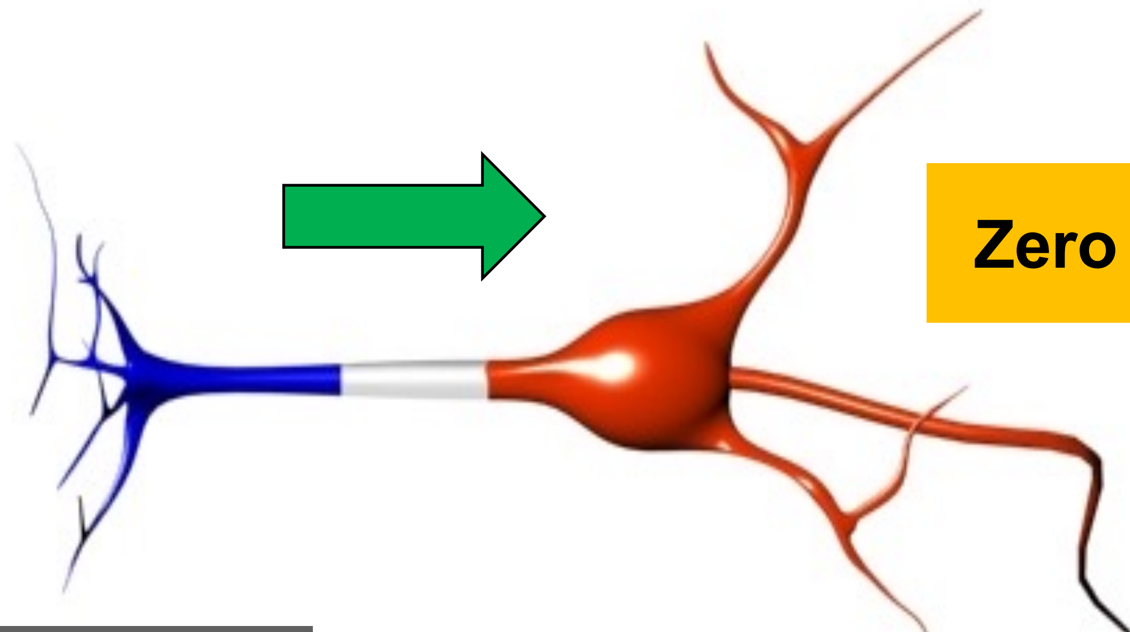


The idea of current flowing into the neurons **hyperpolarizing** and current flowing out of the membrane **depolarizing** extends to more realistic neurons shapes.



Computer simulations predict exact polarization based on neuron shape and membrane properties.

For example: A stimulation device generates **Current Density** around a neuron of 1 mA/m^2 (or an Electric field of 1 V/m). The results is -20 mV **hyperpolarization** in some membrane parts (compartment) of the neuron, and +20 mV **depolarization** other membrane parts.

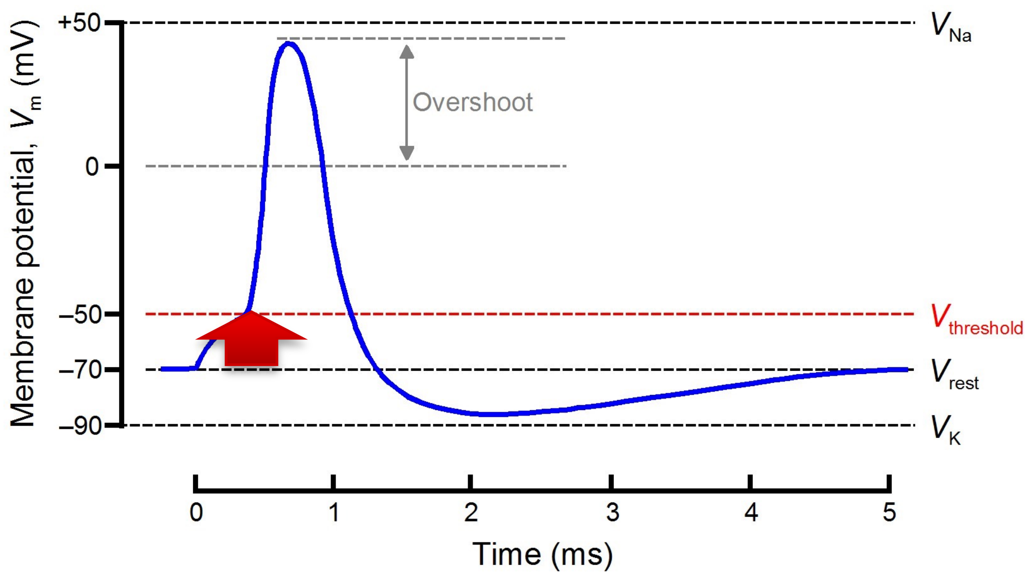


Zero sum??

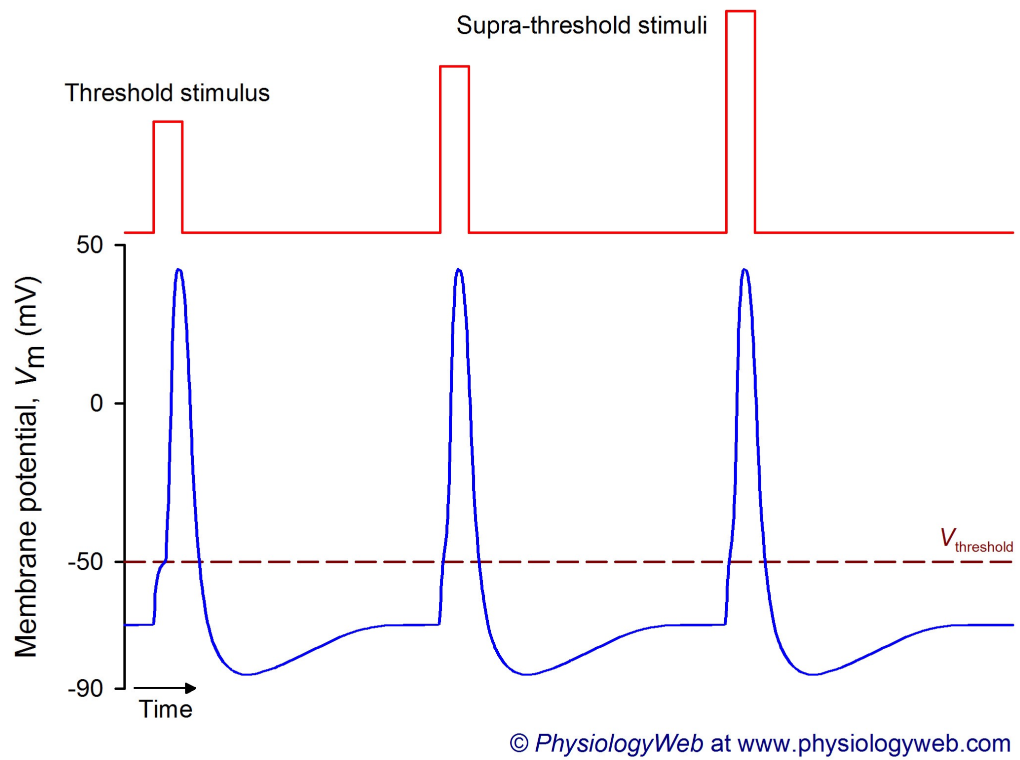
-20 mV hyper-polarization: membrane potential goes from -70 mV to -90 mV

+20 mV de-polarization: membrane potential goes from -70 mV to -50 mV

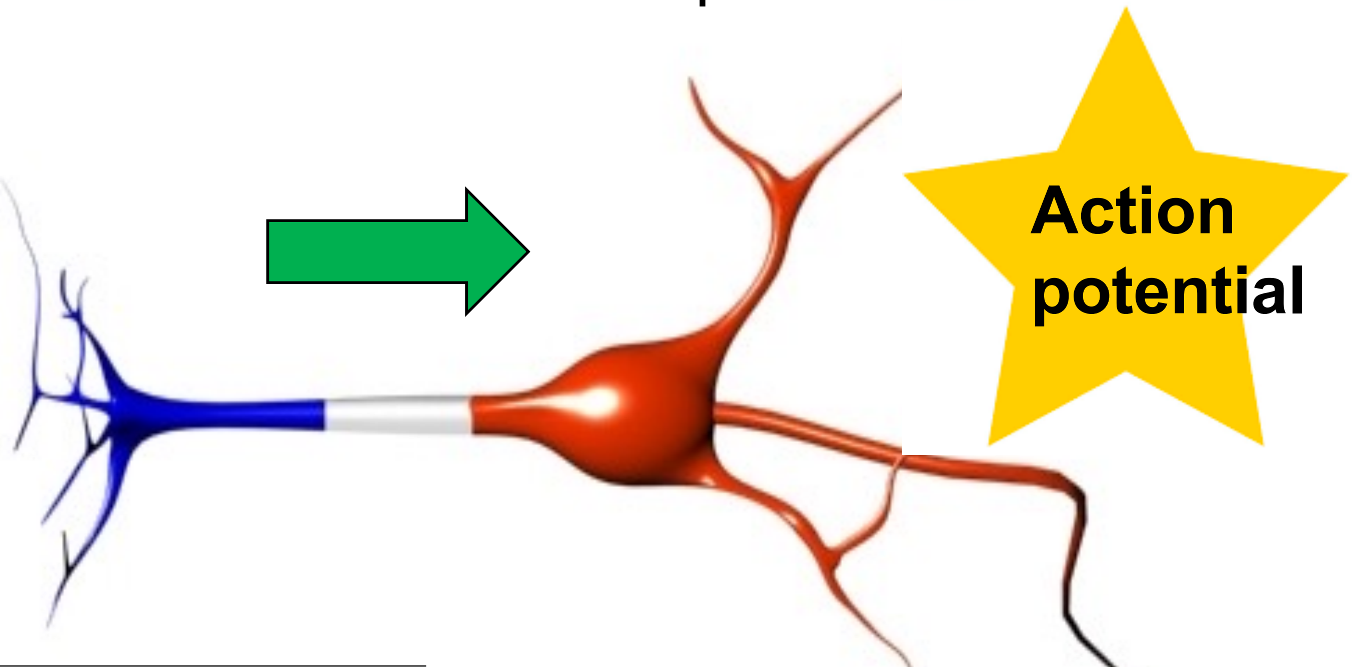
- To make a neuron fire, stimulation needs to bring the membrane potential to threshold.



- Action potentials are all or none



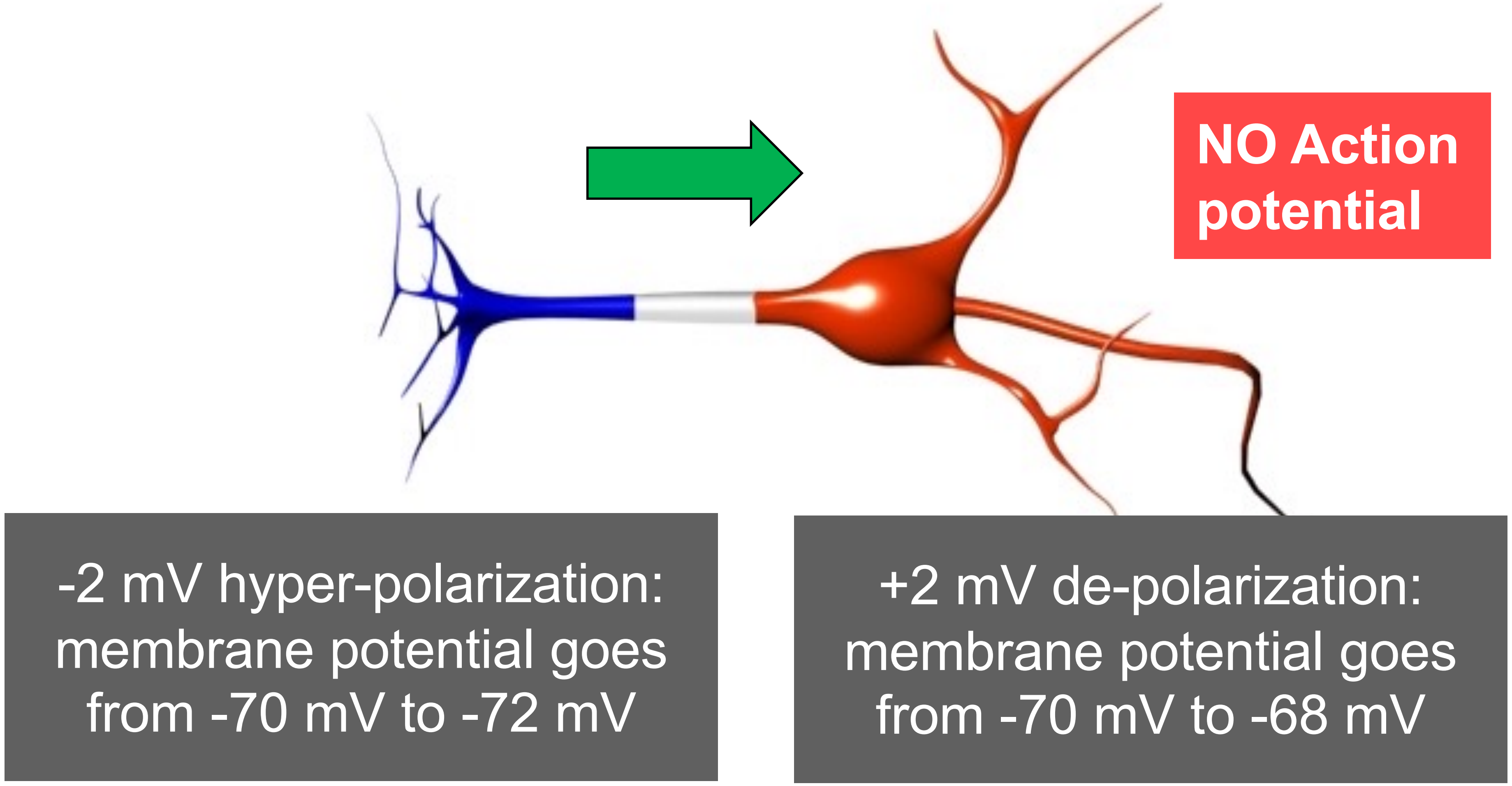
For example: A stimulation device generates **Current Density** around a neuron of 1 mA/m^2 (or an Electric field of 1 V/m). The results is -20 mV **hyperpolarization** in some membrane parts (compartment) of the neuron, and +20 mV **depolarization** other membrane parts.

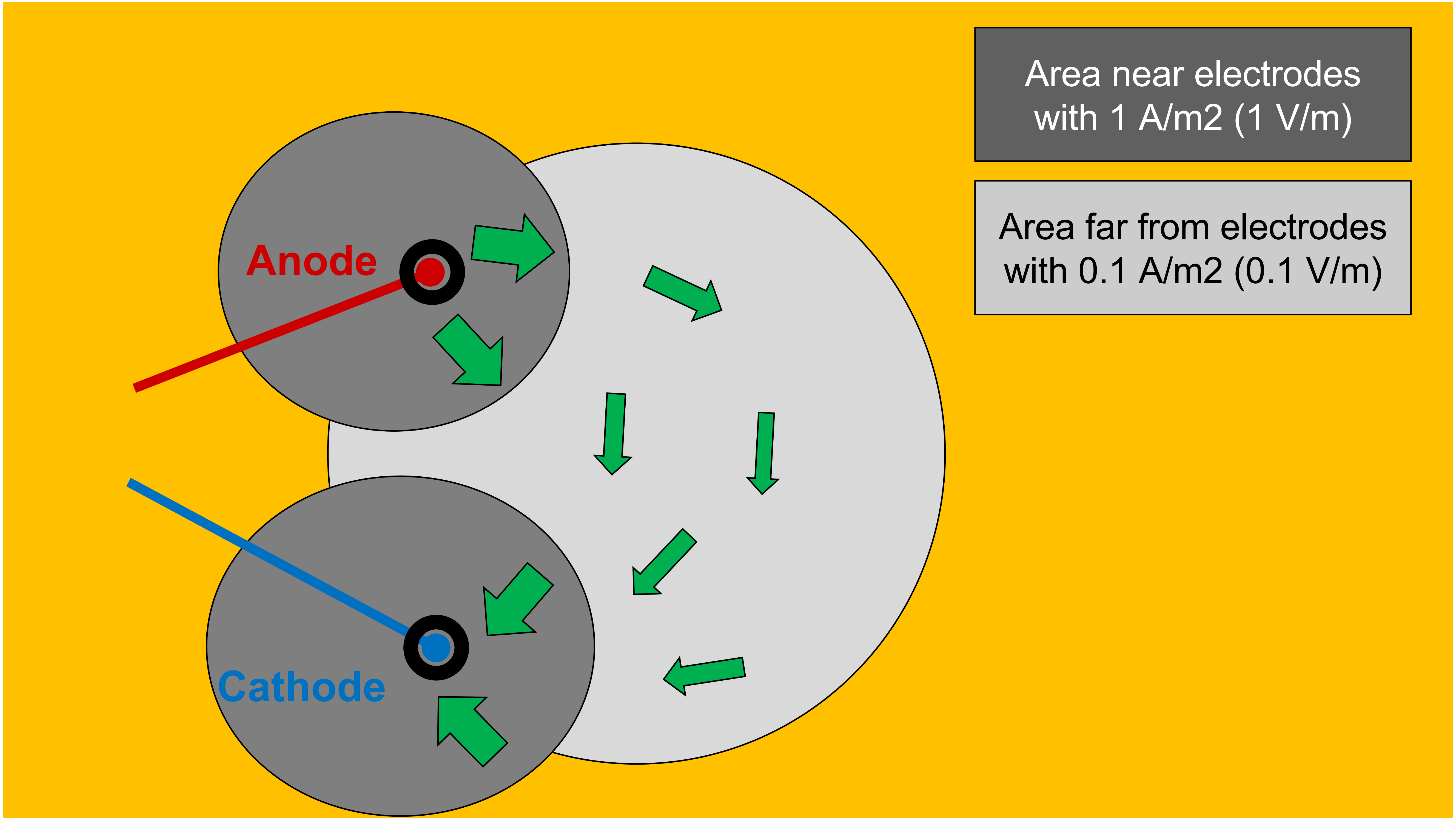


-20 mV hyper-polarization: membrane potential goes from -70 mV to -90 mV

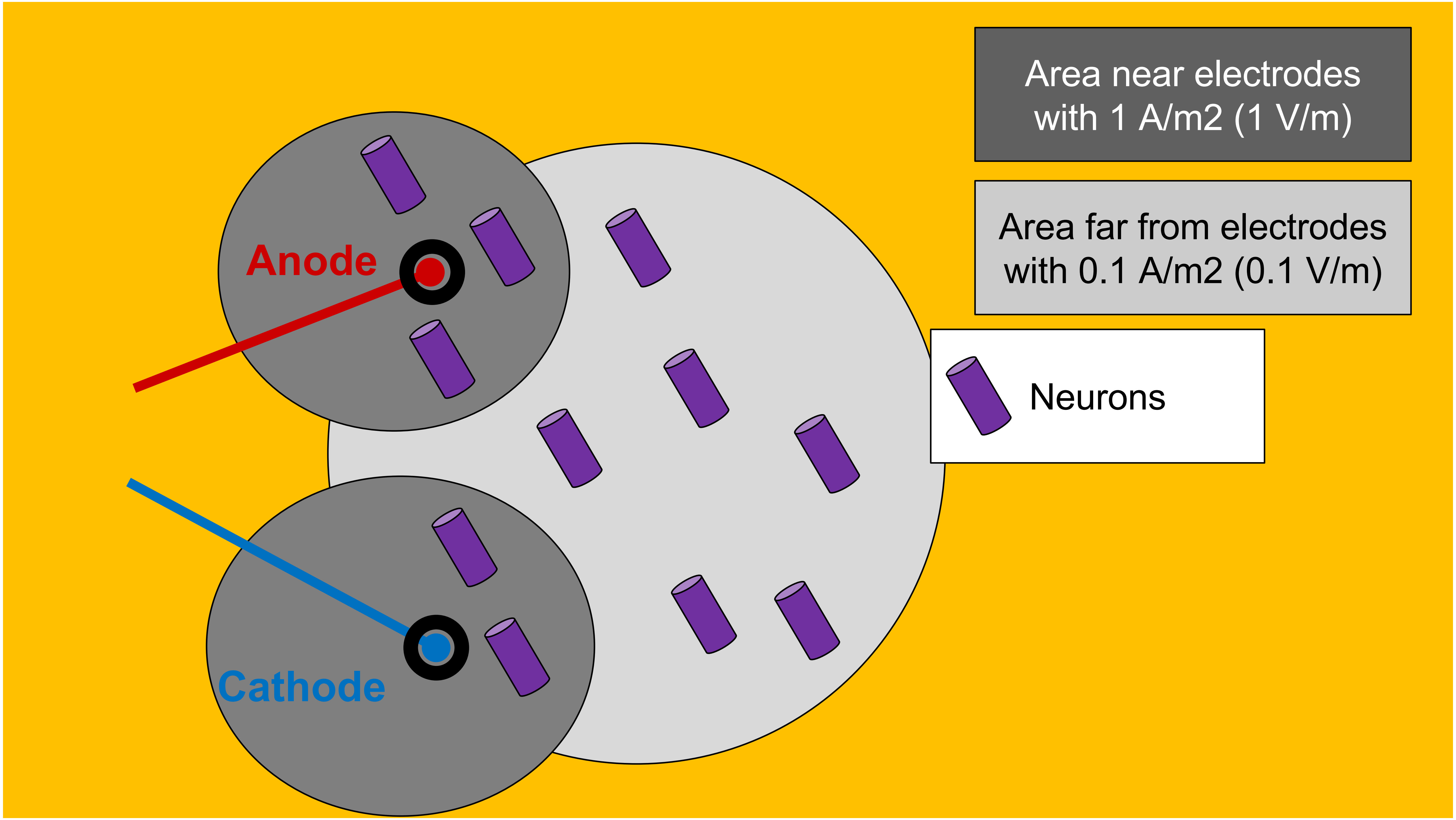
+20 mV de-polarization: membrane potential goes from -70 mV to -50 mV

For example: A stimulation device generates **Current Density** around a neuron of 0.1 mA/m^2 (or an Electric field of 0.1 V/m). The results is -2 mV **hyperpolarization** in some membrane parts (compartment) of the neuron, and +2 mV **depolarization** other membrane parts.

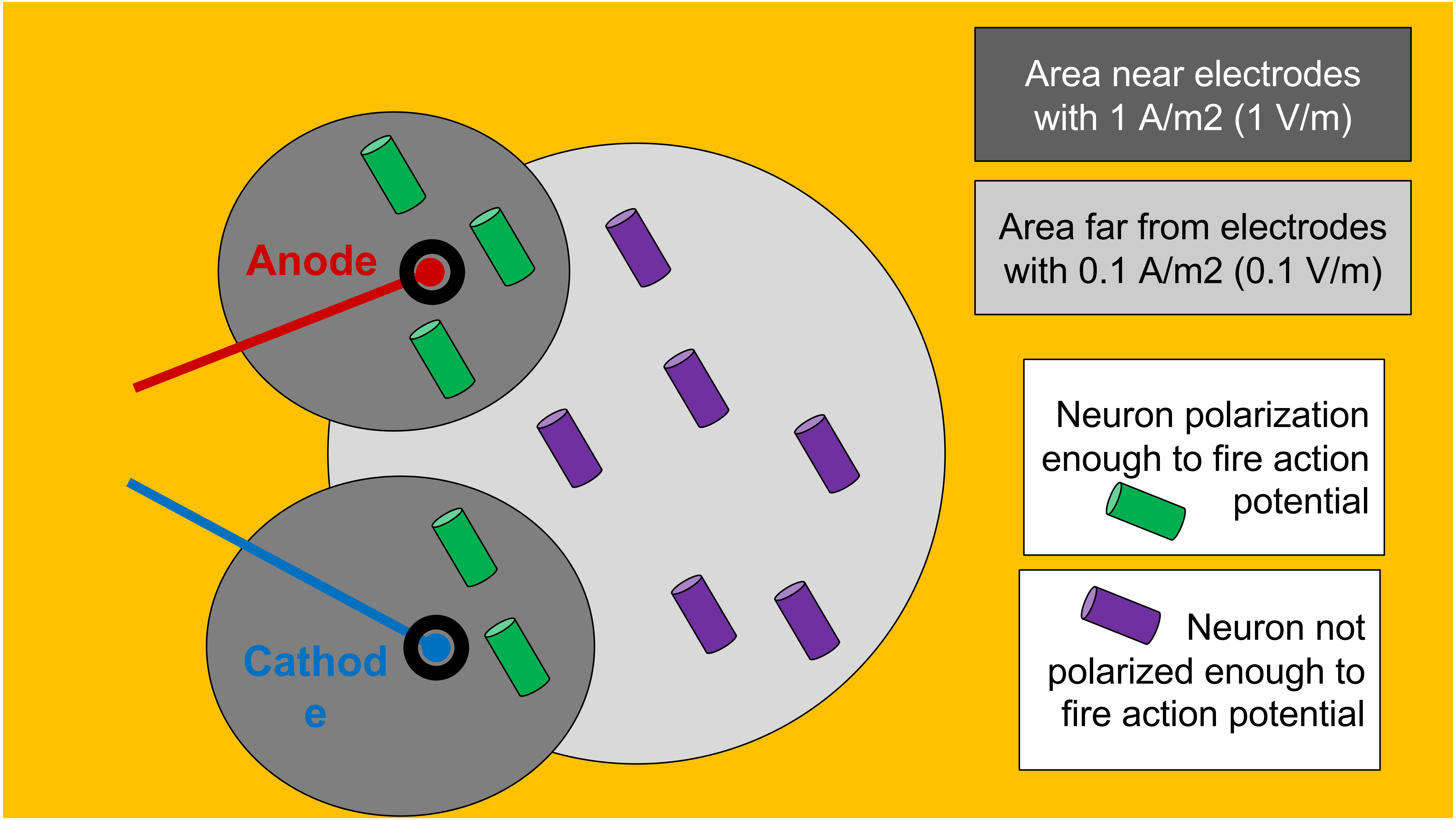


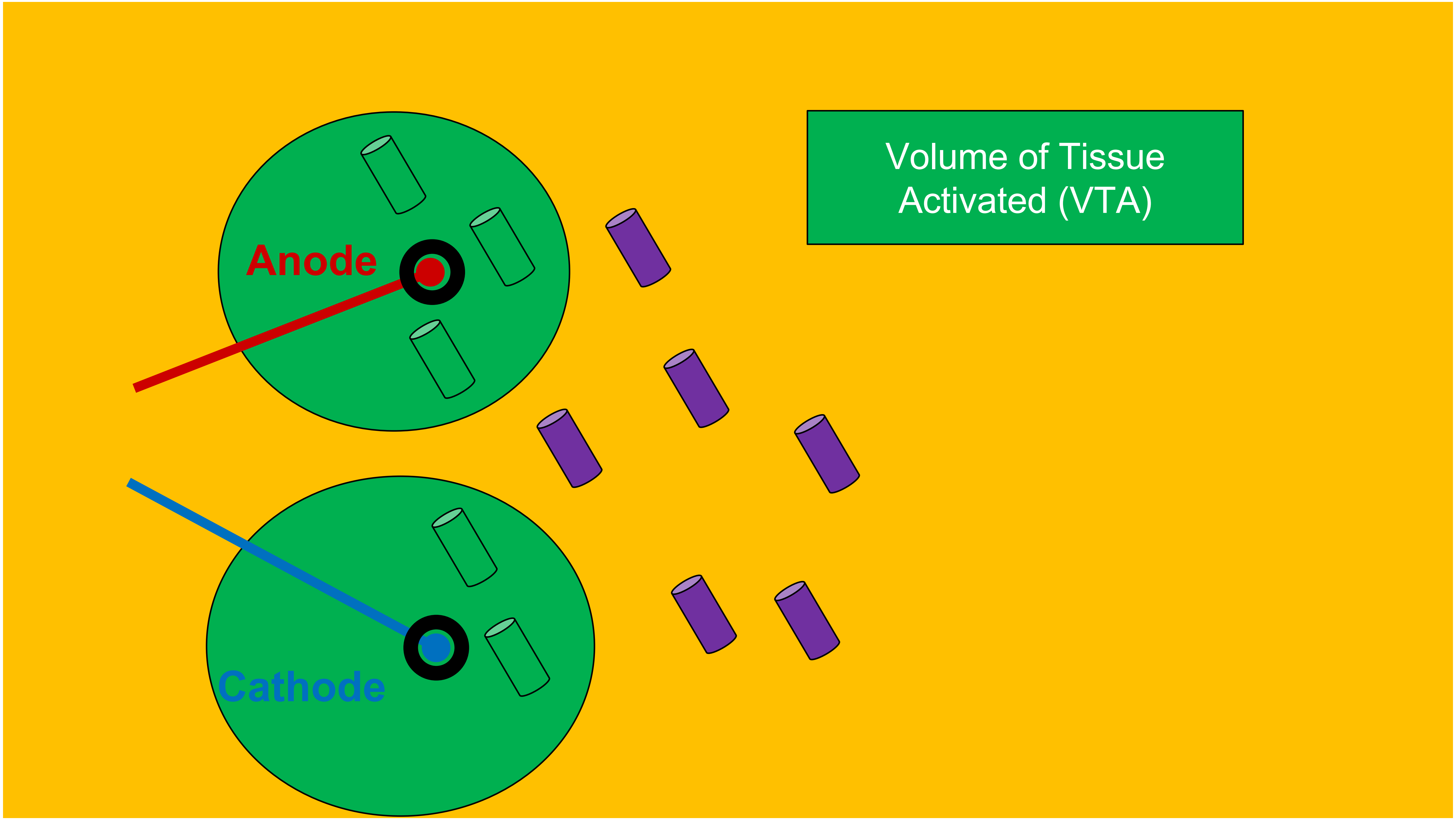


Area near electrodes
with 1 A/m2 (1 V/m)
Area far from electrodes
with 0.1 A/m2 (0.1 V/m)
Anode
Cathode



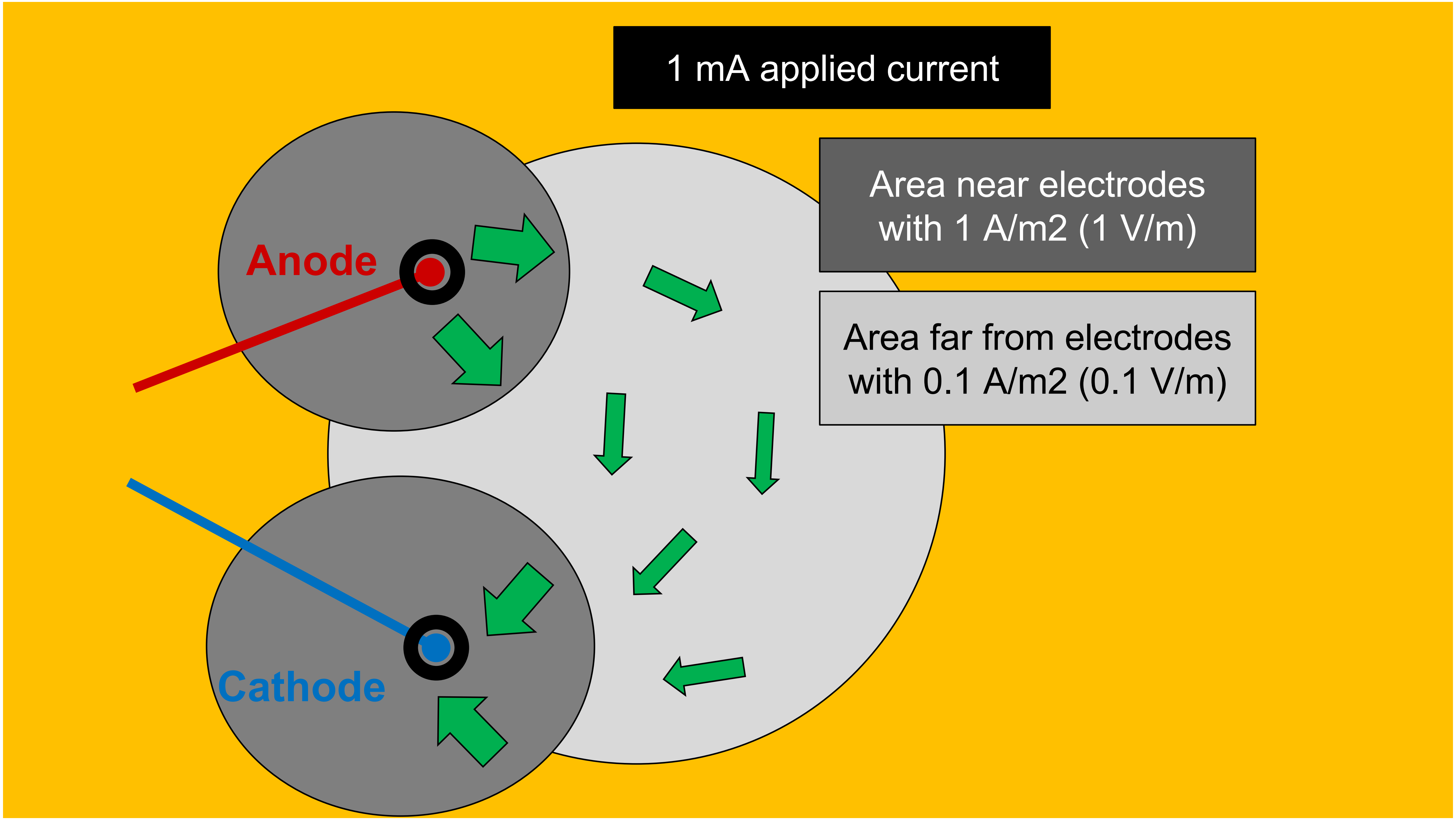
Area near electrodes with 1 A/m2 (1 V/m)
Area far from electrodes with 0.1 A/m2 (0.1 V/m)
Neurons
Anode
Cathode

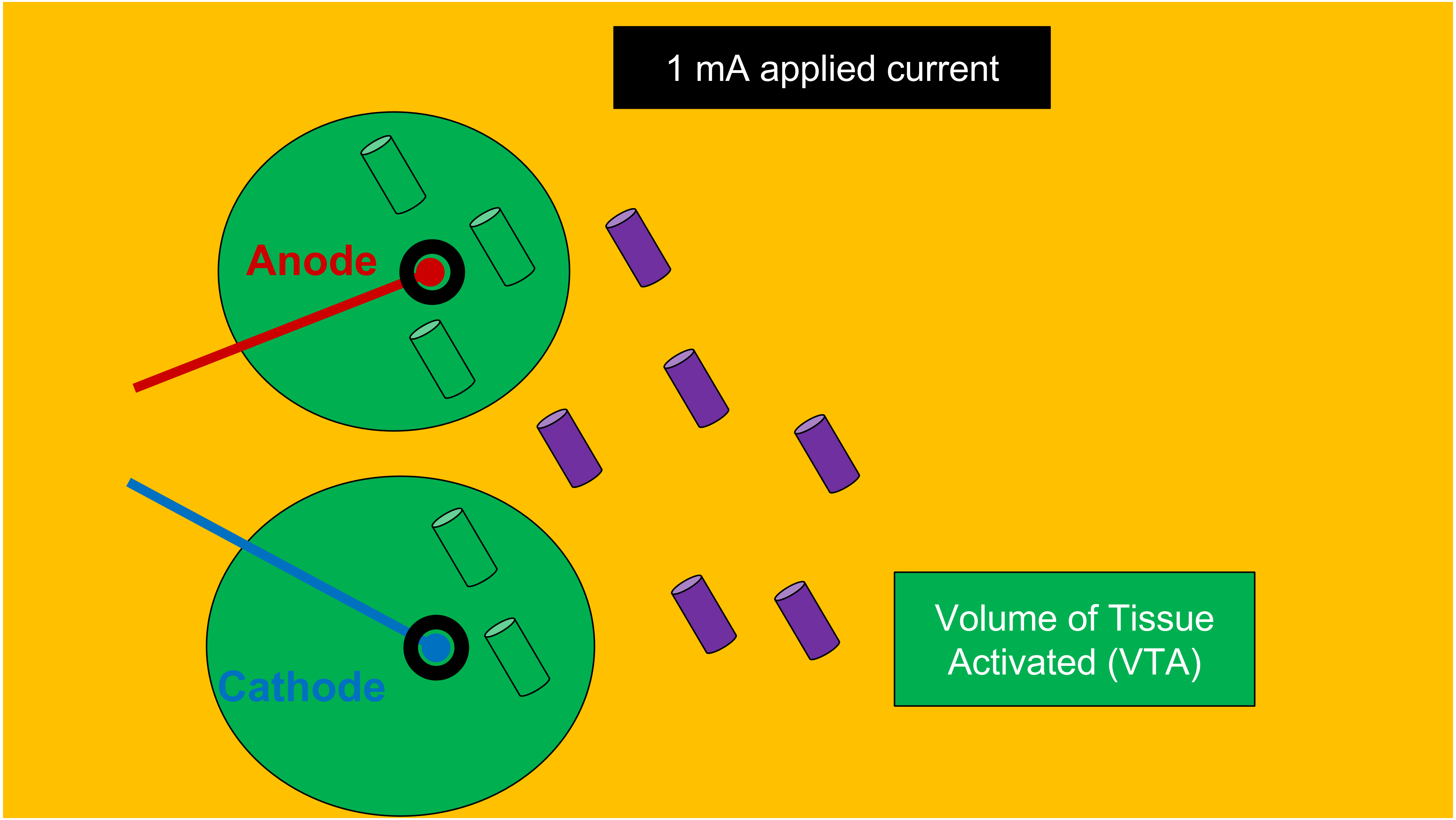

Area near electrodes with 1 A/m2 (1 V/m)
Area far from electrodes with 0.1 A/m2 (0.1 V/m)
Anode
Cathod
e
Neuron polarization enough to fire action potential
Neuron not polarized enough to fire action potential

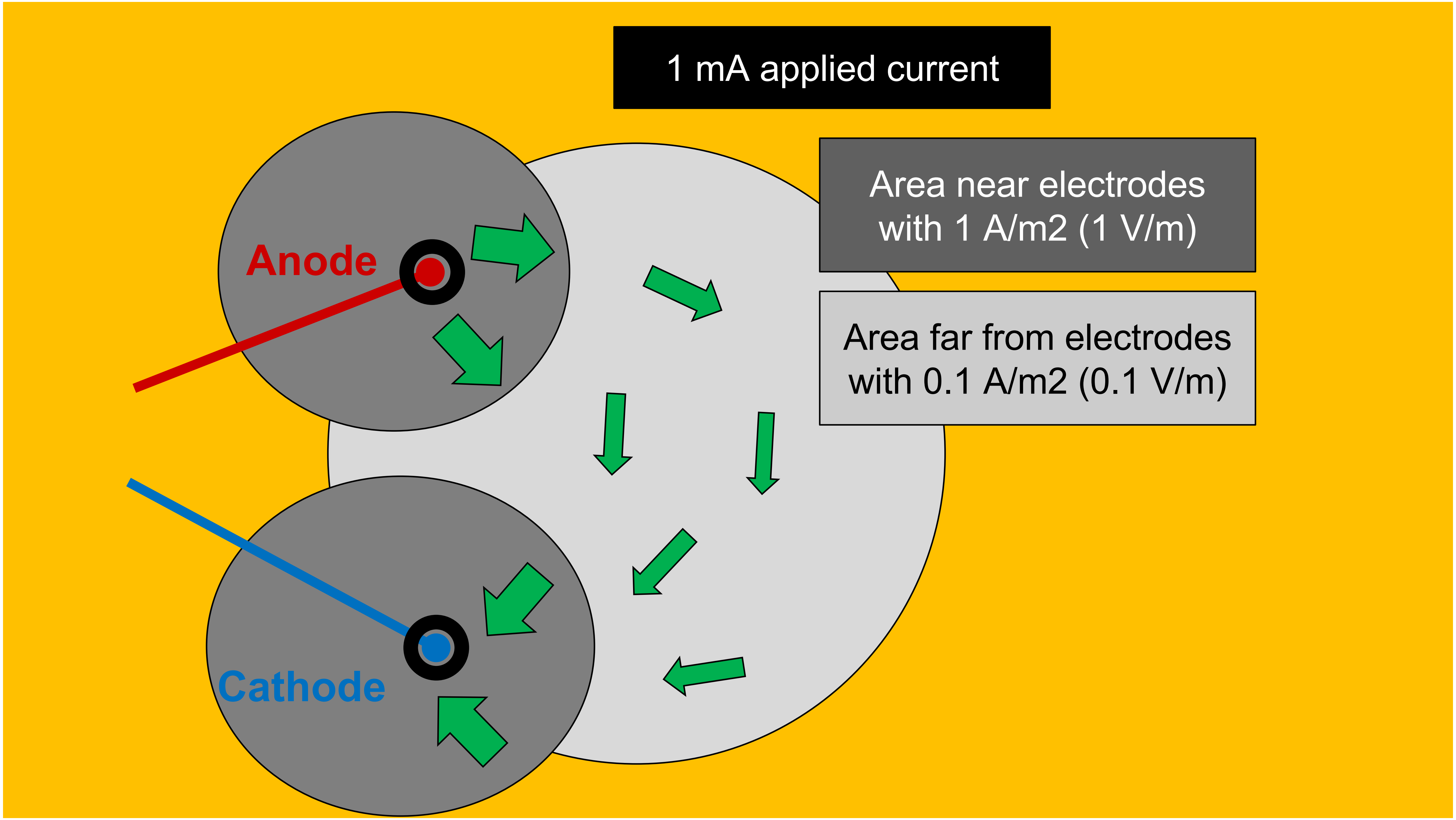


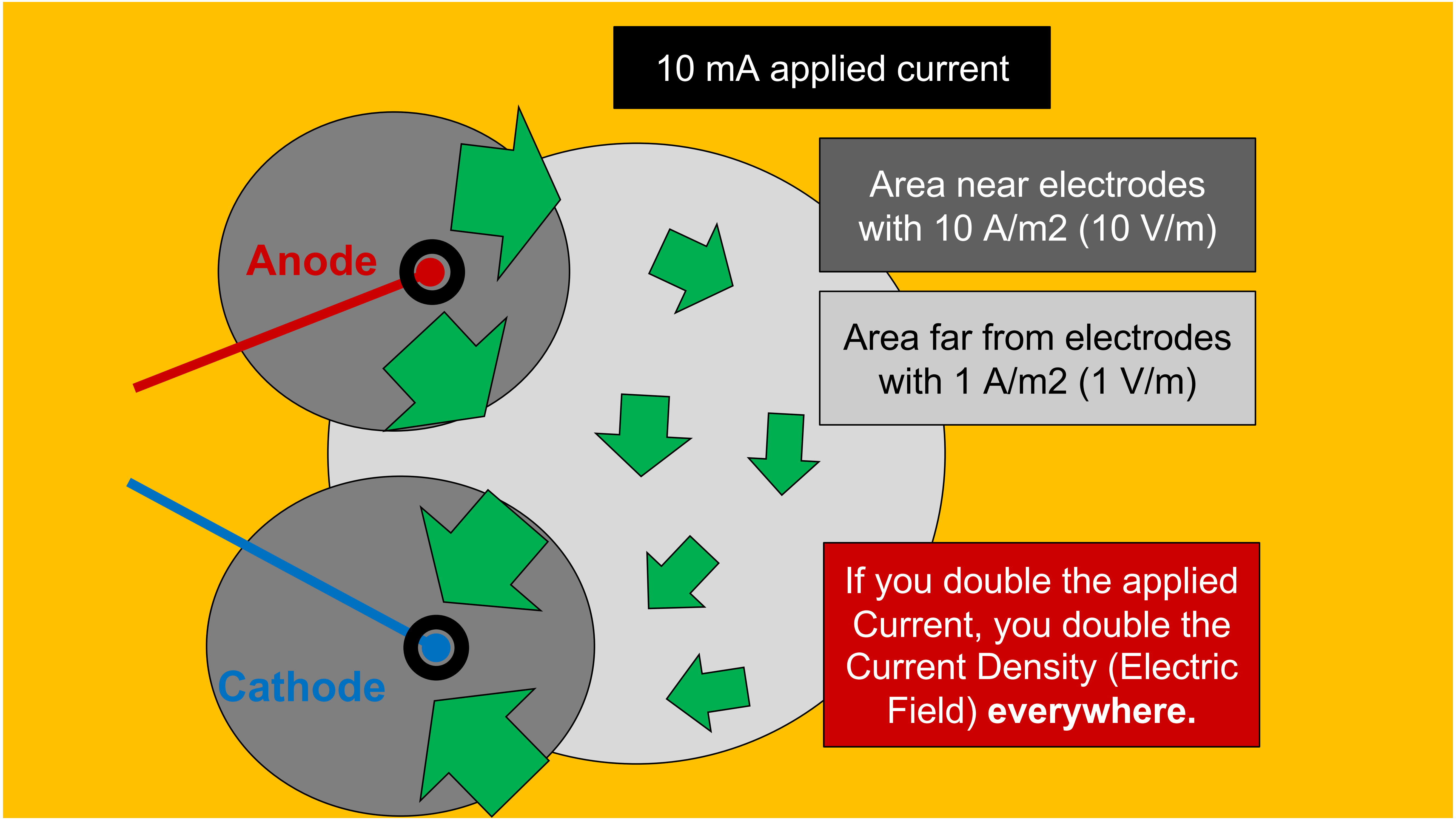
Volume of Tissue Activated (VTA)
Anode
Cathode

Part 3: Stimulation waveform, Intensity, Pulse Duration, Biphasic, Frequency, Bipolar/Monopolar


1 mA applied current
Area near electrodes with 1 A/m2 (1 V/m)
Area far from electrodes with 0.1 A/m2 (0.1 V/m)
Anode
Cathode

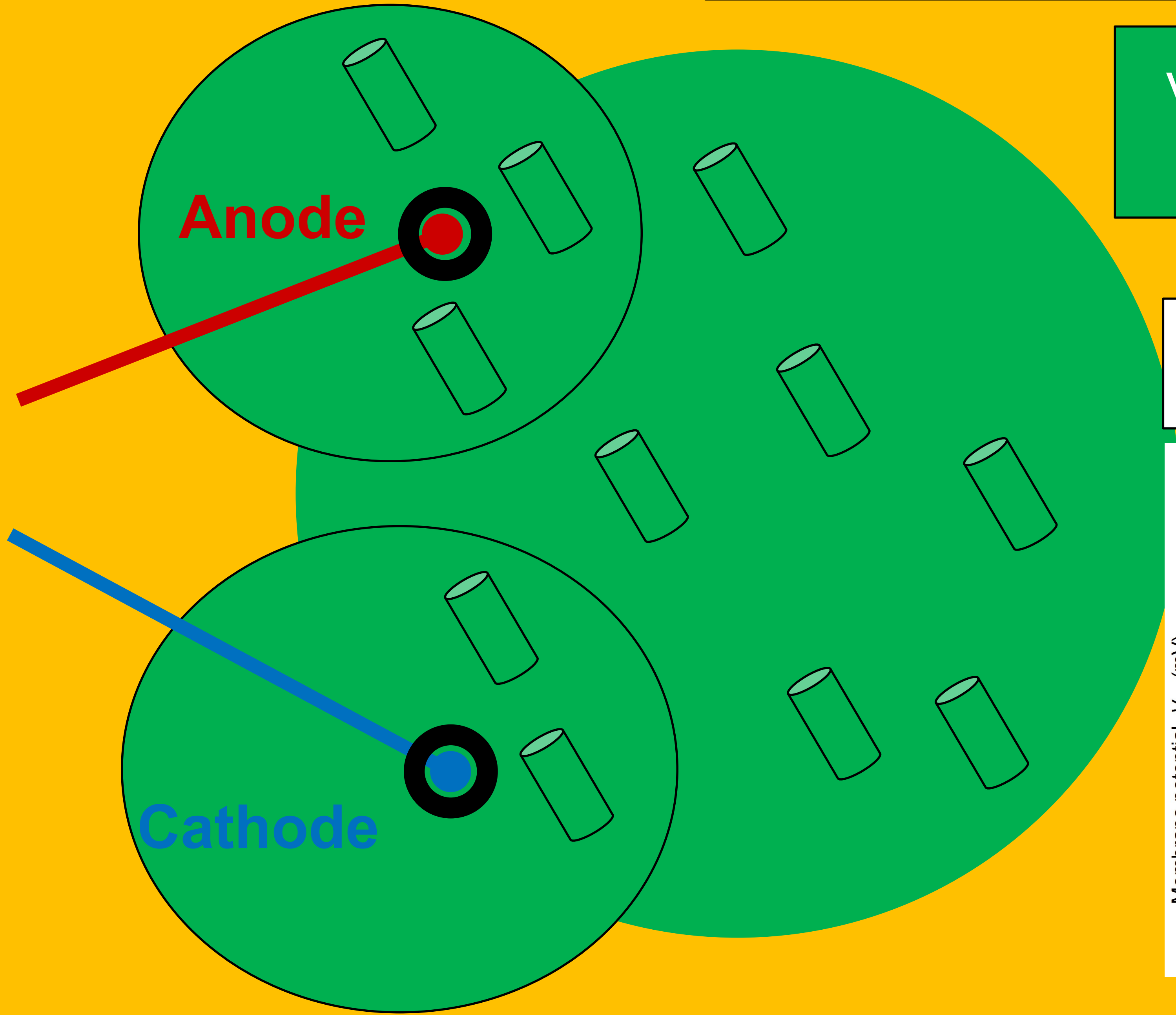

1 mA applied current
Anode
Cathode
Volume of Tissue Activated (VTA)


1 mA applied current
Area near electrodes with 1 A/m2 (1 V/m)
Area far from electrodes with 0.1 A/m2 (0.1 V/m)
Anode
Cathode

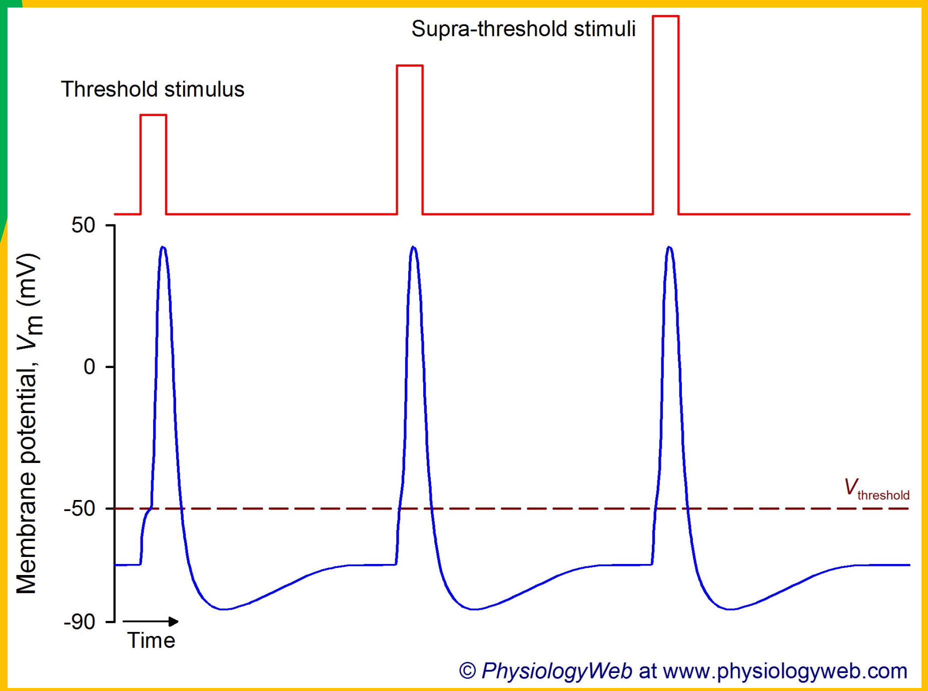

10 mA applied current
Anode
Area near electrodes with 10 A/m2 (10 V/m)
Area far from electrodes with 1 A/m2 (1 V/m)
Cathode
If you double the applied Current, you double the Current Density (Electric Field) **everywhere.**

10 mA applied current

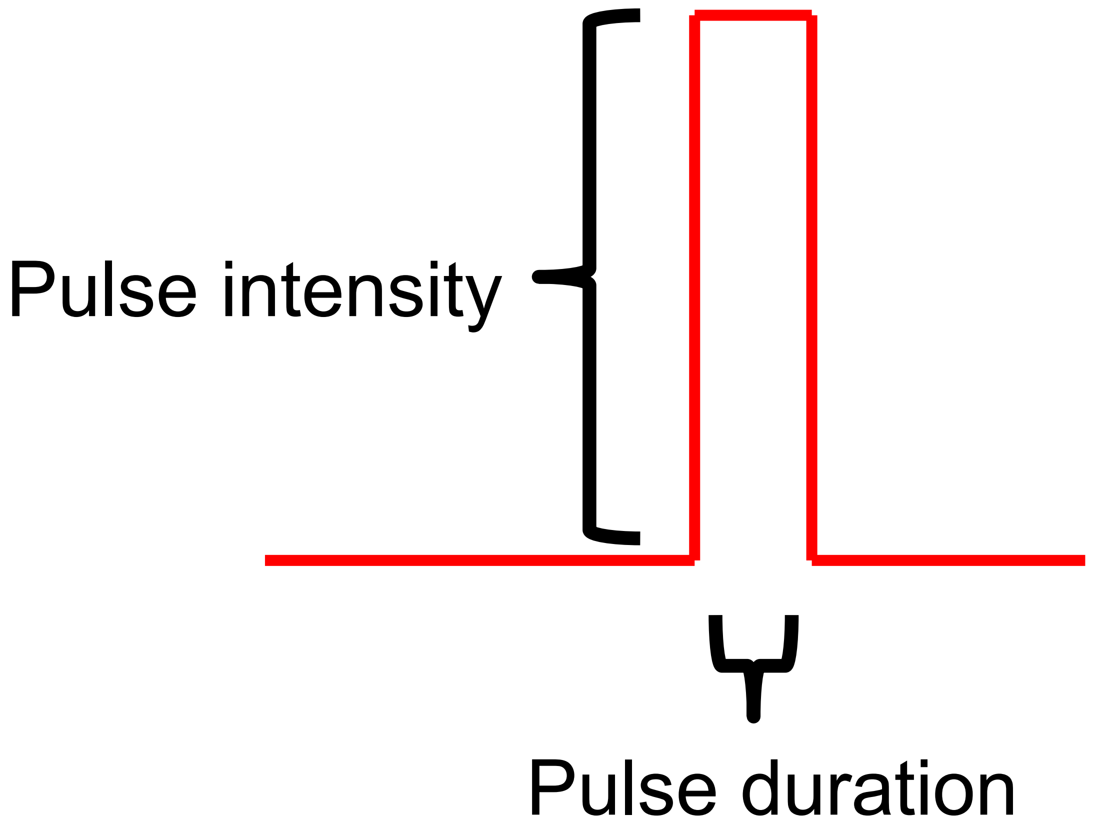
Volume of Tissue Activated (VTA)



Supra-threshold is threshold

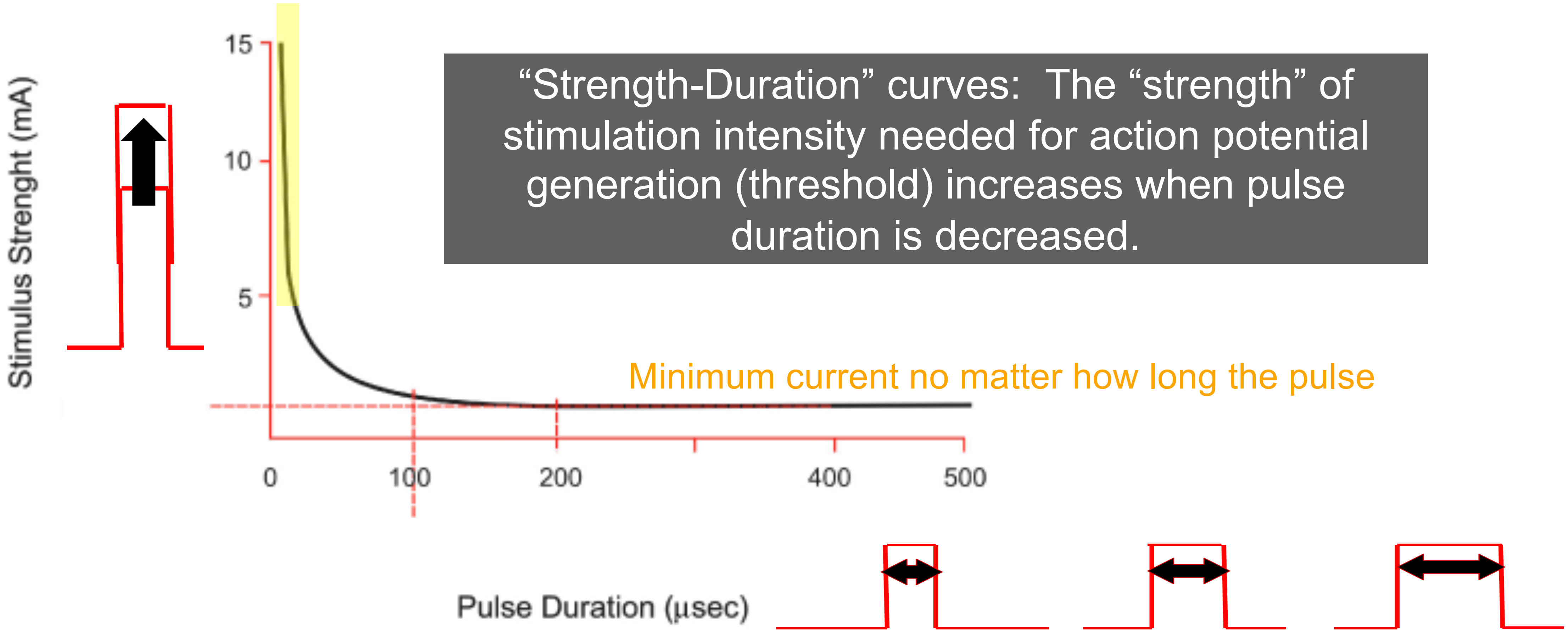


Duration of stimulation pulse (in units of **ms** or **us**)



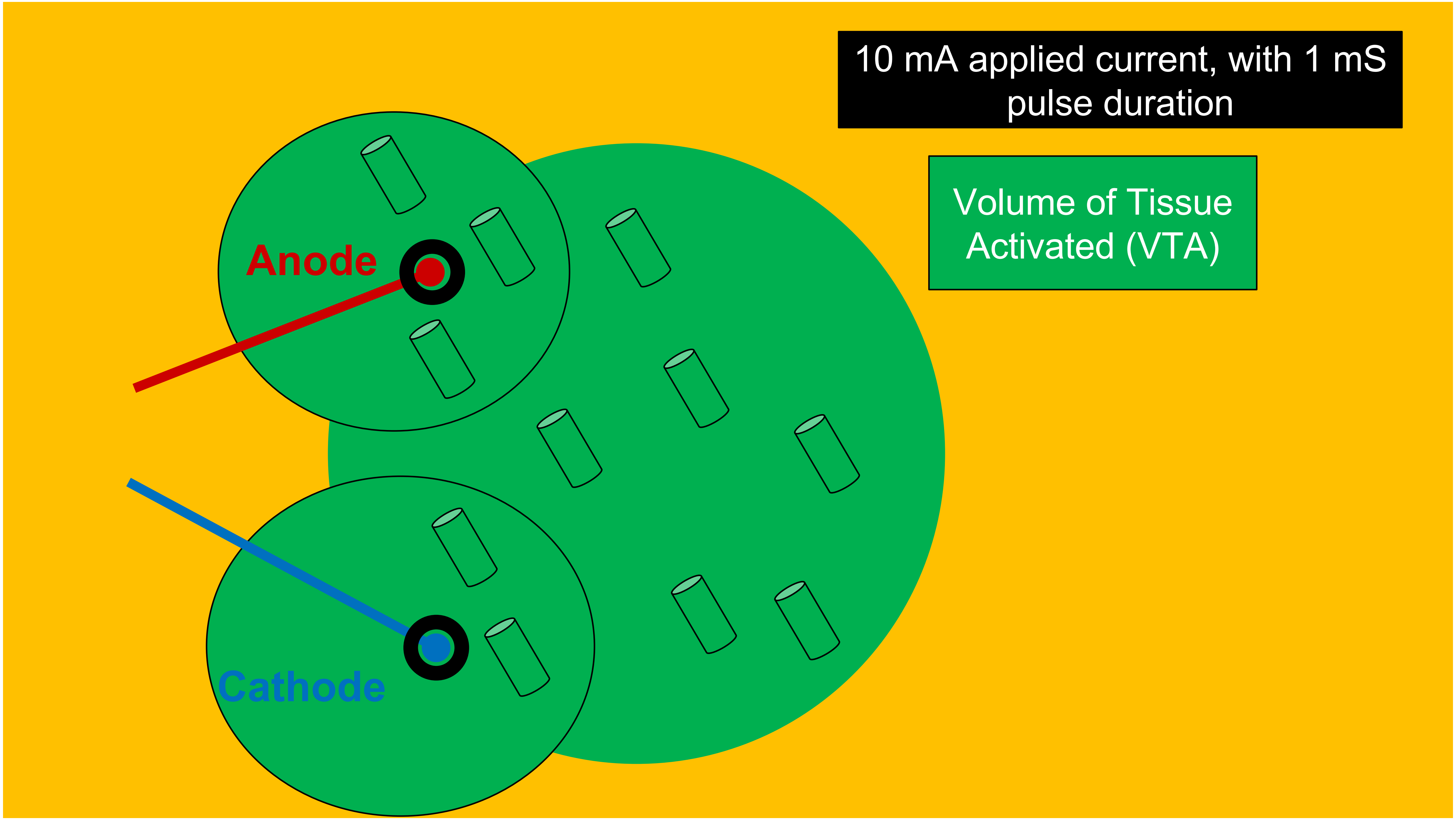
Duration of stimulation pulse (in units of **ms** or **us**)

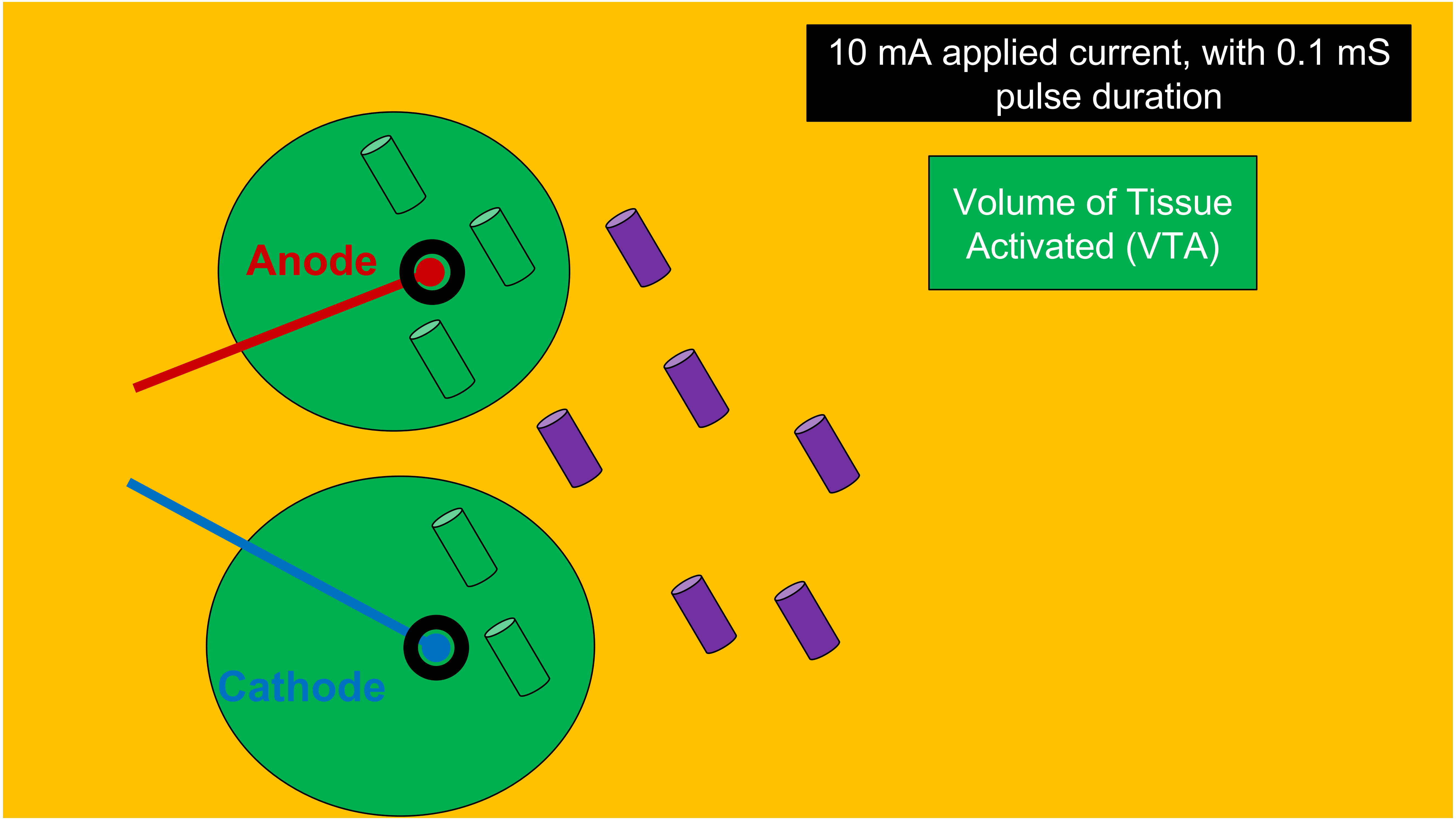
“Strength-Duration” curves: The “strength” of stimulation intensity needed for action potential generation (threshold) increases when pulse duration is decreased.



Source: Hadzic A: *The New York School of Regional Anesthesia Textbook of Regional Anesthesia and Acute Pain Management:* http://www.accessanesthesiology.com

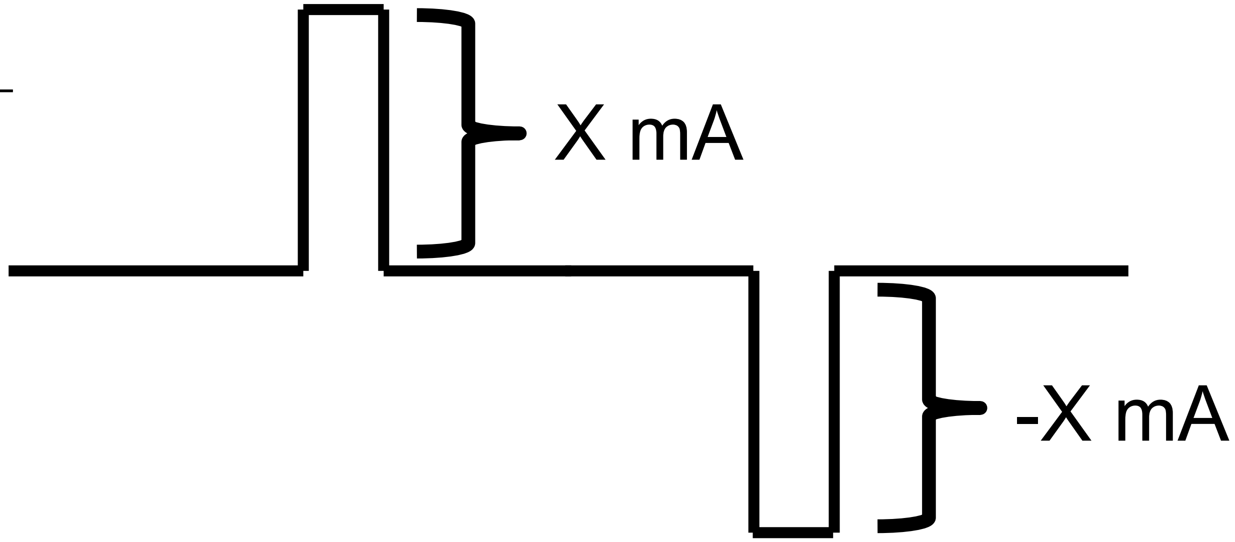
With very short duration pulses, you may need much more current to trigger action potentials.

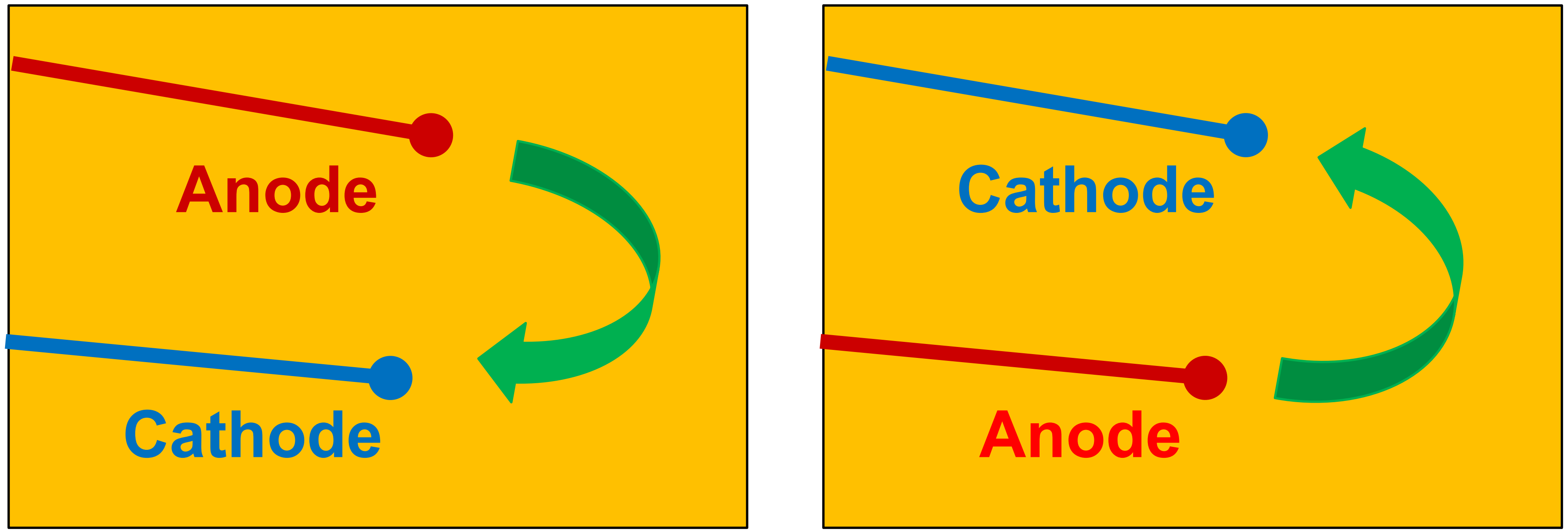

10 mA applied current, with 1 mS pulse duration
Volume of Tissue Activated (VTA)
Anode
Cathode


10 mA applied current, with 0.1 mS pulse duration
Volume of Tissue Activated (VTA)
Anode
Cathode

Pulse **polarity**

Biphasic stimulation: Alternate polarity pulses are provided

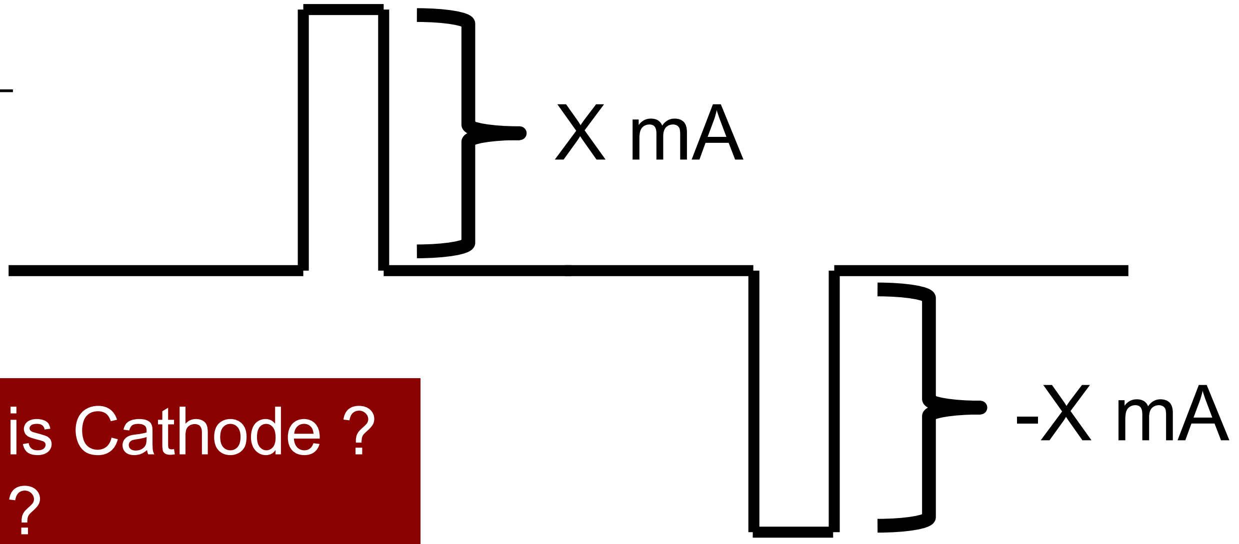


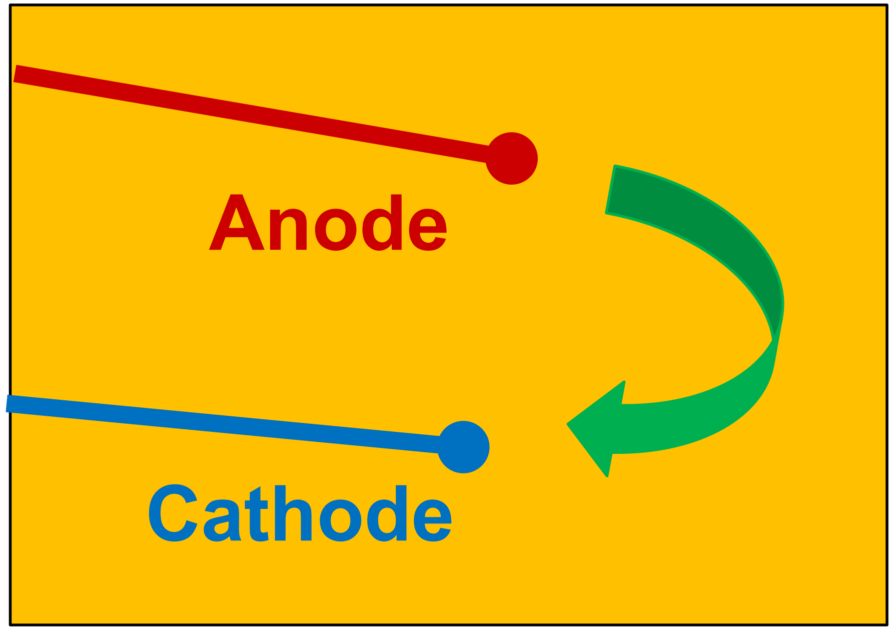


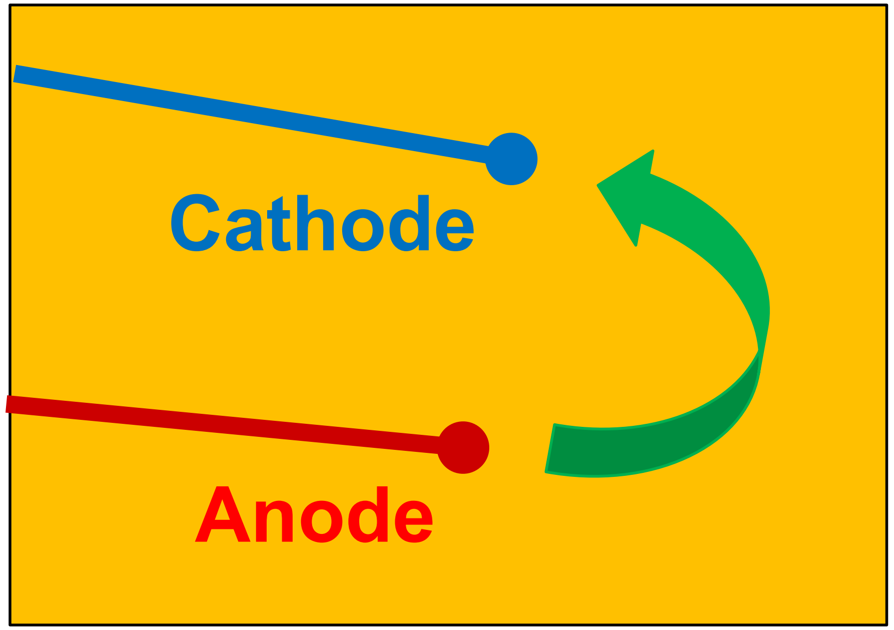
Pulse **polarity**

Biphasic stimulation: Alternate polarity pulses are provided

Which electrode is the Anode ? Which is Cathode ?
Which way does current flow for X mA ?
Which way does current flow for -X mA ?

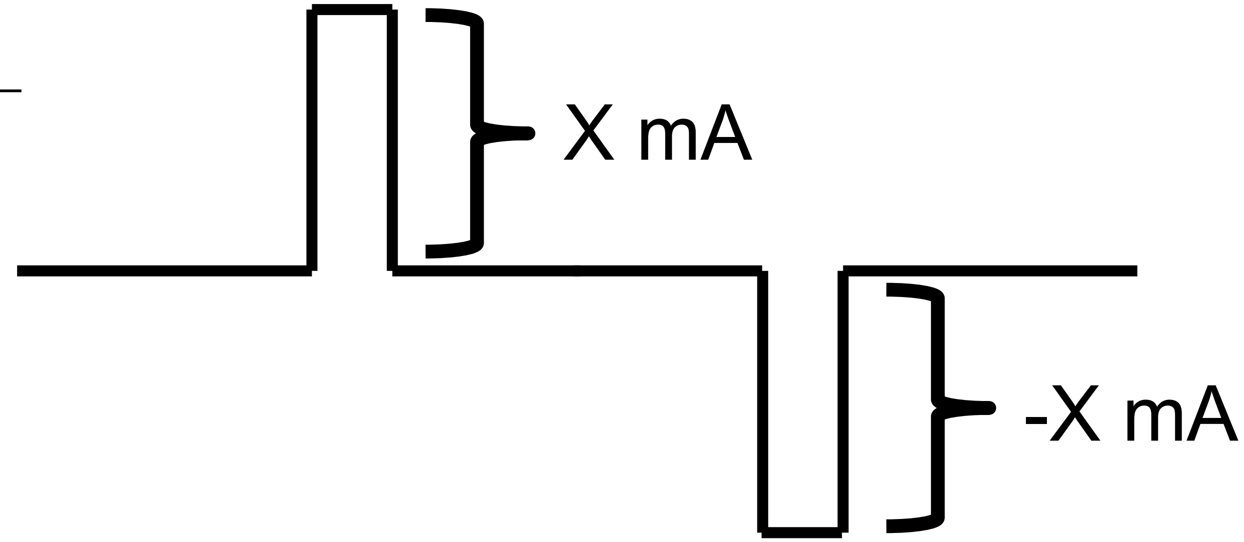


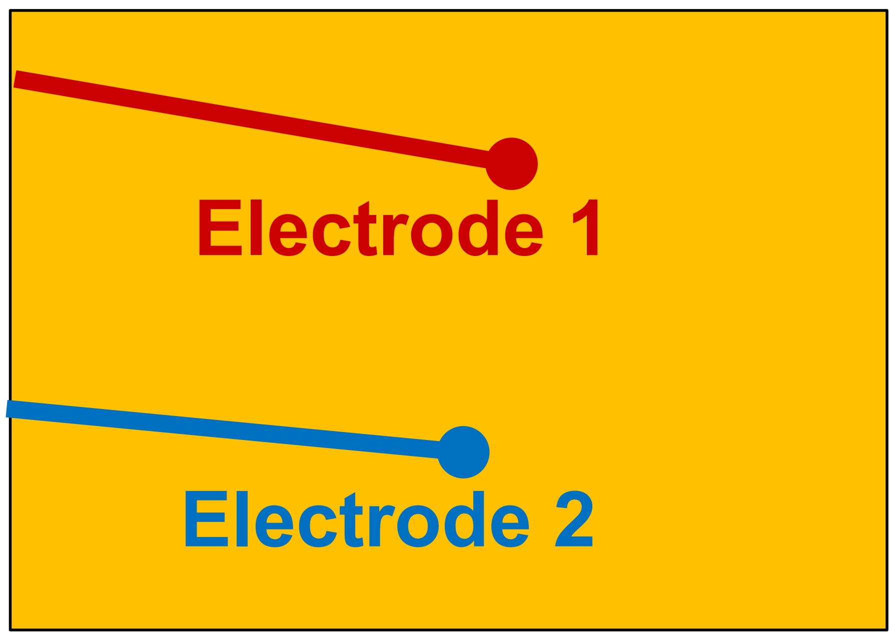




Pulse **polarity**

Biphasic stimulation: Alternate polarity pulses are provided



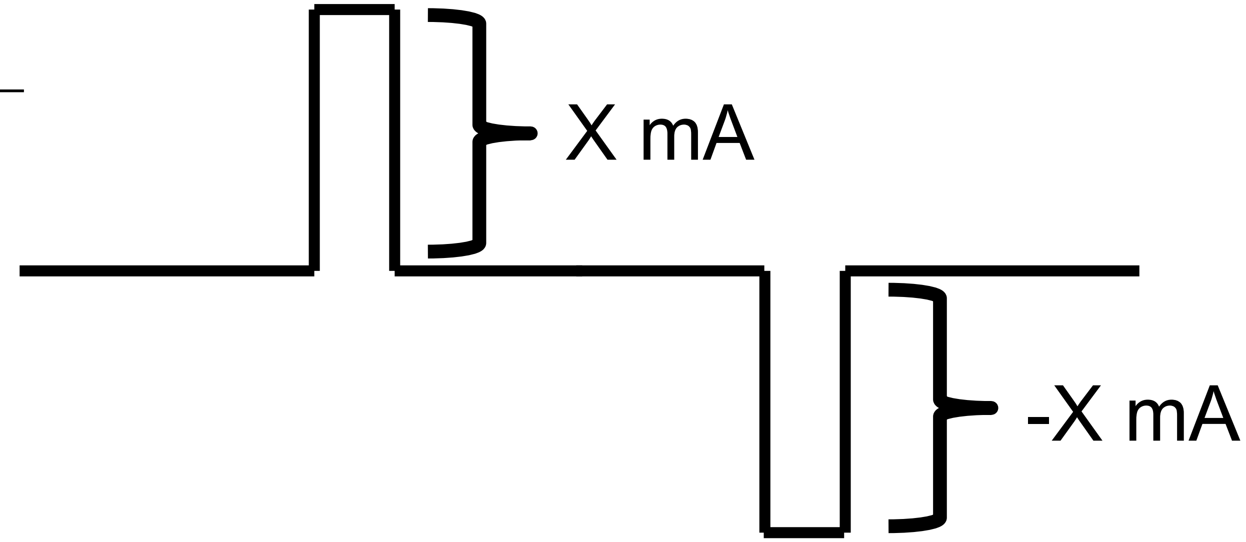


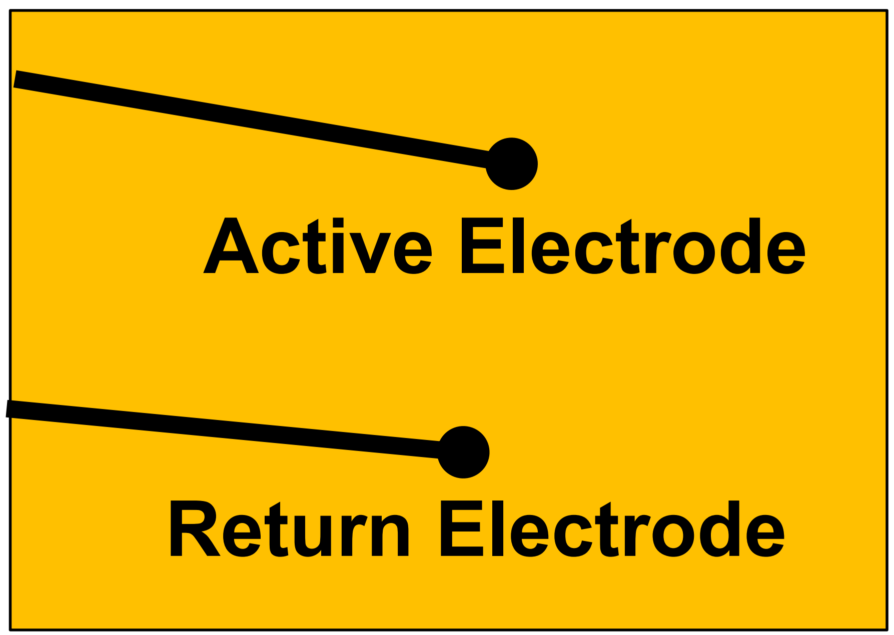
Define stimulation **Polarity** (direction of current flow) relative to one electrode.

For example, Electrode 1.
X mA means Electrode 1 is **Anode**.
–X mA means Electrode 1 is **Cathode**.

Pulse **polarity**

Biphasic stimulation: Alternate polarity pulses are provided





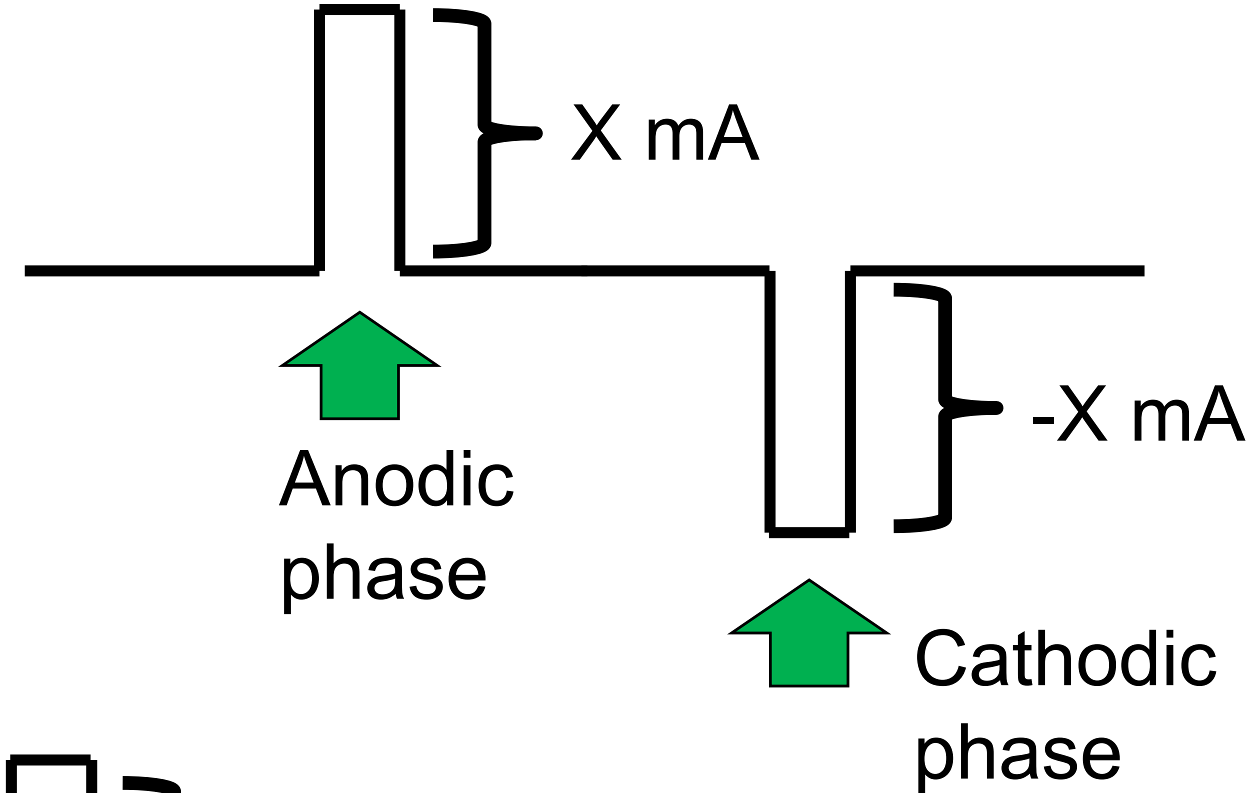
Define stimulation **Polarity** (direction of current flow) relative to one electrode.

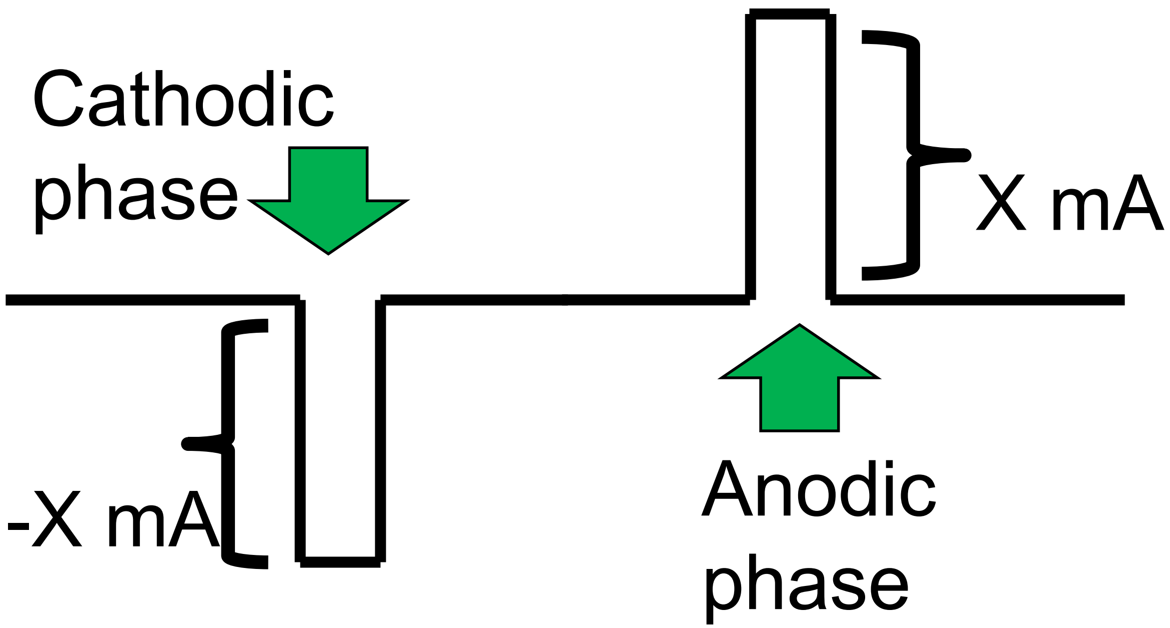
For example, Electrode 1.
X mA means Electrode 1 is **Anode**.
–X mA means Electrode 1 is **Cathode**.

Pulse **polarity**

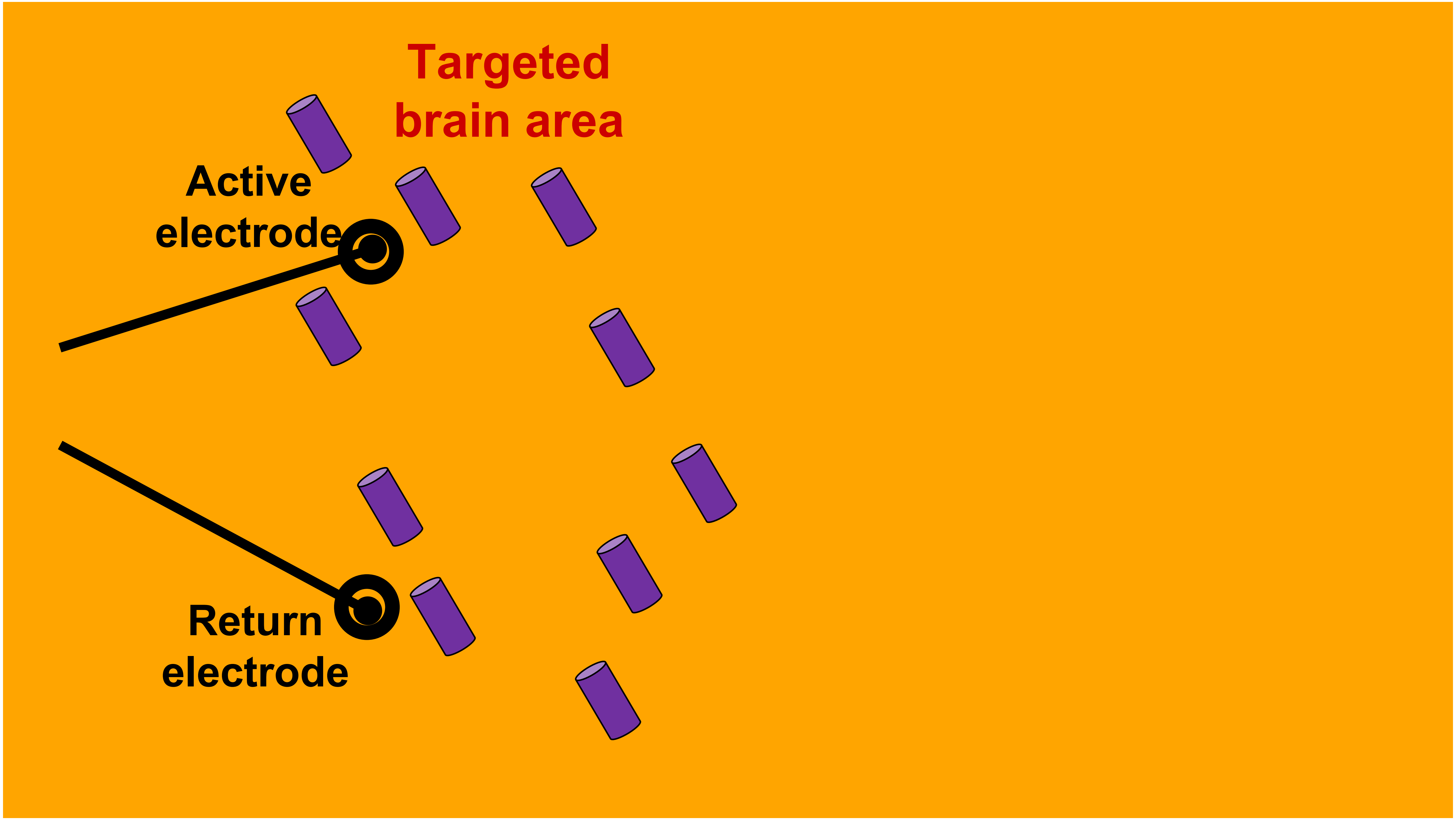
All invasive device use **Biphasic** stimulation.

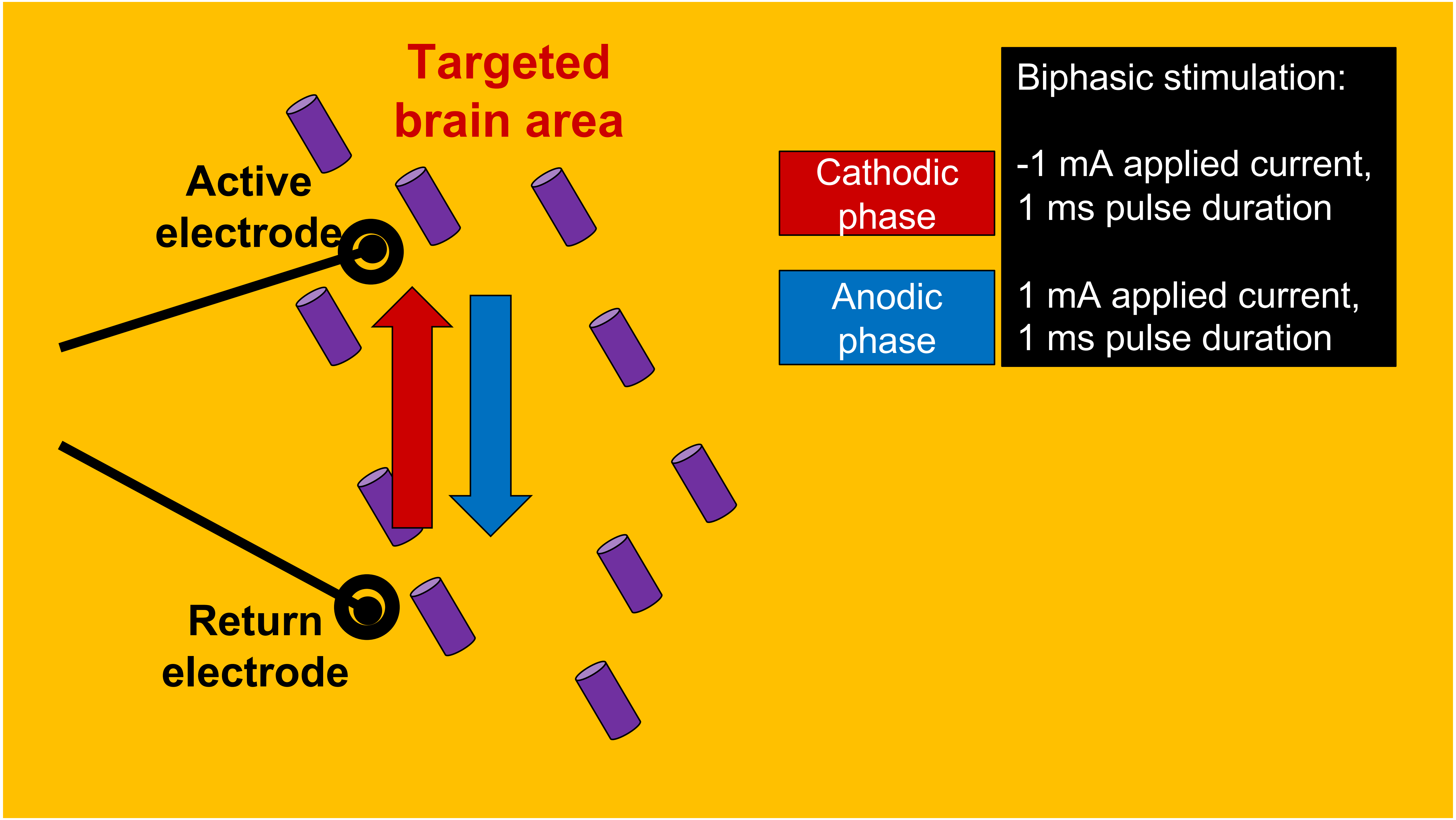
Phase (anodic, cathodic) is always relative to a given electrode (eg. the 'active' electrode)

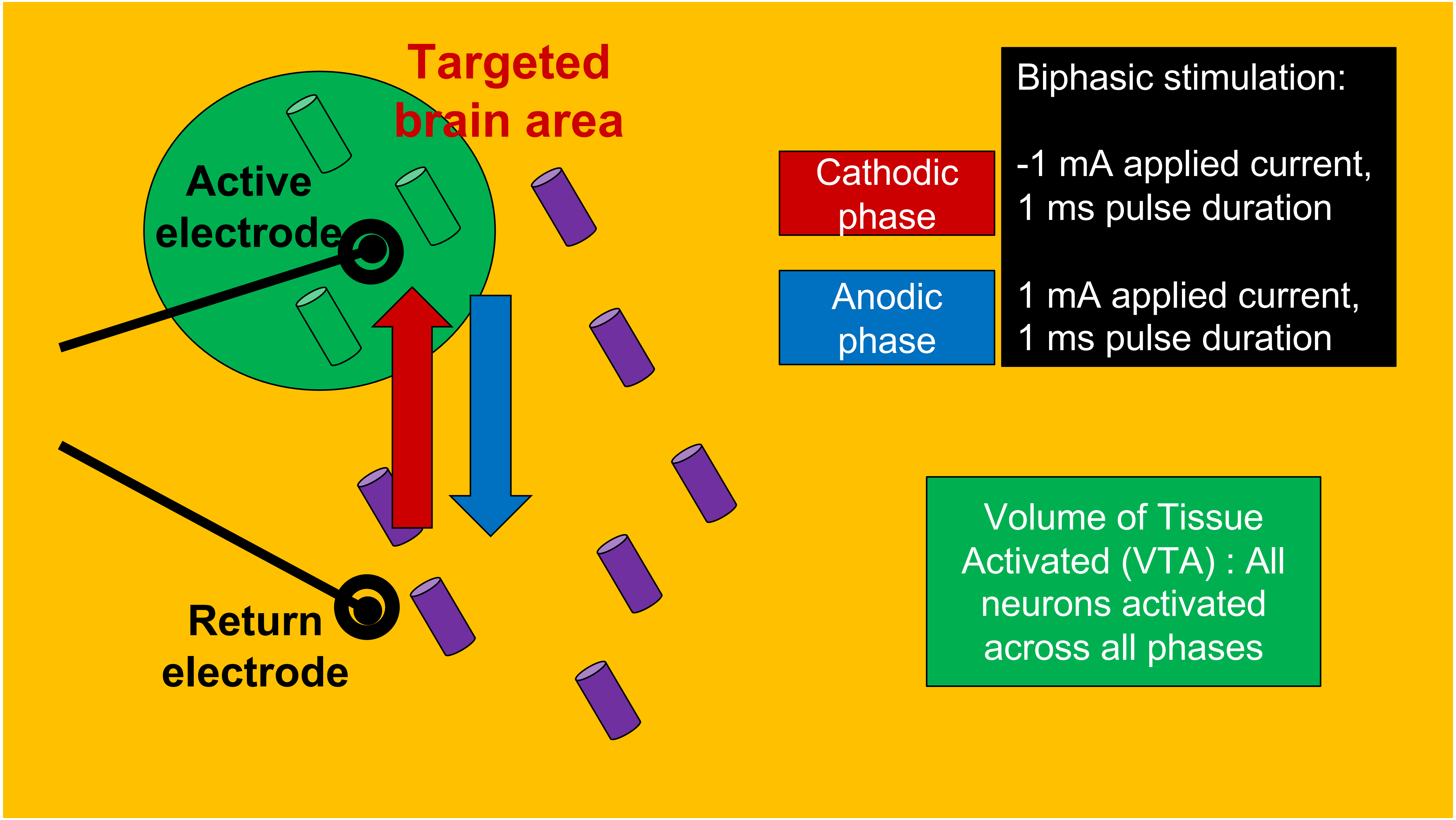


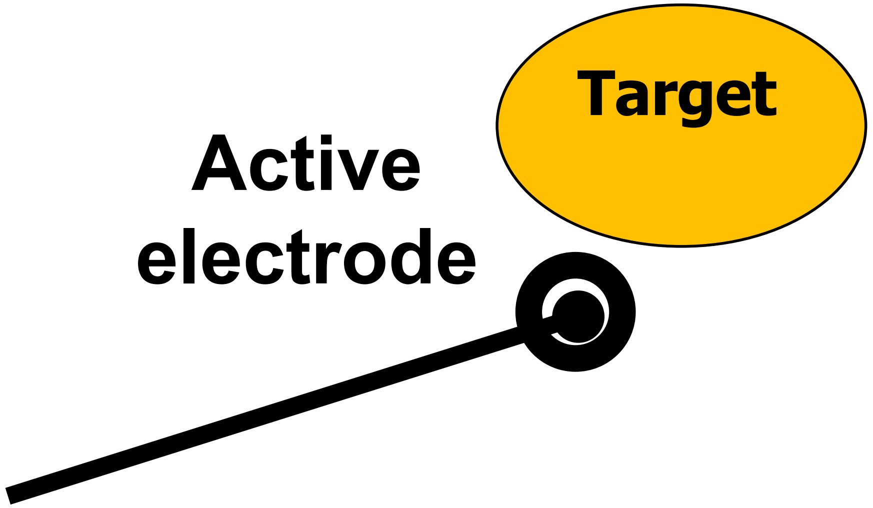


Anodic vs **Cathodic Stimulation** refers to the phase considered most important for stimulation

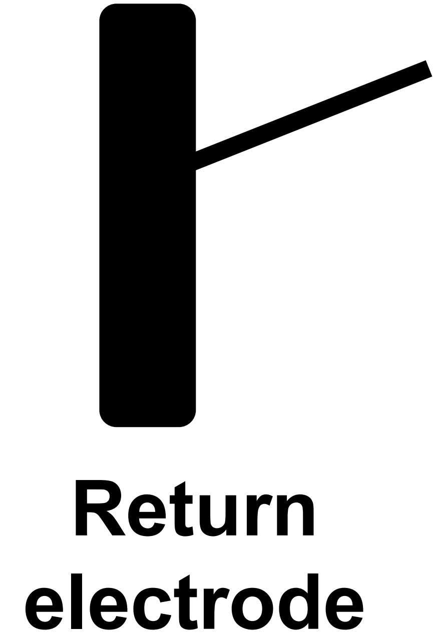

Targeted
brain area
Active
electrode
Return
electrode

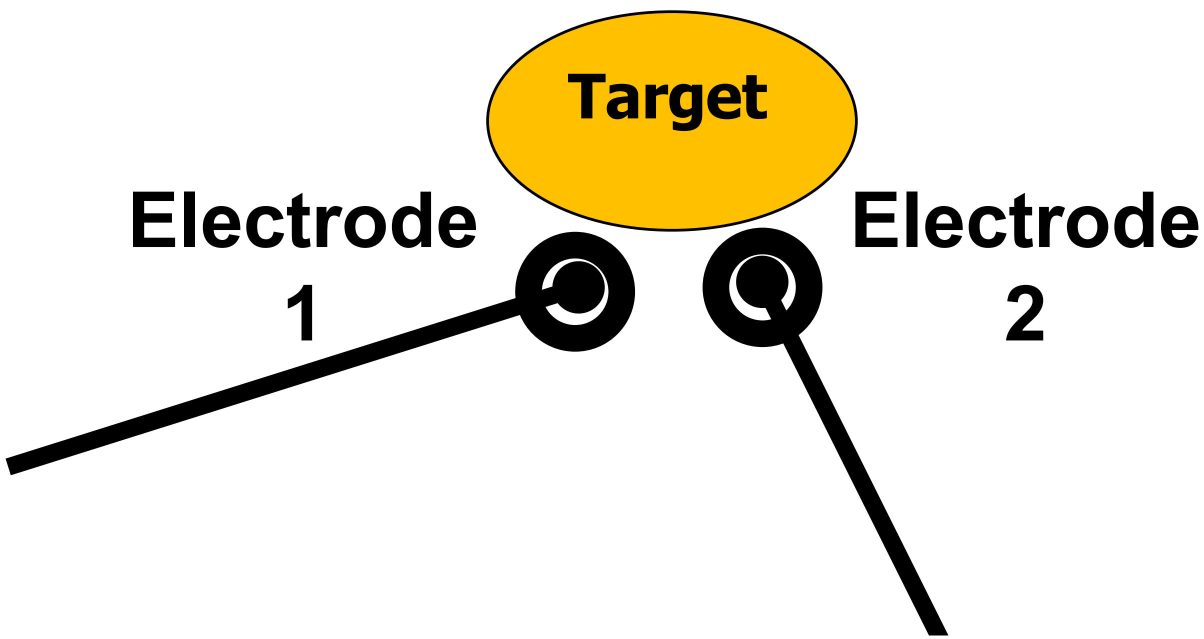

Targeted
brain area
Active
electrode
Return
electrode
Cathodic
phase
Anodic
phase
Biphasic stimulation:
-1 mA applied current,
1 ms pulse duration
1 mA applied current,
1 ms pulse duration


Targeted brain area
Active electrode
Return electrode
Cathodic phase
Anodic phase
Biphasic stimulation:
-1 mA applied current, 1 ms pulse duration
1 mA applied current, 1 ms pulse duration
Volume of Tissue Activated (VTA) : All neurons activated across all phases

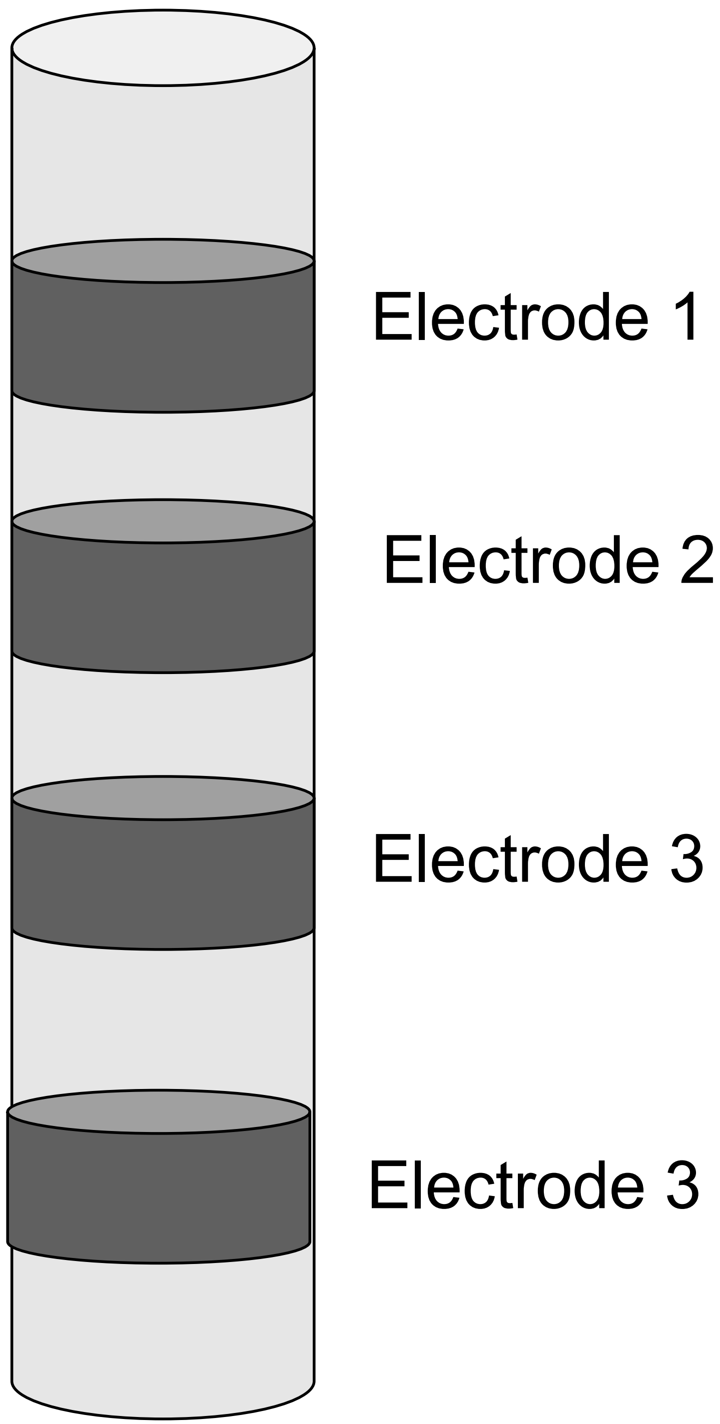


Monopolar Stimulation: When Return electrode is larger and/or farther from Target. (technically still bi-poles).
Waveform: "Biphasic"



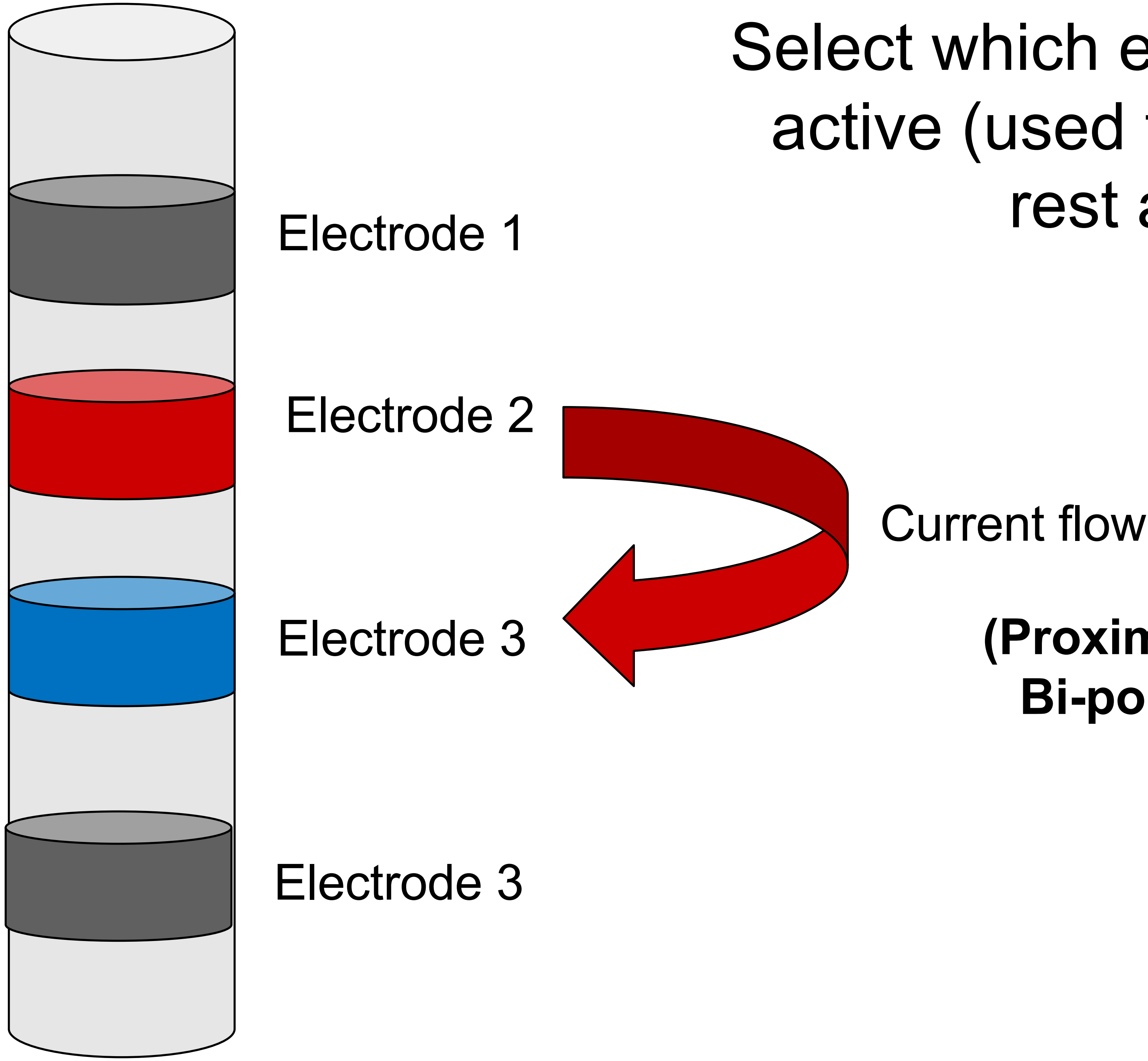


Bipolar Stimulation: When both electrodes are the same size (and proximity to Target)



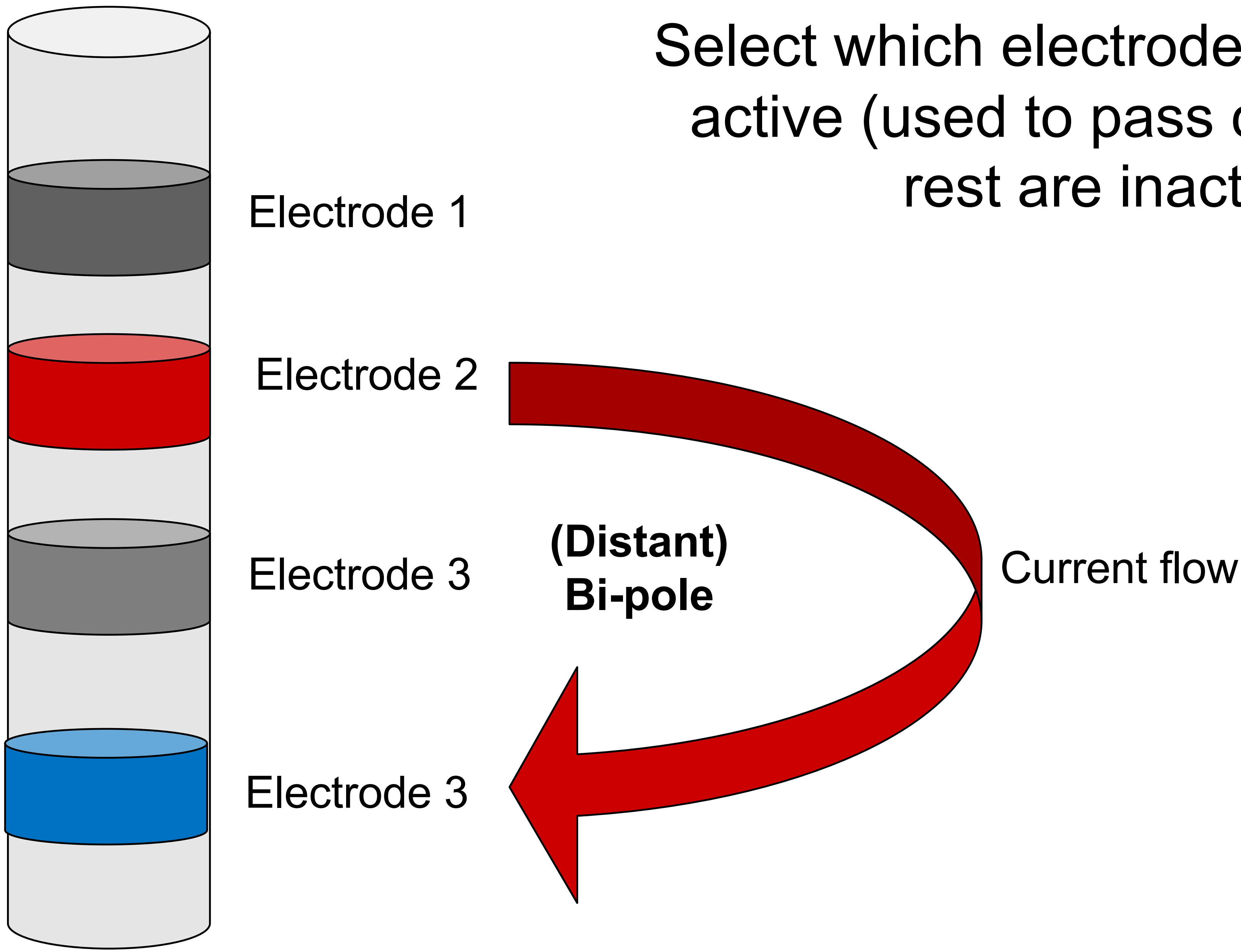
Select which electrodes on lead are active (used to pass current), the rest are inactive.

Select which electrodes on lead are active (used to pass current), the rest are inactive.

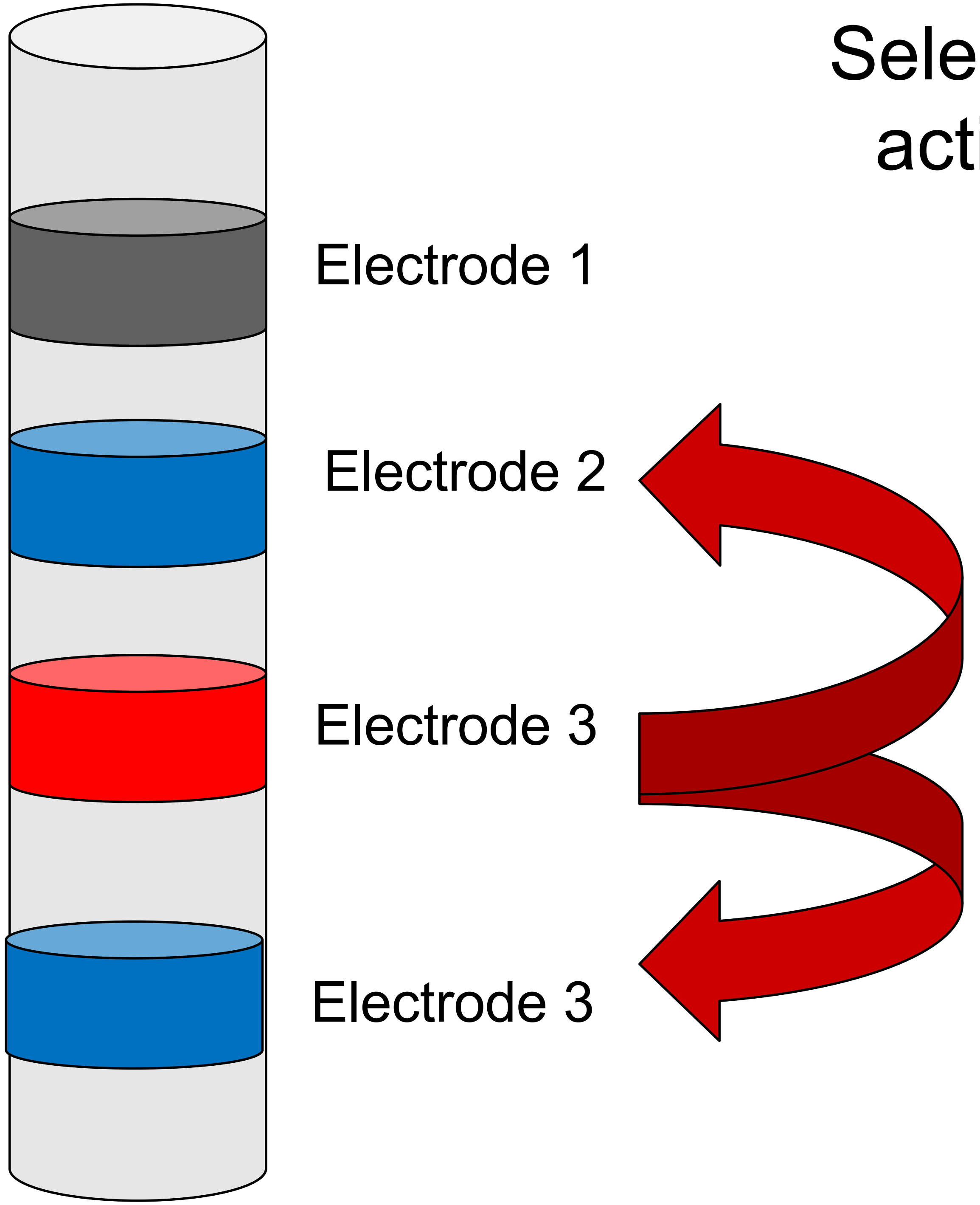


(Proximal) Bi-pole

Select which electrodes on lead are active (used to pass current), the rest are inactive.



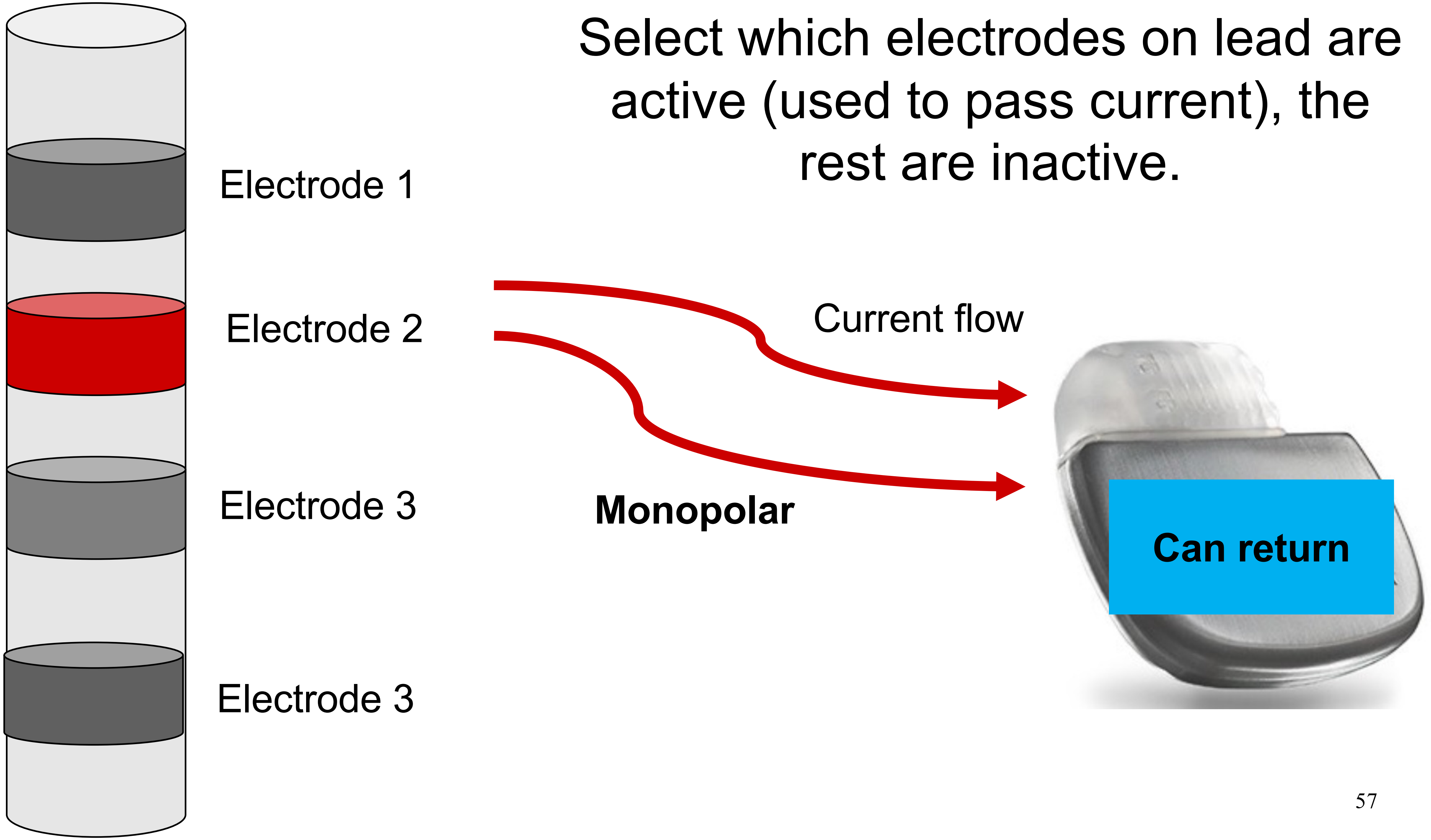
Select which electrodes on lead are active (used to pass current), the rest are inactive.



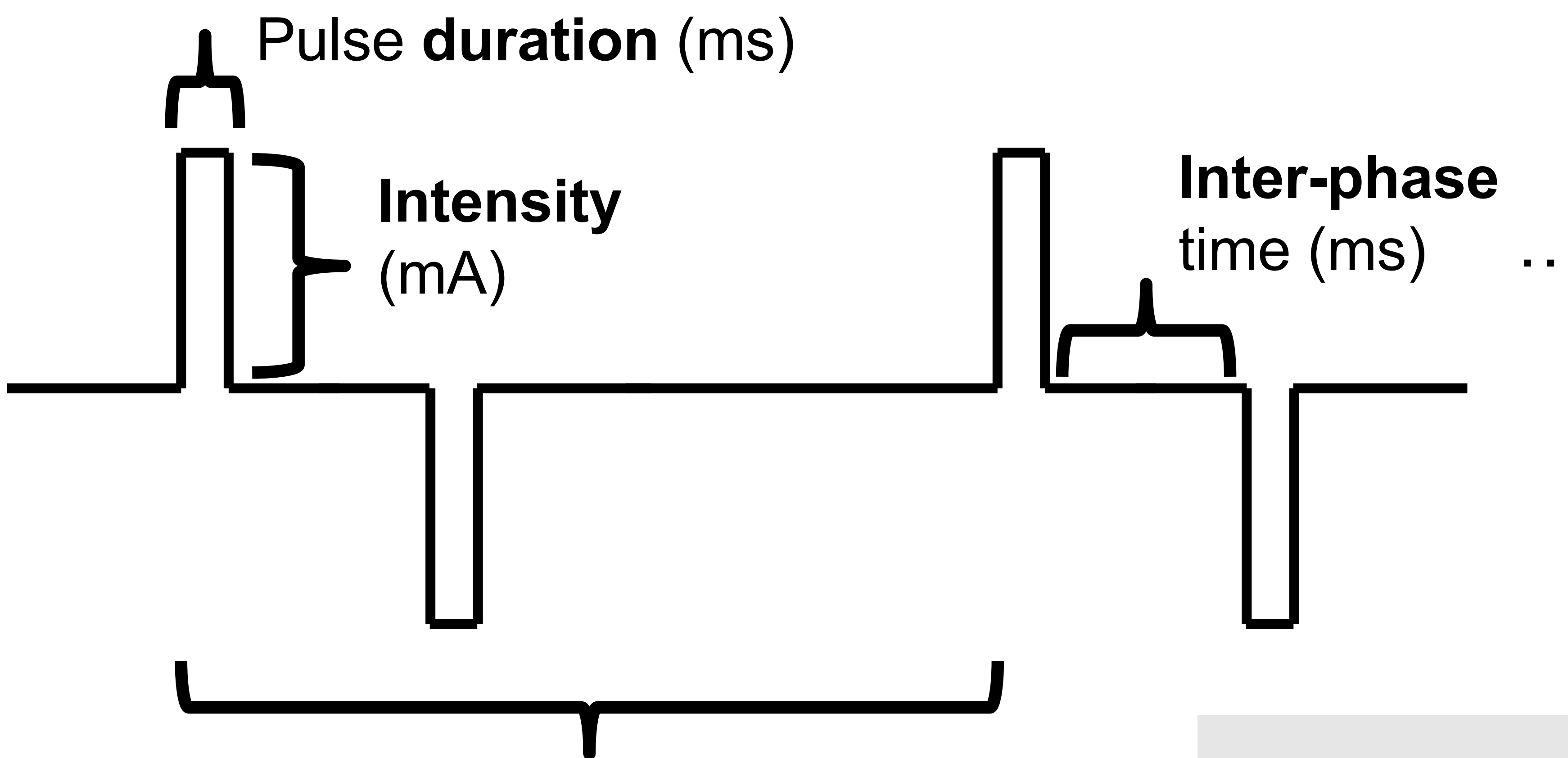
“Guarded” Tri-pole

Current flow

Select which electrodes on lead are active (used to pass current), the rest are inactive.



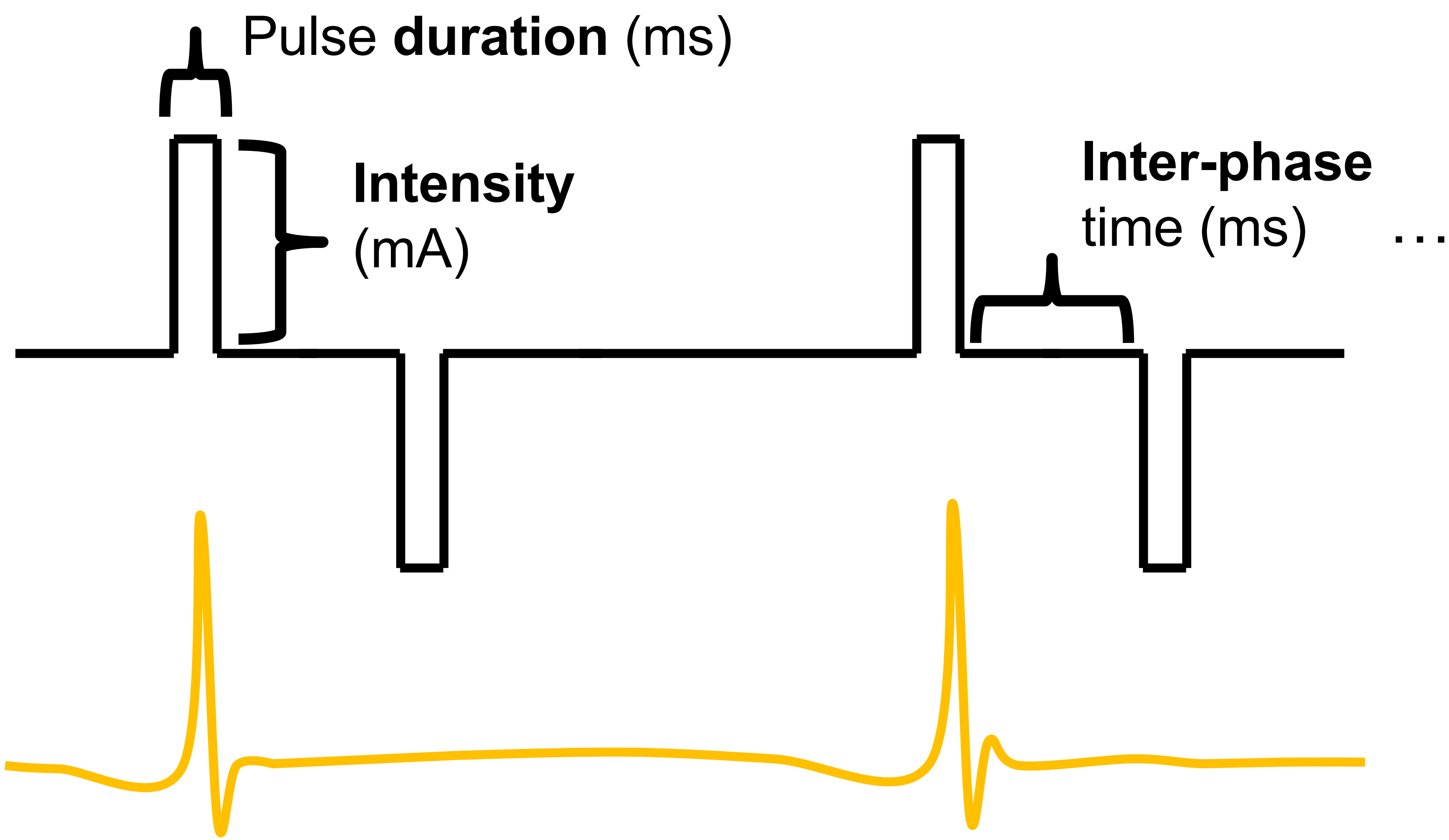
Stimulation is provided in pulse pairs (of opposite polarity) repeated at a **Pulse Period**



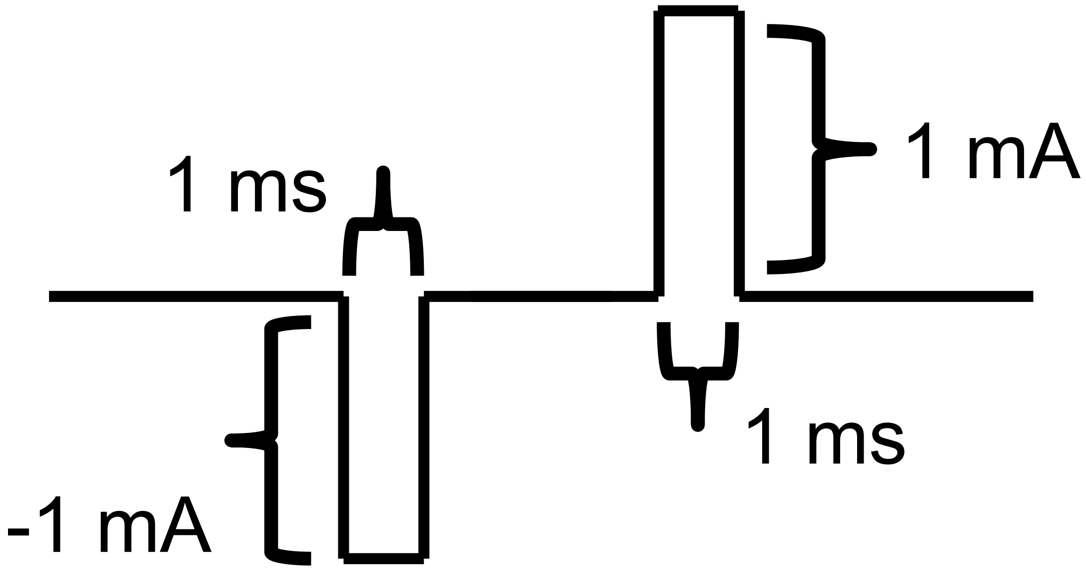
Pulse period (ms): Time from start of the leading pulse (given phase) to the next leading pulse (same phase)

Frequency (Hz) = 1 / Pulse period
Example: 1 ms pulse period is 1000 Hz

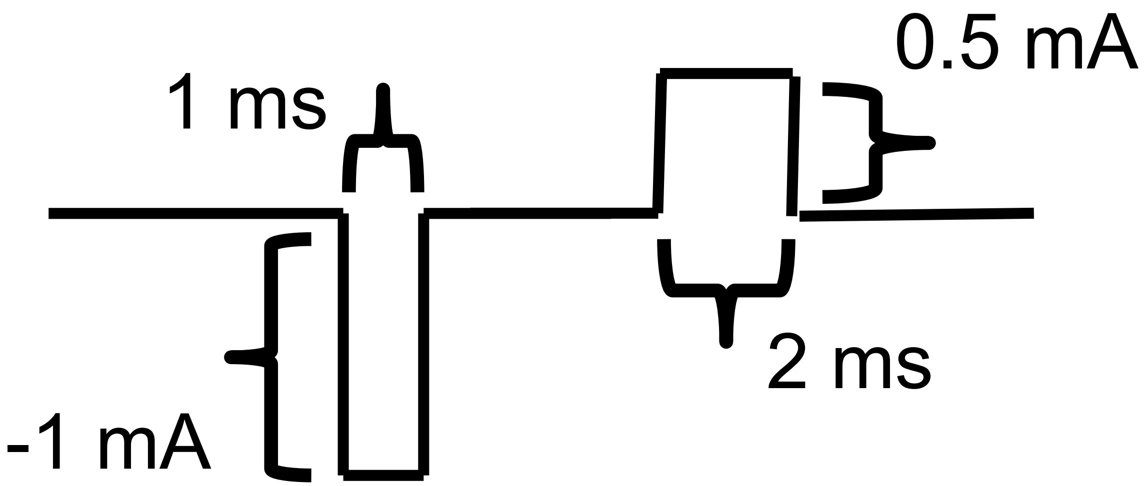
Stimulation is provided in pulse pairs (of opposite polarity) repeated at a **Pulse Period**



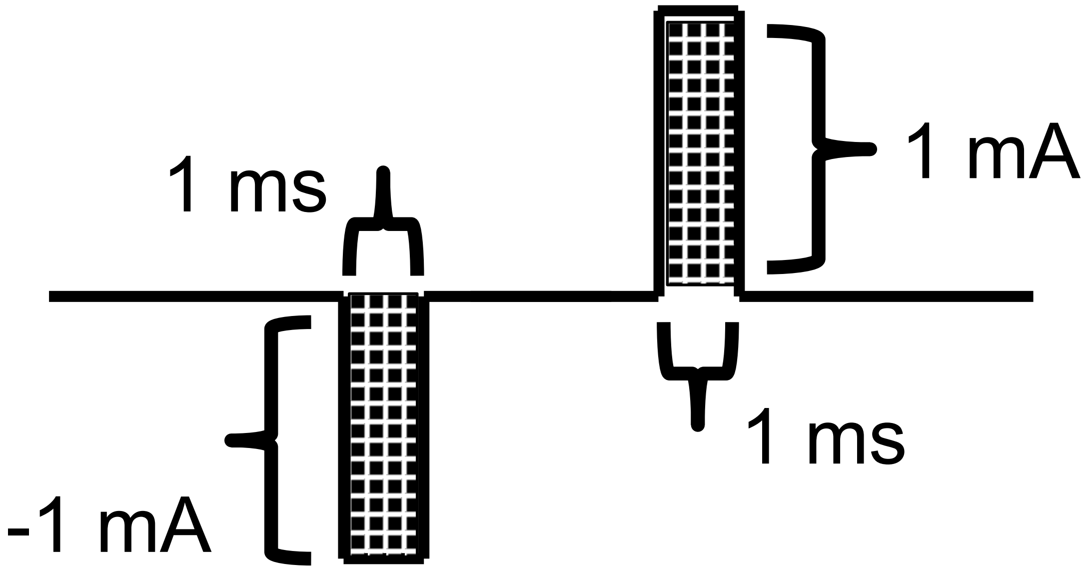
Action potentials may be triggered by just one phase, so at the stimulation ”frequency”.



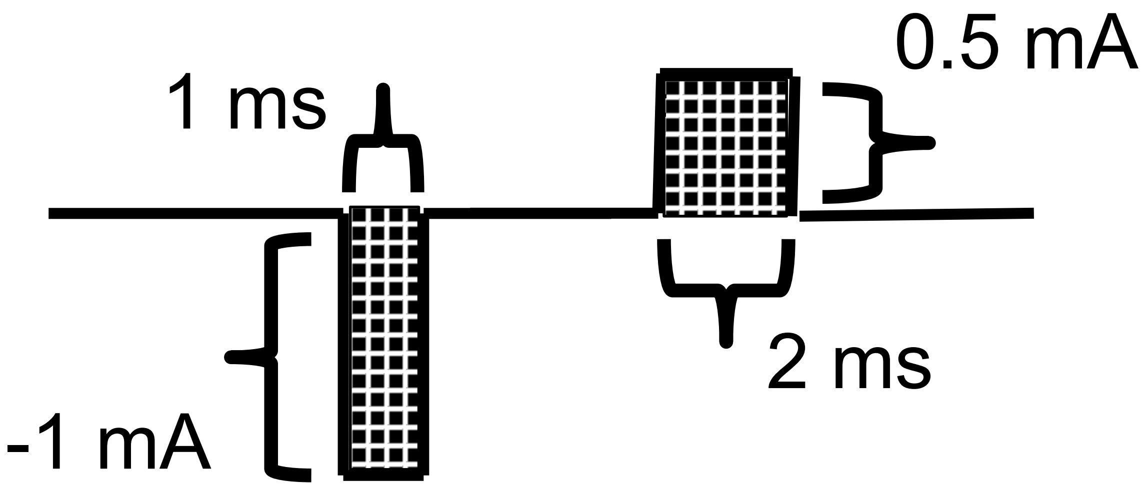
Symmetric biphasic stimulation: When the two pulse phases have the same duration and magnitude



Asymmetric biphasic stimulation: When the two pulse phases have different shape



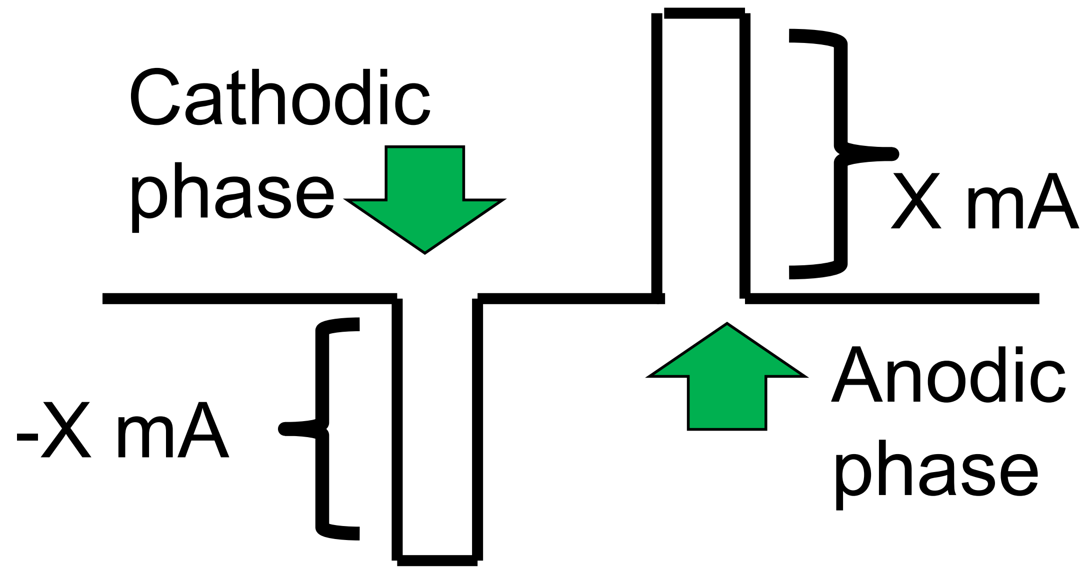
Symmetric biphasic stimulation: When the two pulse phases have the same duration and magnitude



Asymmetric biphasic stimulation: When the two pulse phases have different shape

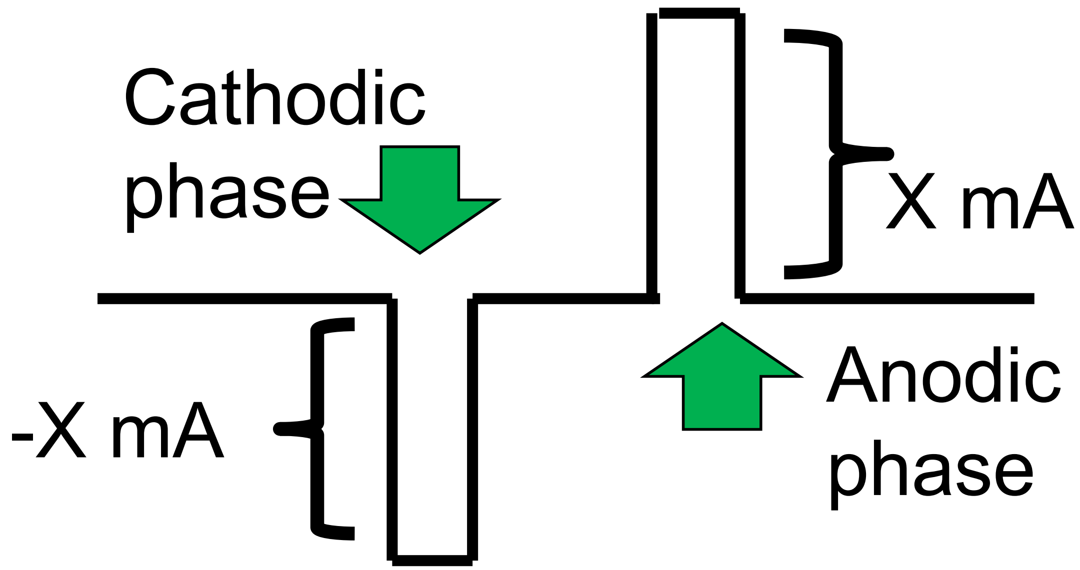
But invasive stimulation always **Charge Balanced**: Charge of the two phases add to zero.

Why **biphasic stimulation?**



- Only one phase (can be the leading cathodic phase) triggers action potential stimulation
  eg. 100 Hz stimulation will actually have 200 pulses per second (100 anodic and 100 cathodic) but is intended to produce action potentials at 100 Hz
- **Biphasic** may increase or decrease current threshold compared to **monophasic**

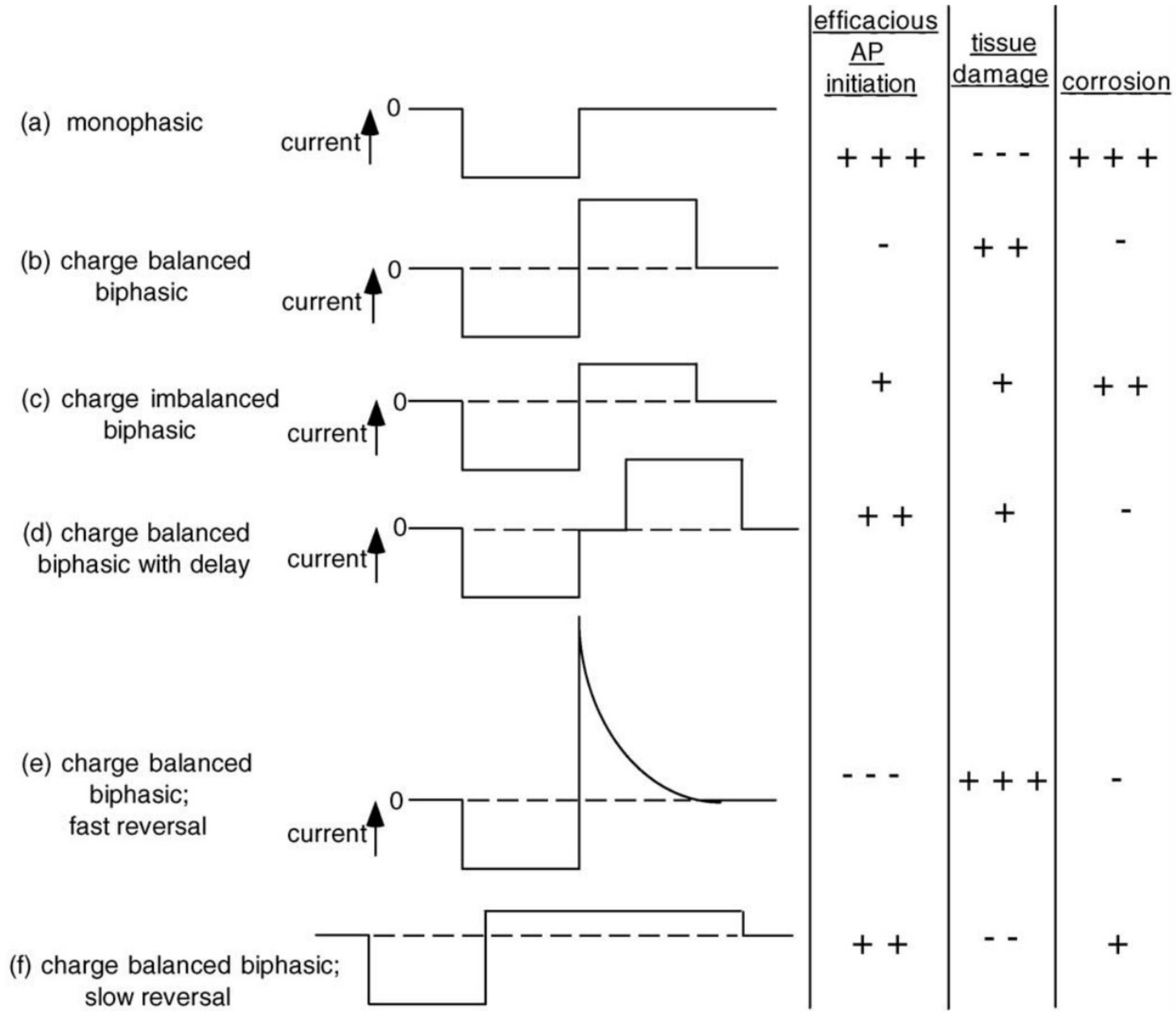
Why **biphasic stimulation?**



- Monophasic, or poorly designed biphasic stimulation, will lead to electrochemical products as electrodes, damaging tissue
- **Biphasic** stimulation essentially design to prevent electrochemical products while not impairing stimulation more then needed
- Note biphasic stimulation can also be injurious if not designed correctly.

- Pulses not always rectangular
- Inter-phase delay.

D.R. Merrill et al. / Journal of Neuroscience Methods 141 (2005) 171–198



Take away: Stimulation **DOSE** is all parameters that impact the location and waveform of current flow through tissue – since this governs what neuron responsible are possible and so therapy outcomes.

1. Which **electrodes** are used (size, position, bipolar, unipolar, tripolar).
2. What f**requency**?
3. Is **anodic or cathodic phase** first (always biphasic)?
4. **Intensity and pulse width** (for both phases if not symmetric. Shape is not rectangular. Inter-phase delay. Always charged balanced)

- Two devices with the same dose will have identical effects on the same body. Reporting dose underpins reproducibility. Summary metrics or terms (eg. "pulse density", "kHz", "Burst"…) don't replace need to fully account for dose.
- Dose may be adjusted (e.g., based on patient response / closed-loop). These "dose instructions" underpin reproducibility.
- The dose <u>governs</u> but does not strictly <u>determine</u> the effects on the body (anatomy and physiological state matter also).

Take away: Stimulation **DOSE** is all parameters that impact the location and waveform of current flow through tissue – since this governs what neuron responsible are possible and so therapy outcomes.

1. Which **electrodes** are used (size, position, bipolar, unipolar, tripolar).
2. What f**requency**?
3. Is **anodic or cathodic phase** first (always biphasic)?
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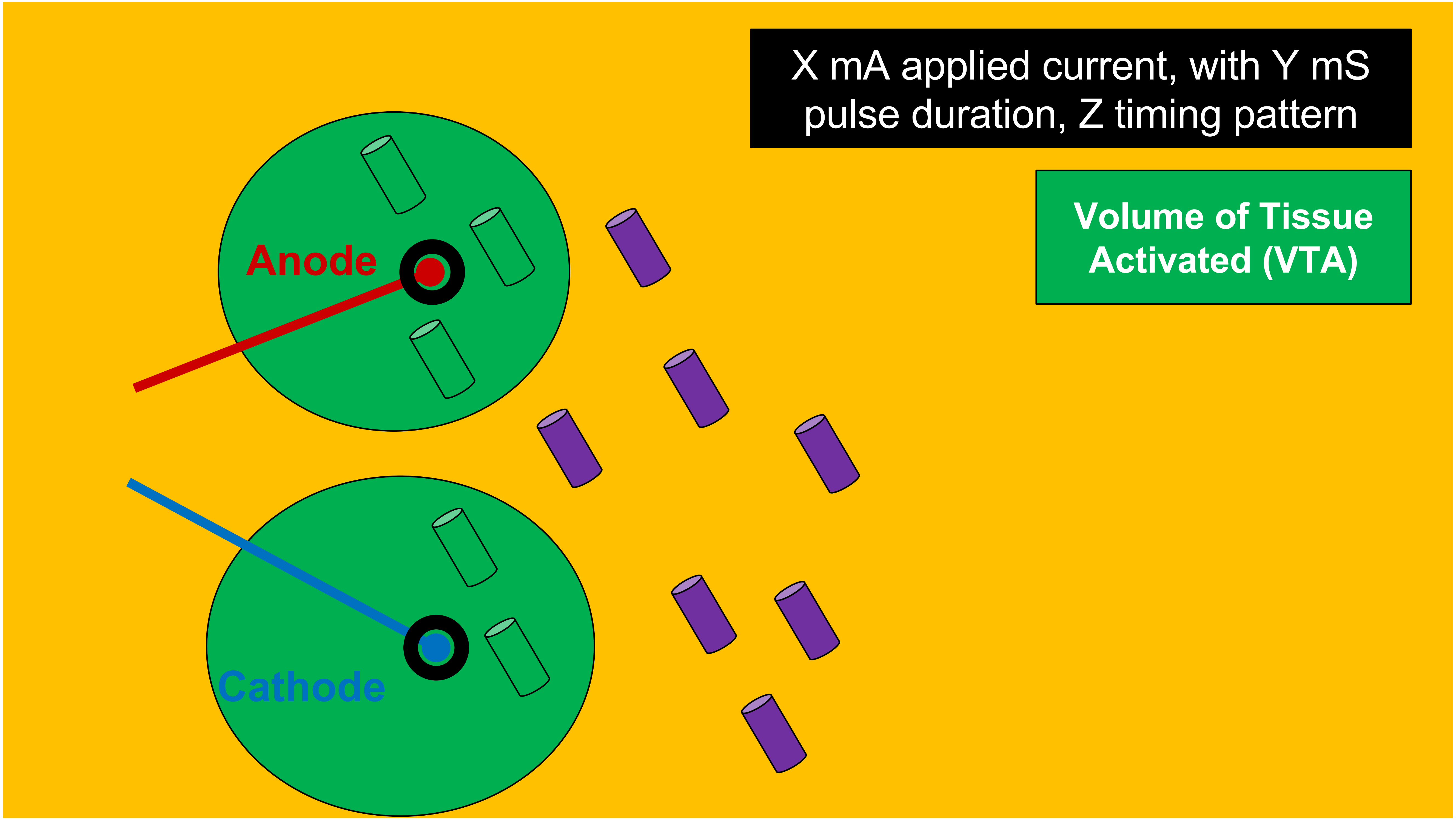
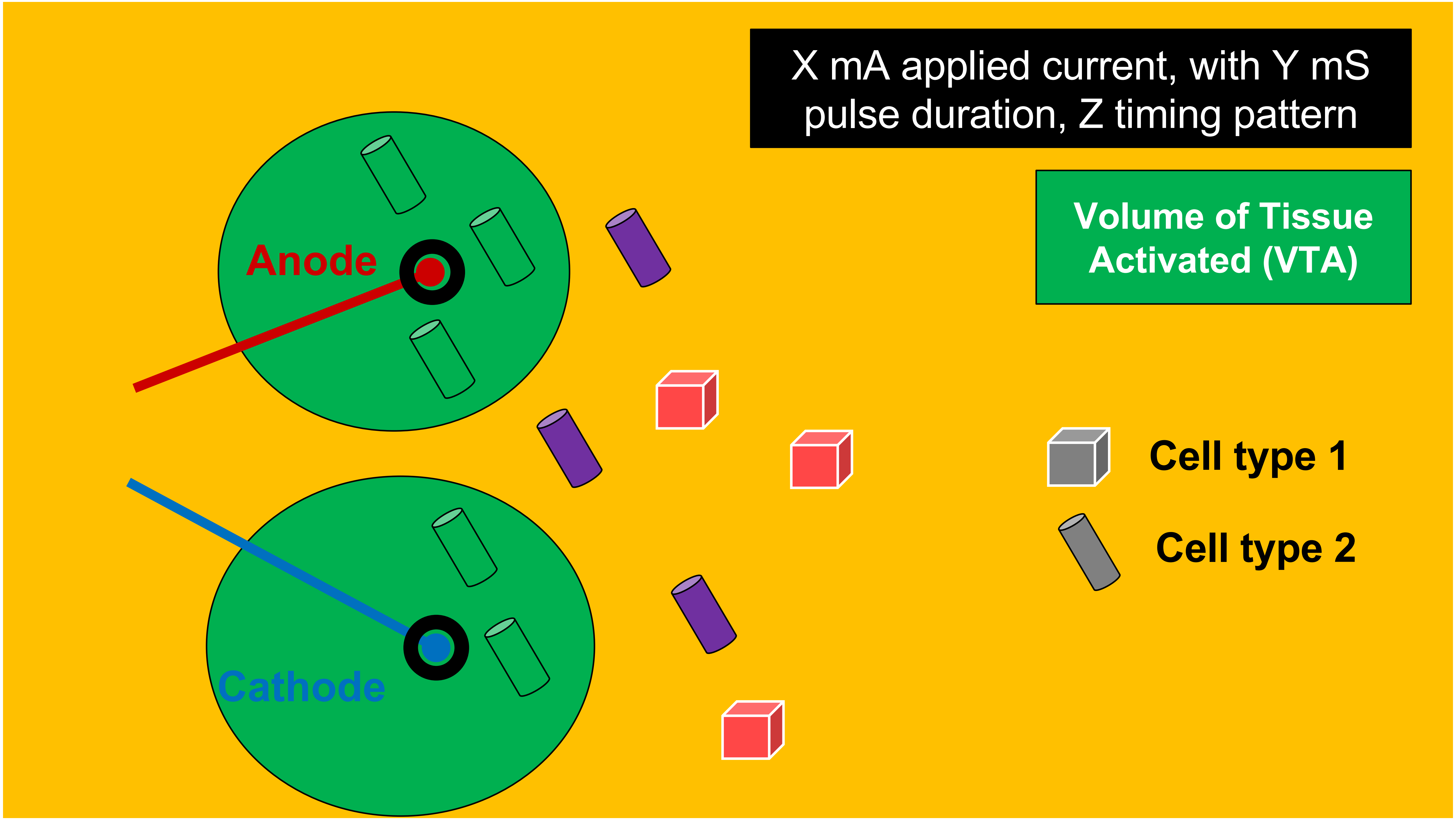
- Two devices with the same dose will have identical effects on the same body. Reporting dose underpins reproducibility. Summary metrics or terms (eg. “duty cycle”, “kHz”, “Burst”…) don’t replac
- Dose may be adjusted (e.g., based instructions” underpin reproducibilit
- The dose governs but does not stric and physiological state matter also)

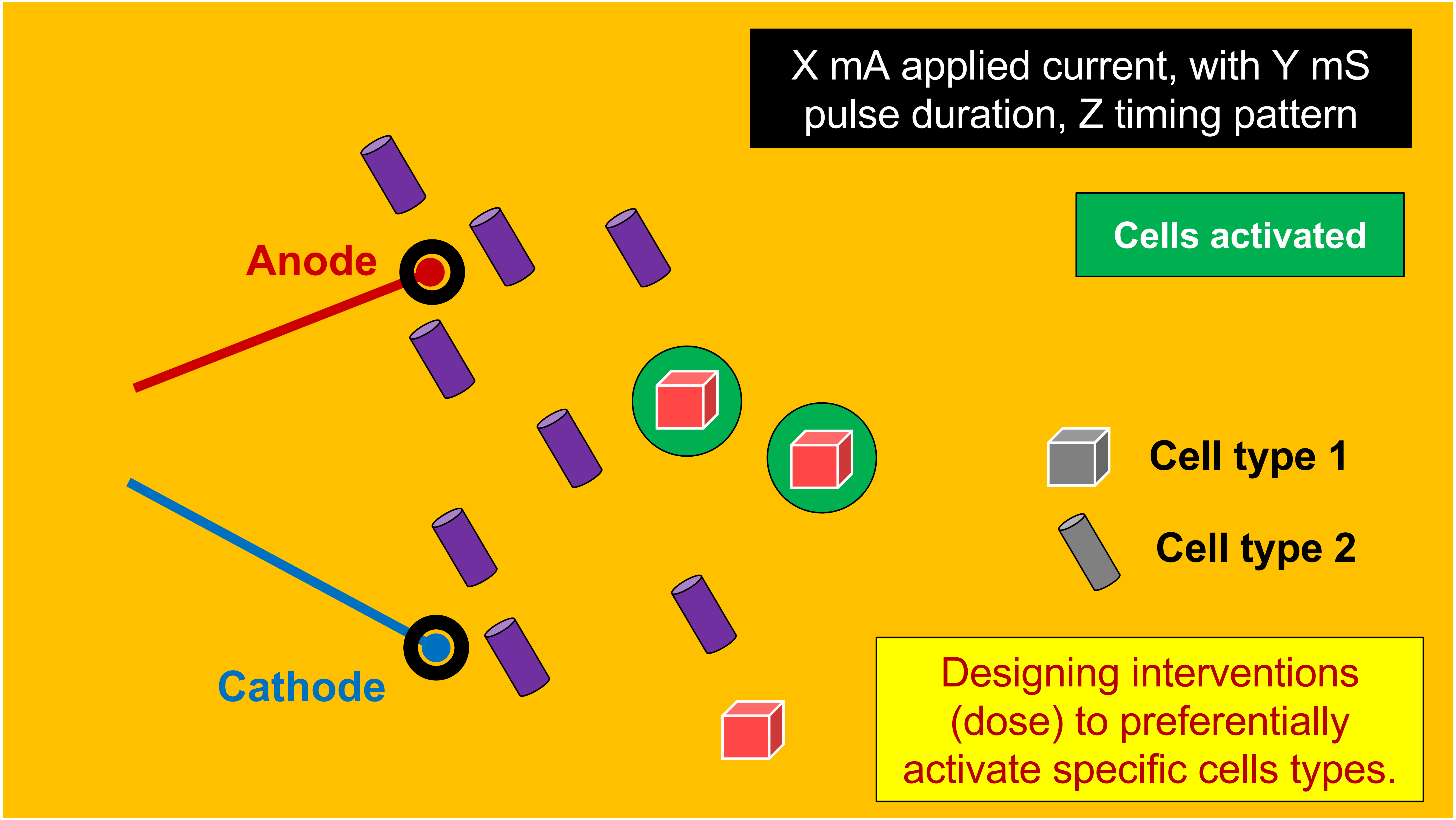
Friday 10:40 AM: F6 - Neural Engineering: Engineering Principles of DBS and SCS in Clinical Practice: Emerging Concepts

Part 3: Three things that change everything.

i. Cell type targeting.
ii. Sub-threshold modulation.
iii. State-dependent stimulation.


X mA applied current, with Y mS pulse duration, Z timing pattern
Volume of Tissue Activated (VTA)
Anode
Cathode


X mA applied current, with Y mS pulse duration, Z timing pattern
Volume of Tissue Activated (VTA)
Anode
Cathode
Cell type 1
Cell type 2


X mA applied current, with Y mS pulse duration, Z timing pattern
Cells activated
Anode
Cathode
Cell type 1
Cell type 2
Designing interventions (dose) to preferentially activate specific cells types.

X mA applied current, with Y mS pulse duration, Z timing pattern

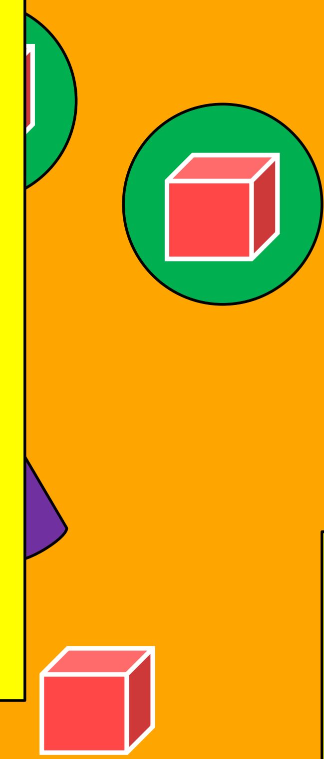
Which cell types ("elements") are activated by stimulation:

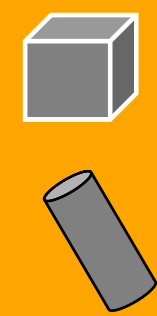
1) Big vs little axons
2) Axon vs dendrite vs soma
3) Glia
4) Endothelial cells (Neurovascular Stimulation)
5) Extracellular changes

....

Friday 4 PM: Session F7: Neuromodulation Fundamentals: Non-Neuronal Effects

Cells activated

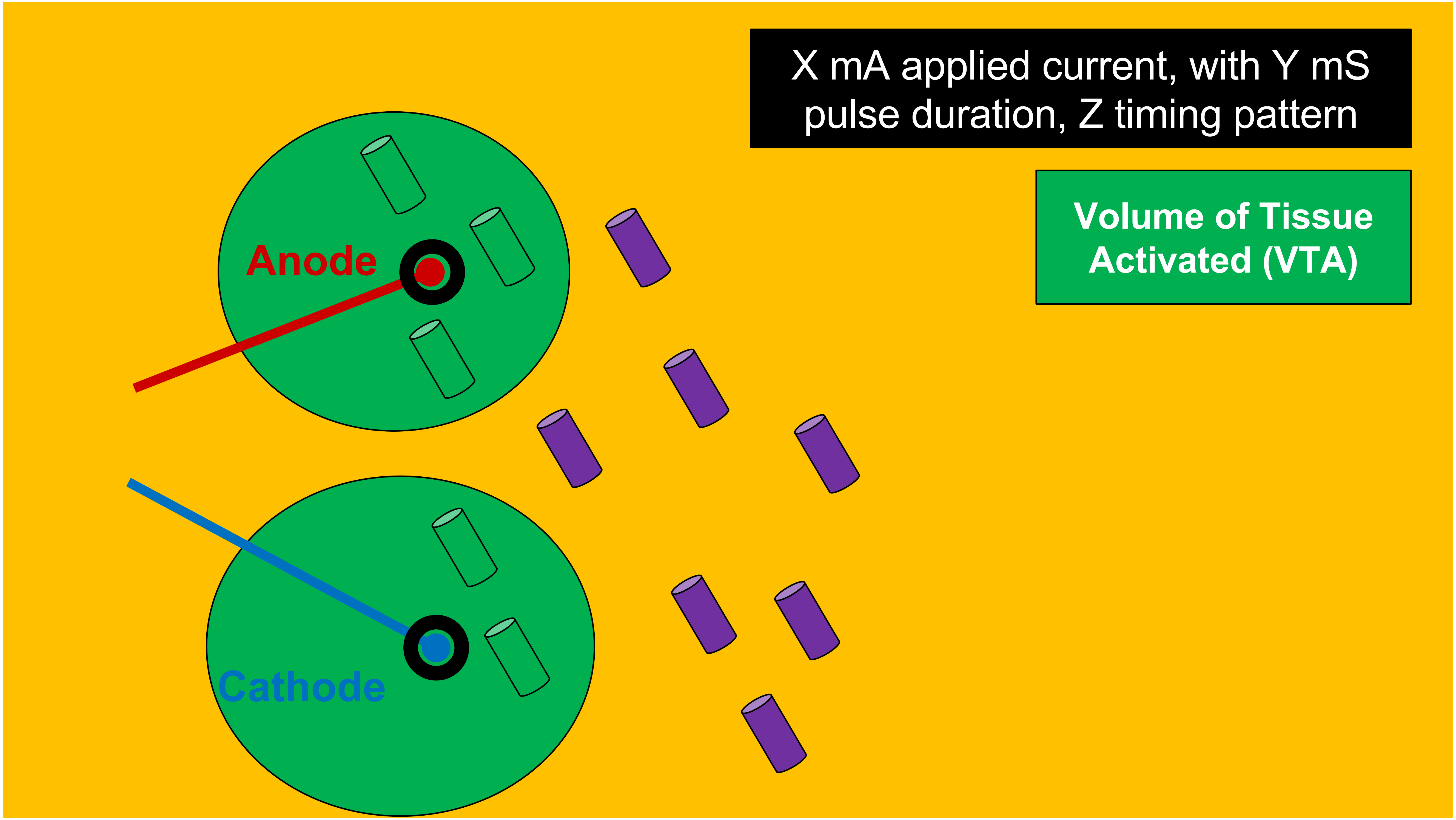


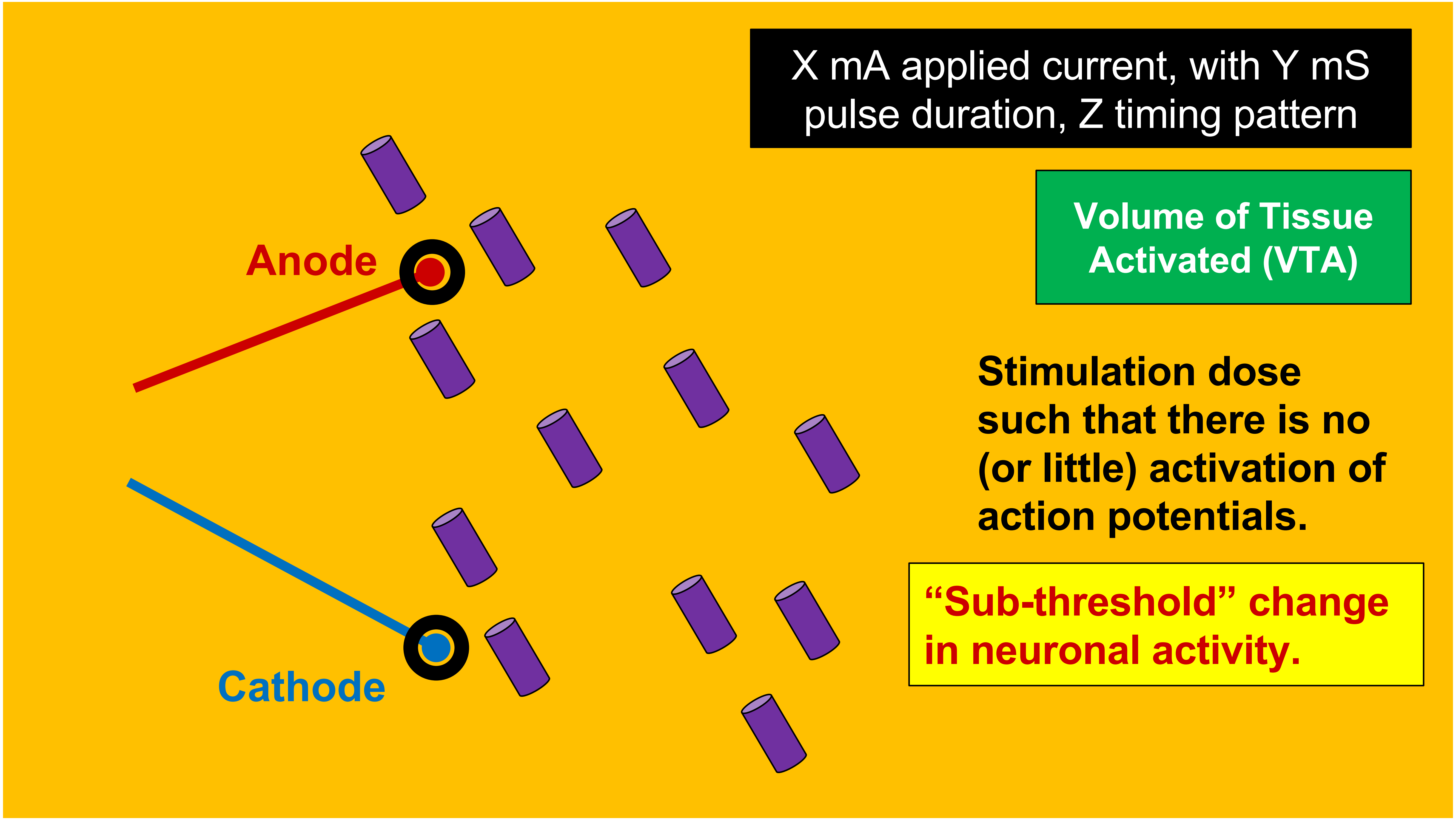


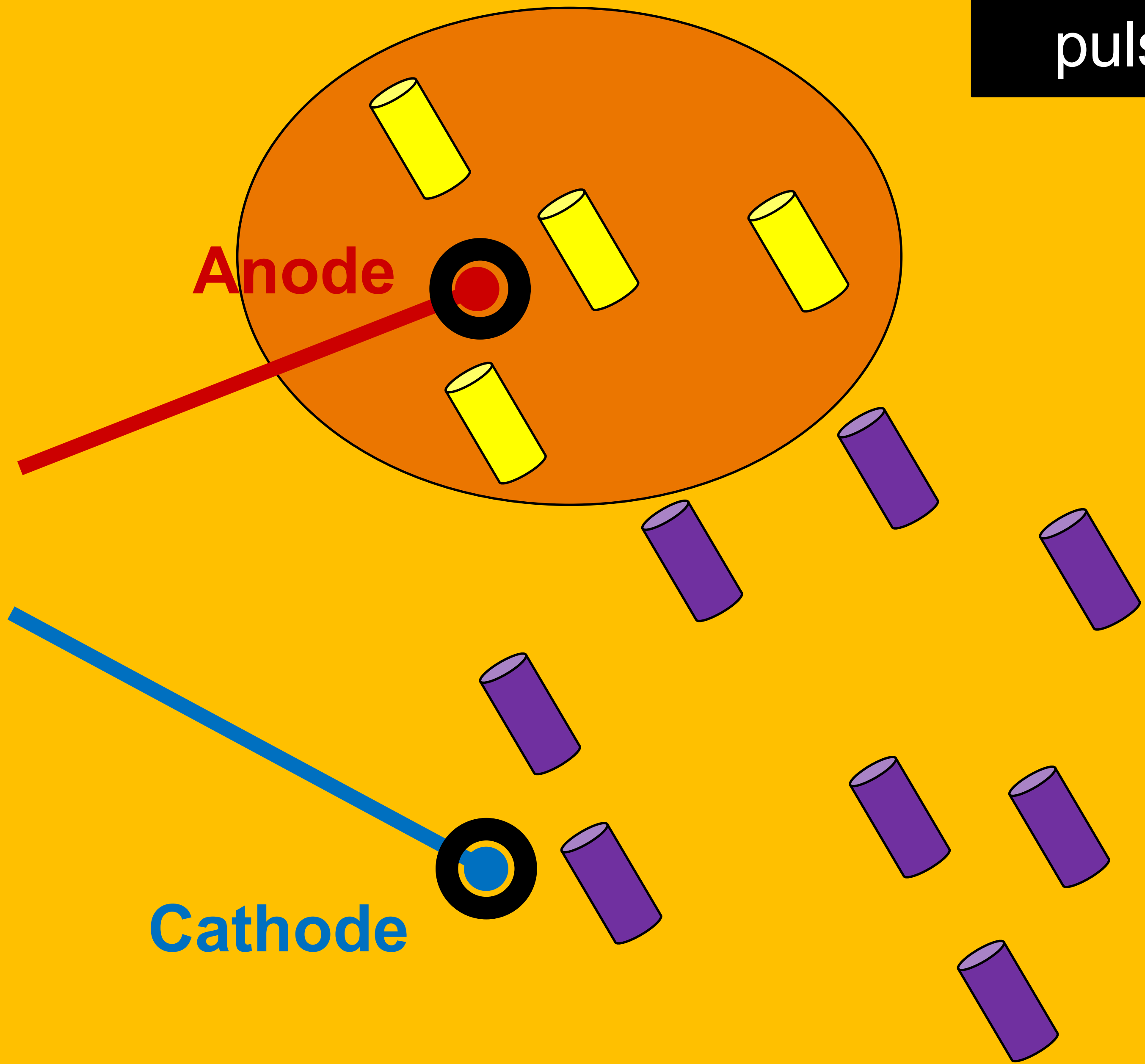
Cell type 1

Cell type 2

Designing interventions (dose) to preferentially activate specific cells types.


X mA applied current, with Y mS pulse duration, Z timing pattern
Volume of Tissue Activated (VTA)
Anode
Cathode


X mA applied current, with Y mS pulse duration, Z timing pattern
Volume of Tissue Activated (VTA)
Anode
Cathode
Stimulation dose such that there is no (or little) activation of action potentials.
"Sub-threshold" change in neuronal activity.

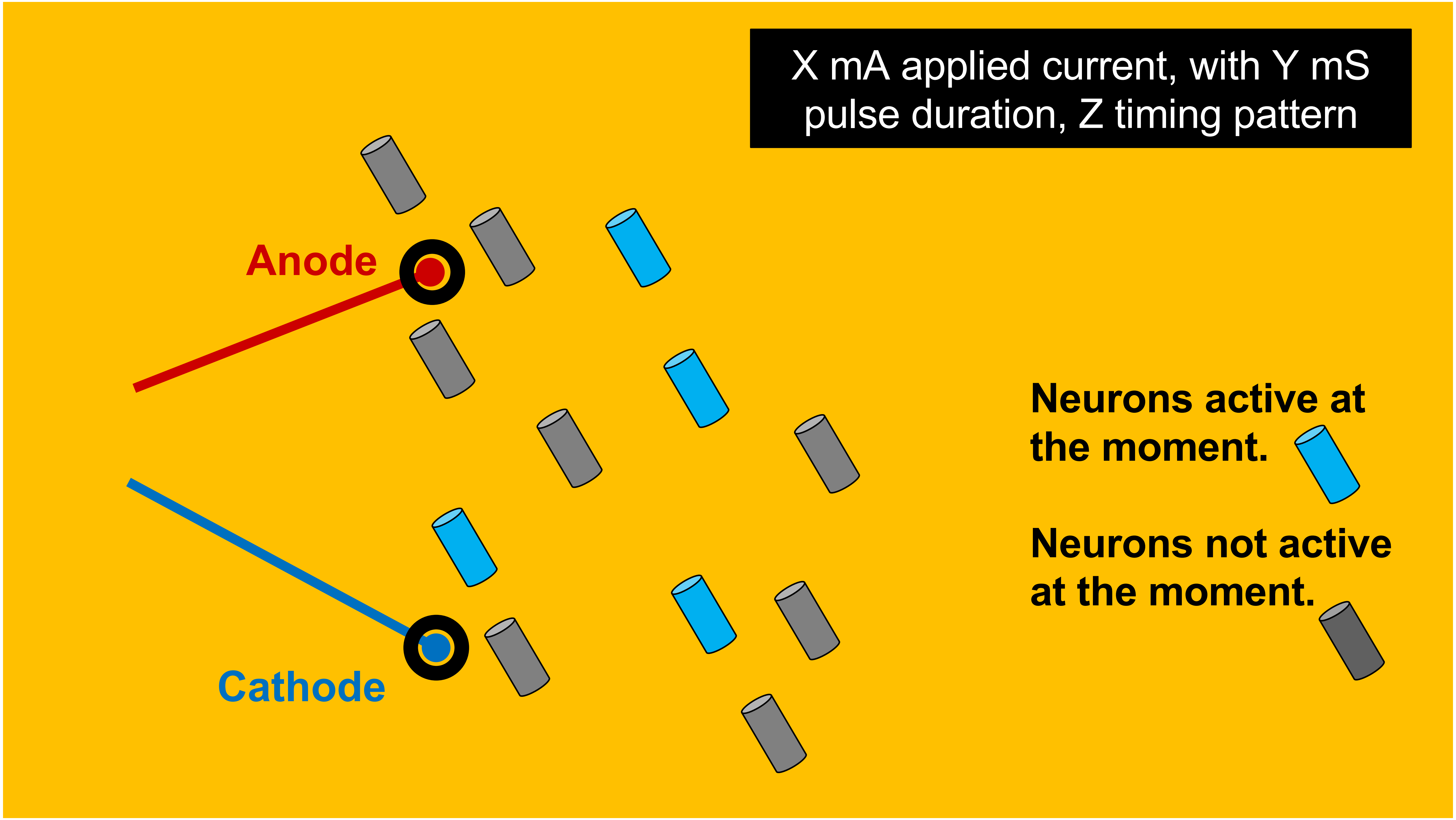


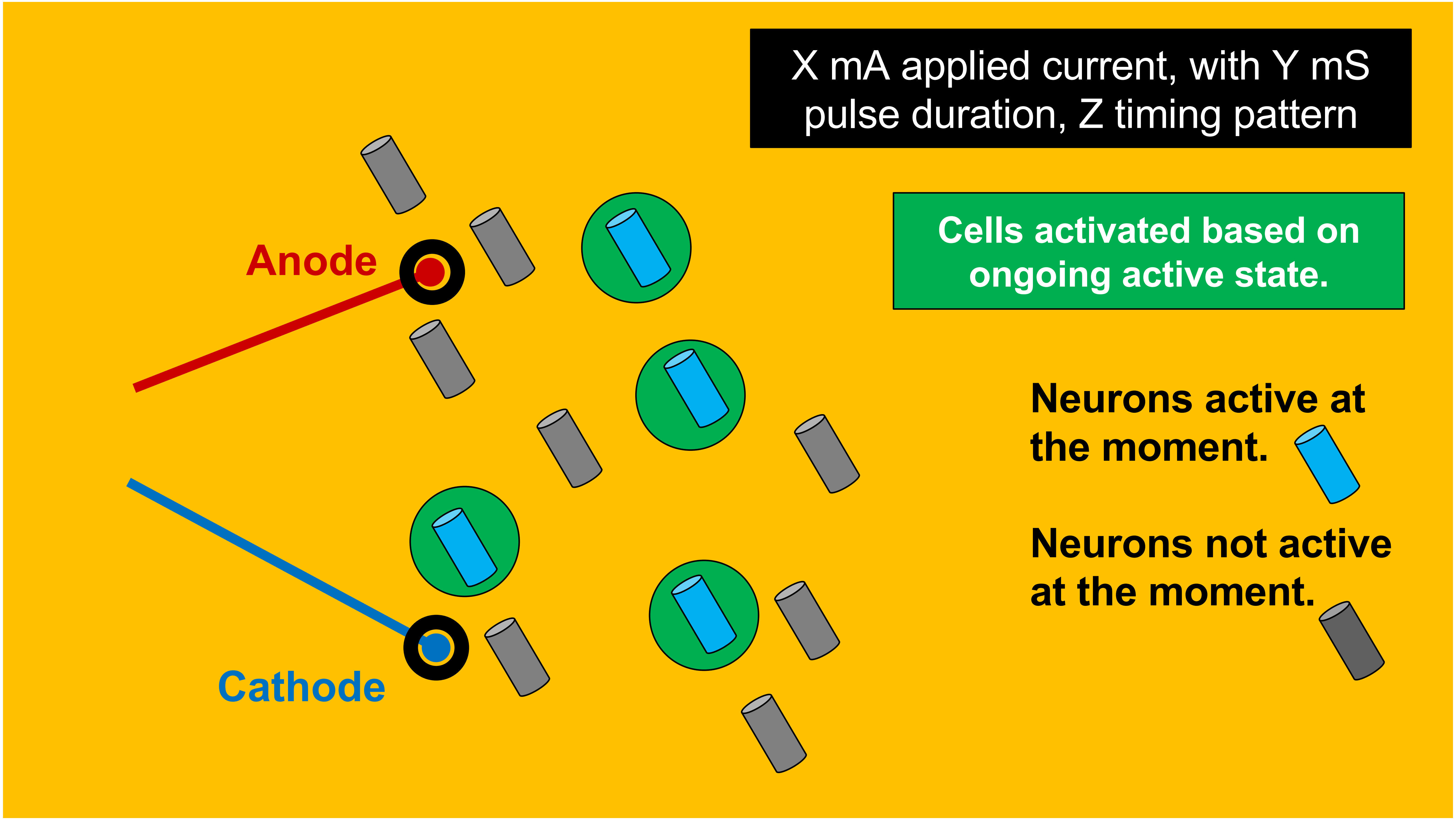
X mA applied current, with Y mS pulse duration, Z timing pattern

Volume of Tissue Modulated

Stimulation dose such that there is no (or little) activation of action potentials.

“Sub-threshold” change in neuronal activity.


X mA applied current, with Y mS pulse duration, Z timing pattern
Anode
Cathode
Neurons active at the moment.
Neurons not active at the moment.


X mA applied current, with Y mS pulse duration, Z timing pattern
Cells activated based on ongoing active state.
Anode
Cathode
Neurons active at the moment.
Neurons not active at the moment.

Part 3: Three things that change everything.

i.	Cell type targeting.	Universal.
ii.	Sub-threshold modulation.	Universal.
iii.	State dependent stimulation.	Universal.

Pre-Meeting Course: **Engineering principles of DBS and SCS in clinical practice: General introduction and emerging concepts**, Jan 12, 2023
Course Directors: Marom Bikson and Scott Lempka

Lecture 1: **Neurostimulation fundamentals: Dose, current flow, and neural activation**

Marom Bikson