A simple introduction to how neuromodulation devices work:

What is neuromodulation dose? What makes difference devices different?
Common terminology in neuromodulation. Basic cellular mechanisms.
Open to discussion on specific clinical applications.

Oct 18, 2023

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

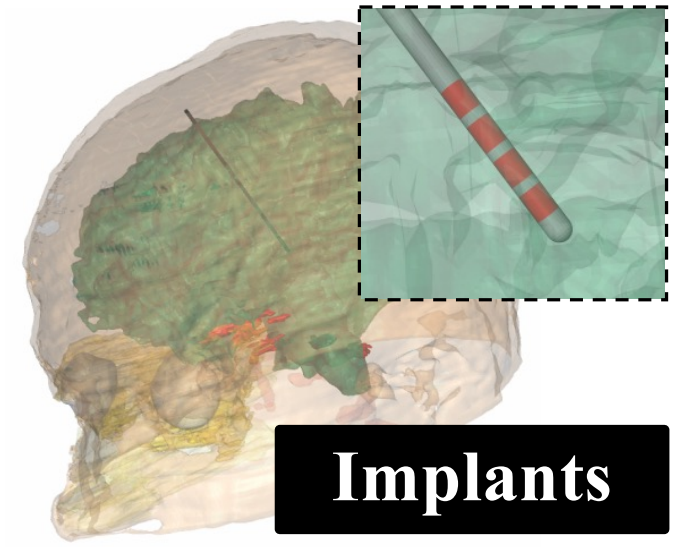
Support

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

Slides @MaromBikson

Part 0: Neuromodulation / Brain Stimulation / Electrical Stimulation **Dose**

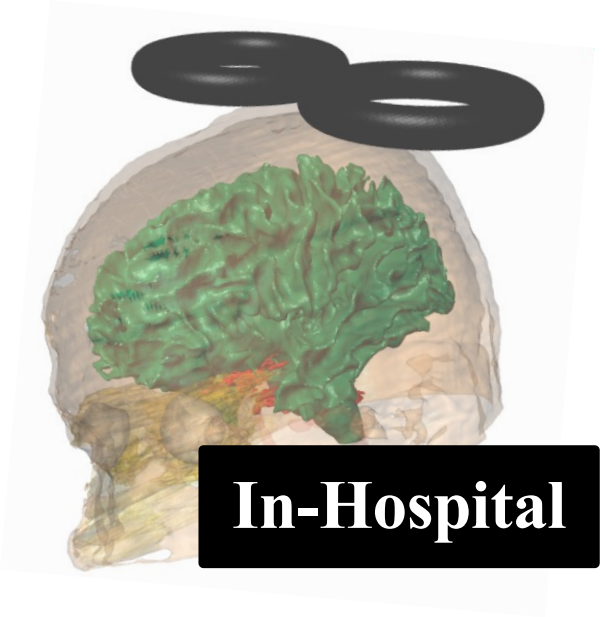
What defines neuromodulation technologies is how energy is delivered to what target



Implants

Deep Brain Stimulation (DBS)

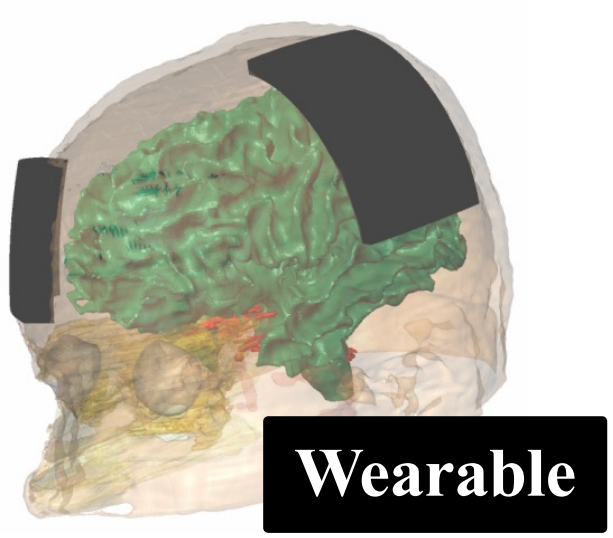
Spinal Cord Stimulation (SCS)



In-Hospital

Transcranial Magnetic Stimulation (TMS)

Electroconvulsive Therapy



Wearable

Transcranial Electrical Stimulation (tES)

Transcranial Direct Current Stimulation (tDCS)

What is Neuromodulation Dose?

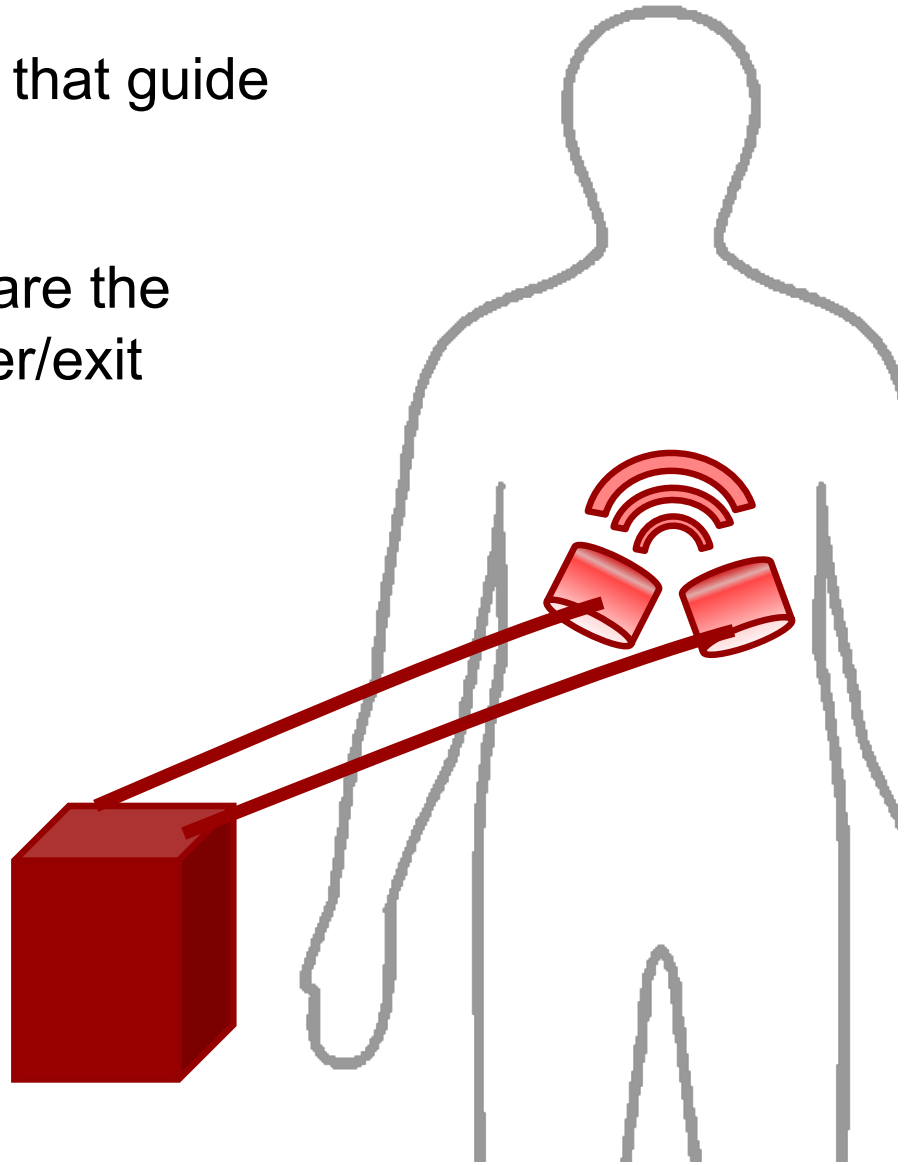
Only those aspects of the neuromodulation device that guide the delivery of energy (electricity) into the body.

1) The position of the electrodes. The electrodes are the only part of the device when electricity can enter/exit from the device. (for TMS its the coils)

Example: 1 cm^2 electrode placed epidurally over T1

2) The intensity and timing of pulses applied by the device through the electrode to the body.

Example: 1 mA amplitude, pulses at 100 Hz



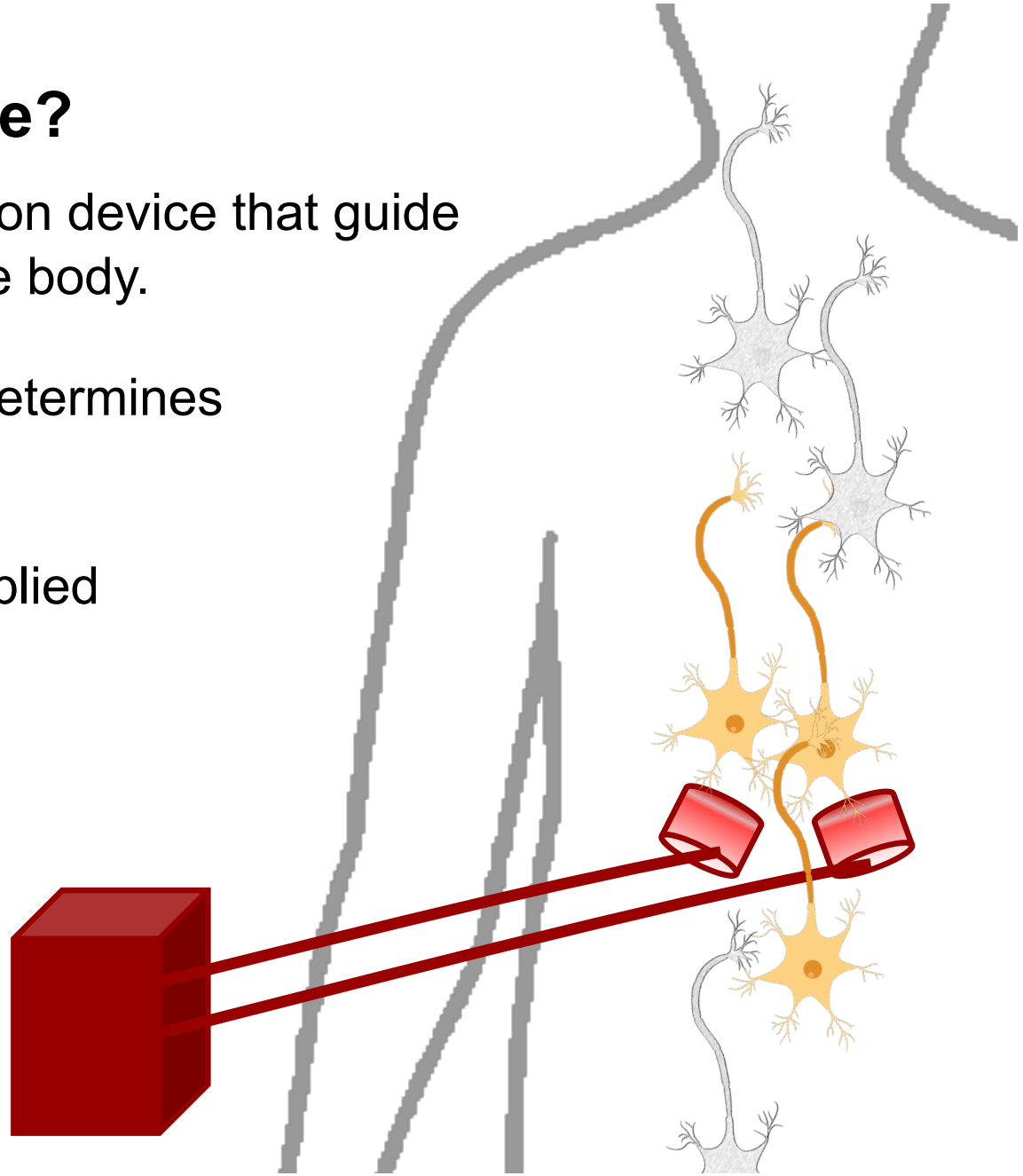
What is Neuromodulation Dose?

Only those aspects of the neuromodulation device that guide the delivery of energy (electricity) into the body.

1) The position of the electrodes (coil) determines what parts /neurons are stimulated.

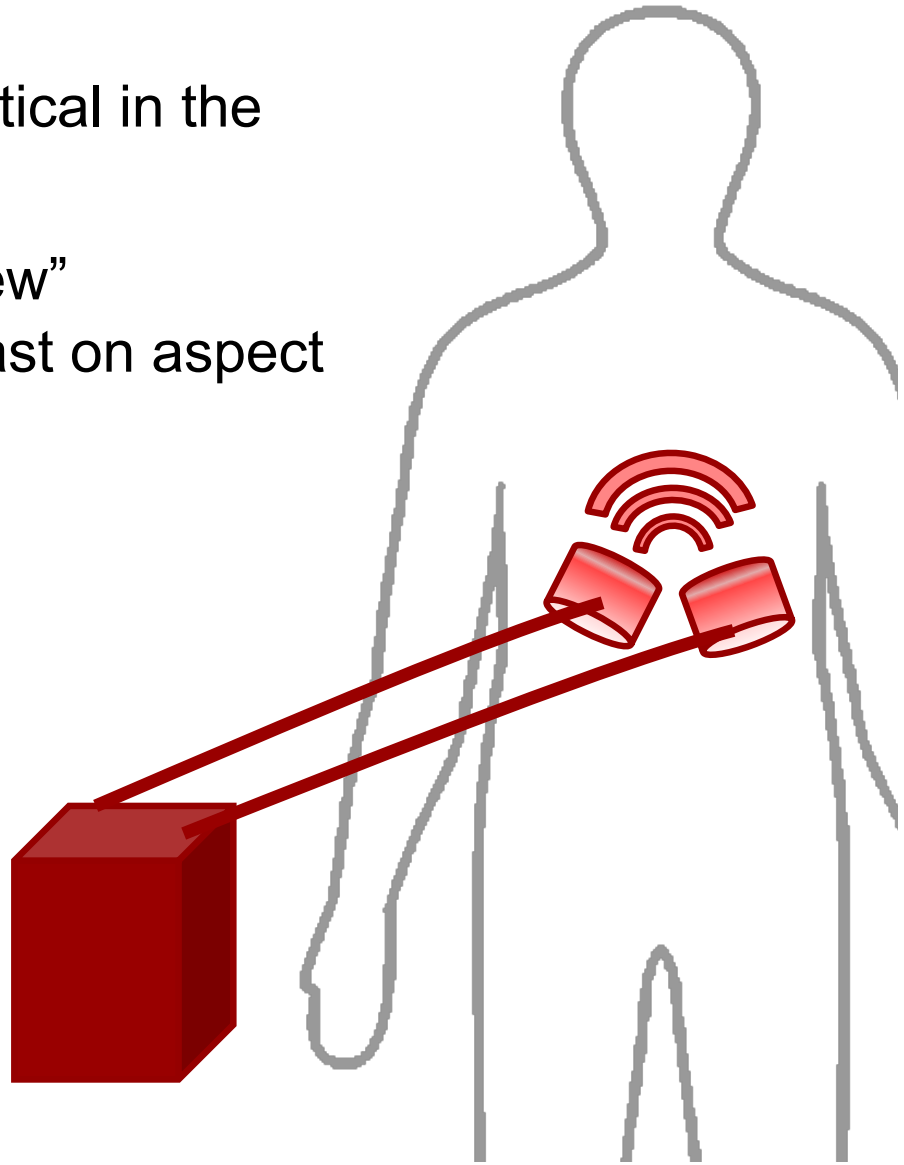
2) The intensity and timing of pulses applied by the device determines how neurons respond.

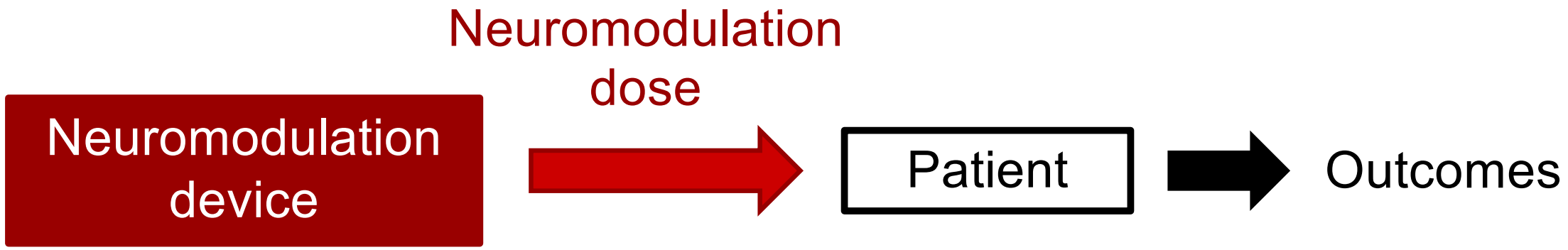
Neurons are exposed to the same waveform (eg. 100 Hz) as generated by the device. And respond more to higher intensity.



What is Neuromodulation Dose?

- Two devices that apply the same dose are identical in the effects they produce on the body
- Conversely, regarding effects on the body a “new” neuromodulation deice should change on at least on aspect of dose.
- Device features of than those governing dose matter (e.g., battery life, MRI conditional…) but for different reasons
- Each device can provide many different doses. And each device need to adjusted to a person / over time. Dose instructions are required guidance on how to adjust dose.





Dose instructions indicate how to adjust dose for each indication / patient

Brain Stimulation (2012) 5, 435–53

ELSEVIER

BRAIN
STIMULATION

www.brainstimjrnl.com

REVIEW ARTICLE

Fundamentals of transcranial electric and magnetic stimulation dose: Definition, selection, and reporting practices

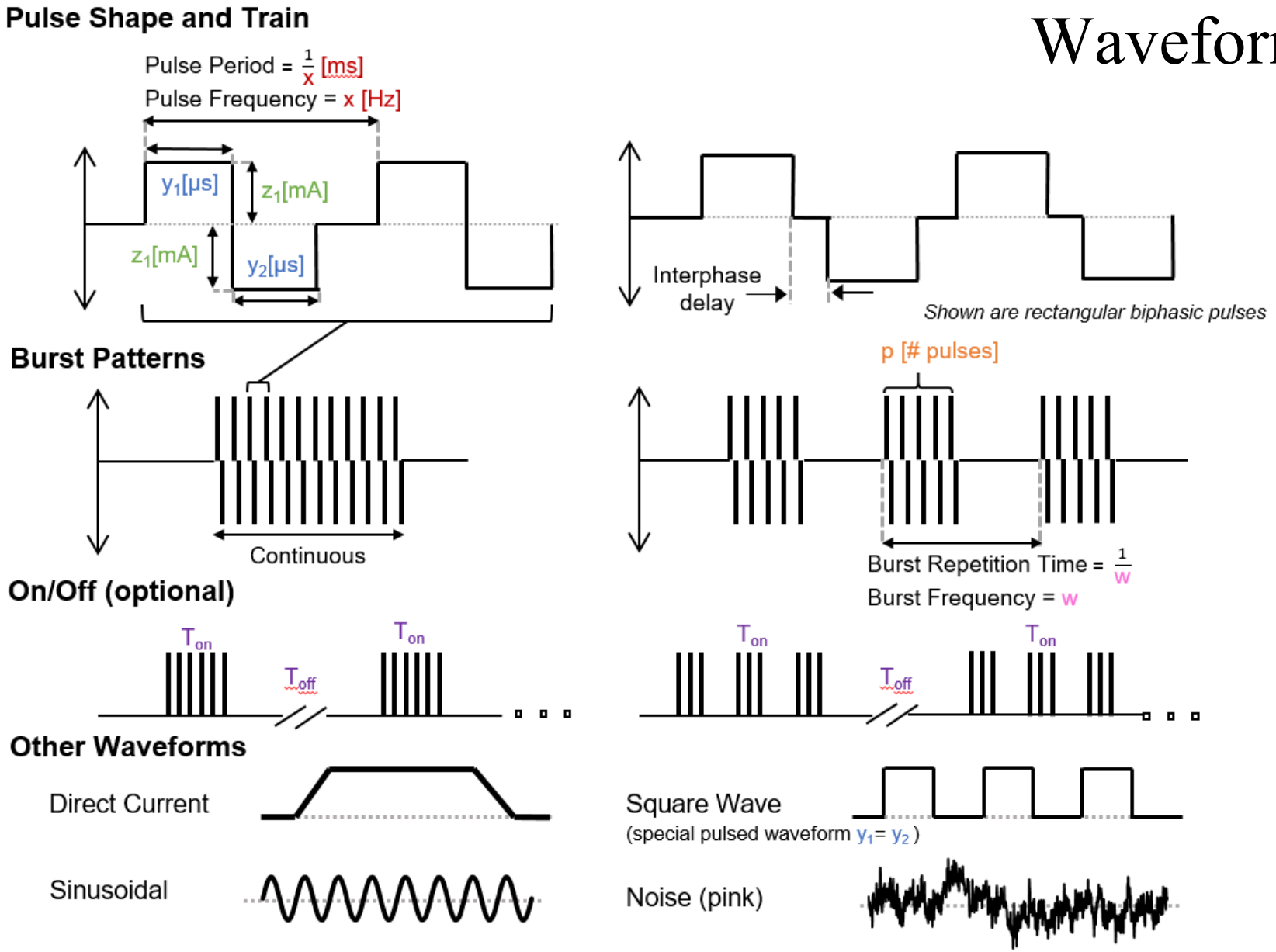
Angel V. Peterchev,[a,b] Timothy A. Wagner,[c,d] Pedro C. Miranda,[e] Michael A. Nitsche,[f] Walter Paulus,[f] Sarah H. Lisanby,[a,g] Alvaro Pascual-Leone,[h] Marom Bikson[i]

“EM stimulation is be defined by all parameters of the stimulation device that affect the electric and current density fields generated in the body”

1) Stimulation electrode configuration parameters: shape, size, position, and electrical properties

2) Electrode current or voltage waveform parameters: pulse amplitude, width, polarity, repetition frequency, train duration, interval and number of stimulation sessions

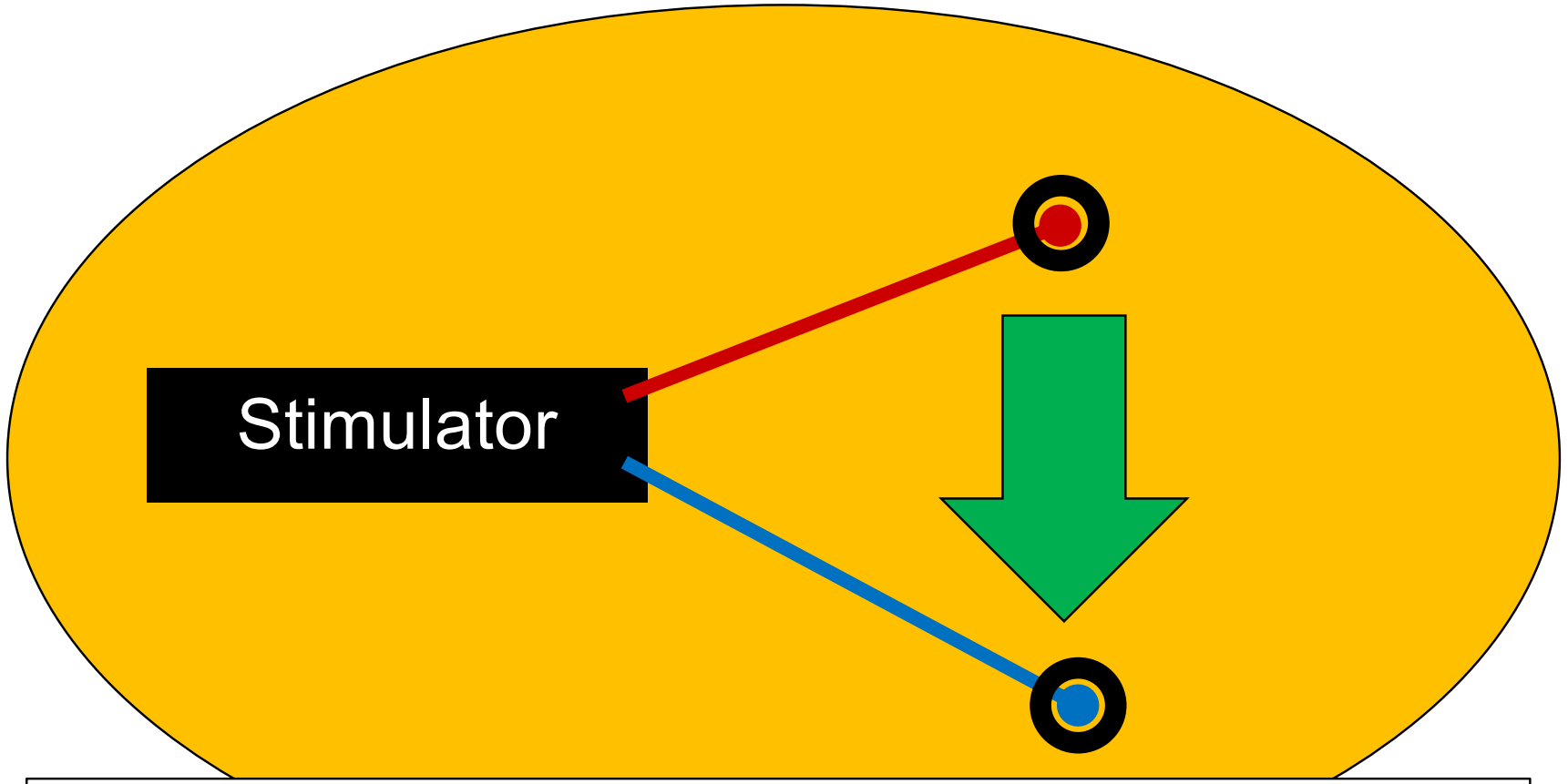
Waveform Option*



*Which options are available depends on device technology (eg. invasive / non-invasive, electric / magnetic)

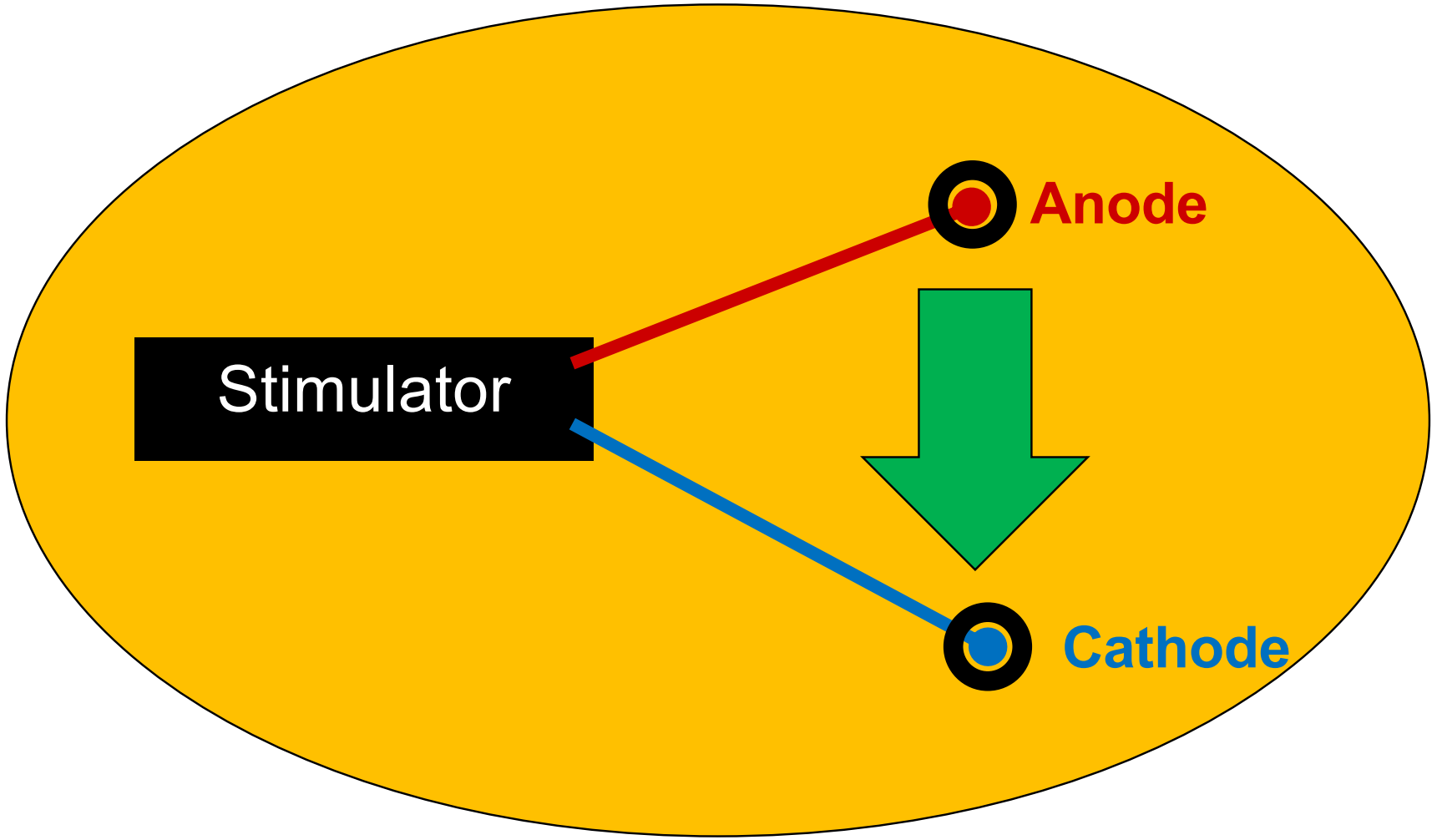
Part 1: Electrodes, current flow patterns, current density, electric field, tissue resistivity and impedance

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

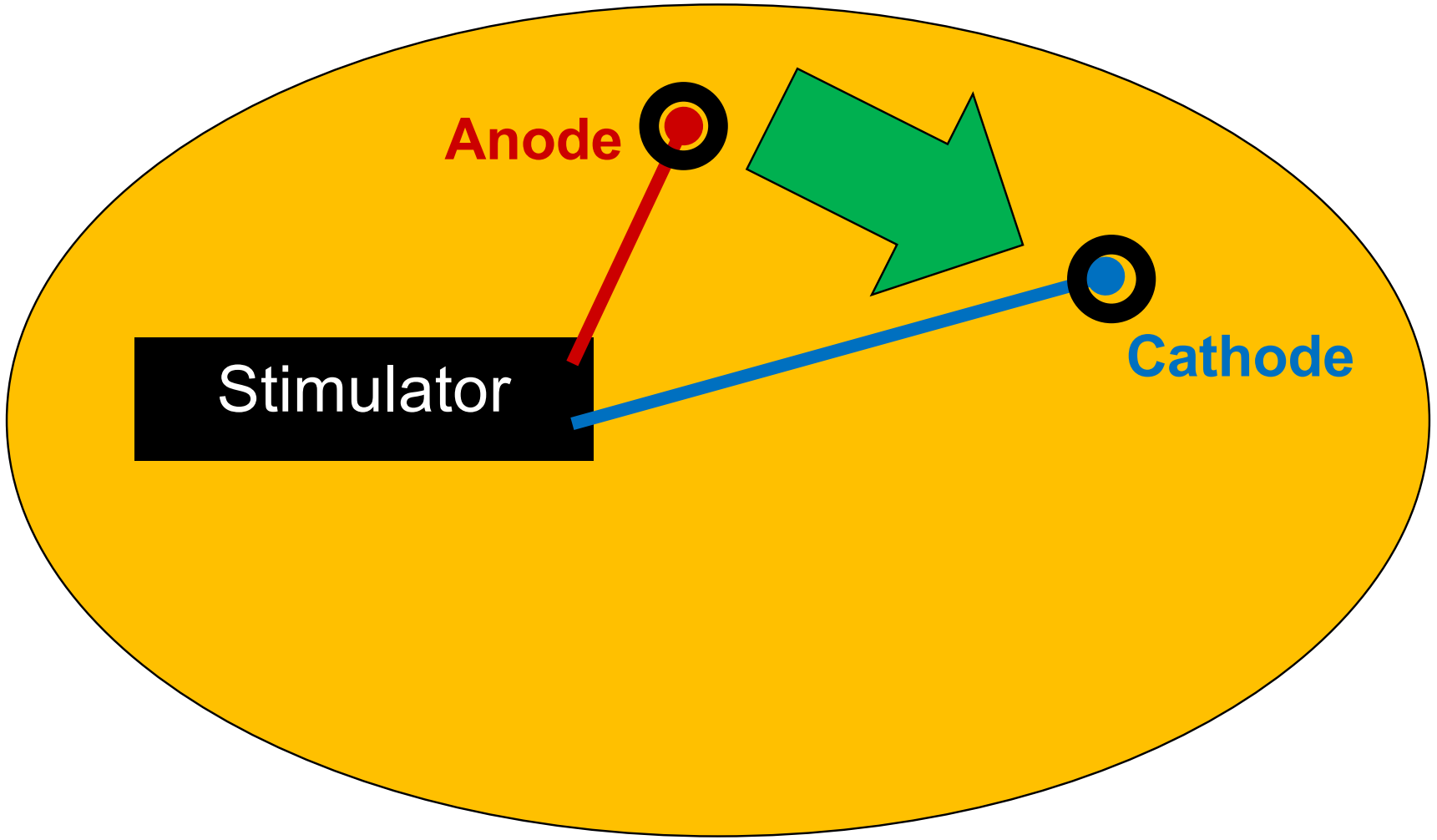


Current flows from the stimulator, through the wires (leads) and to exposed metal contacts (**Electrodes**)

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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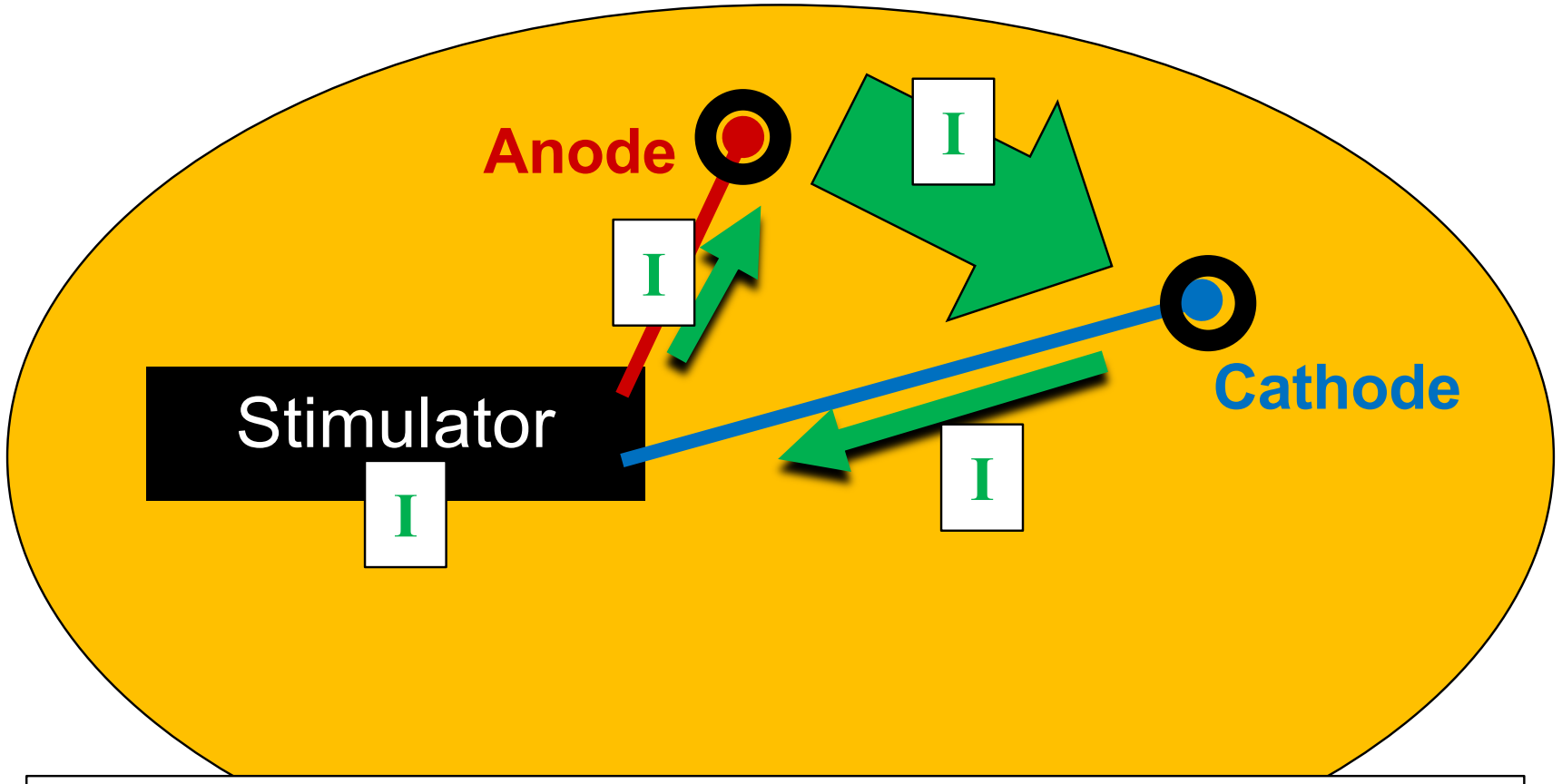
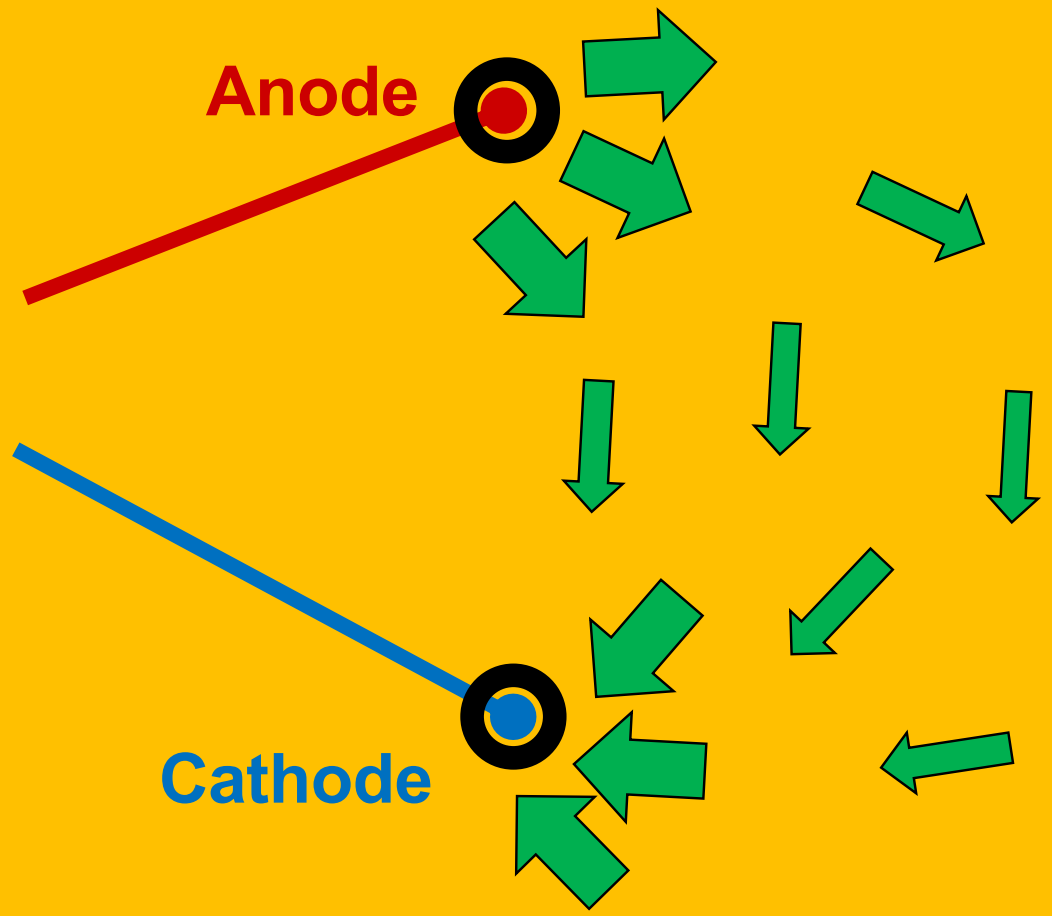


The total current produced by the stimulator (I in mA) is passed through the body

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

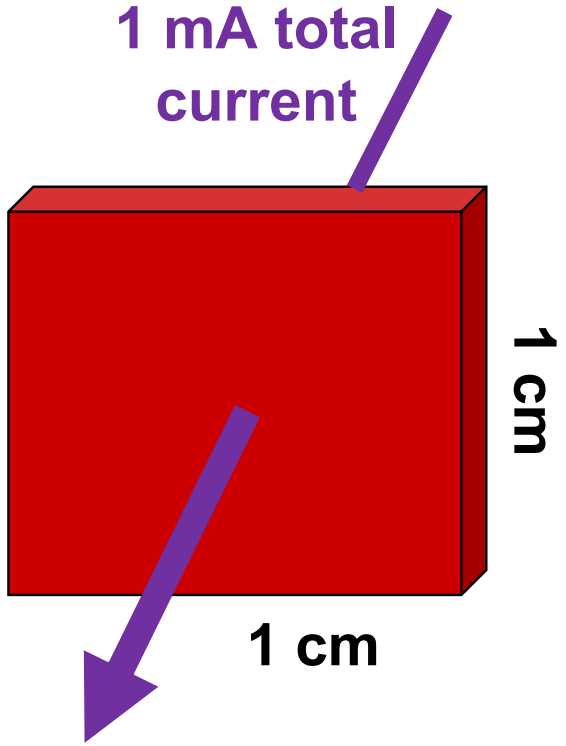


Current does not flow in a straight thin line between electrodes, but is **diffused** through the tissue.

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)

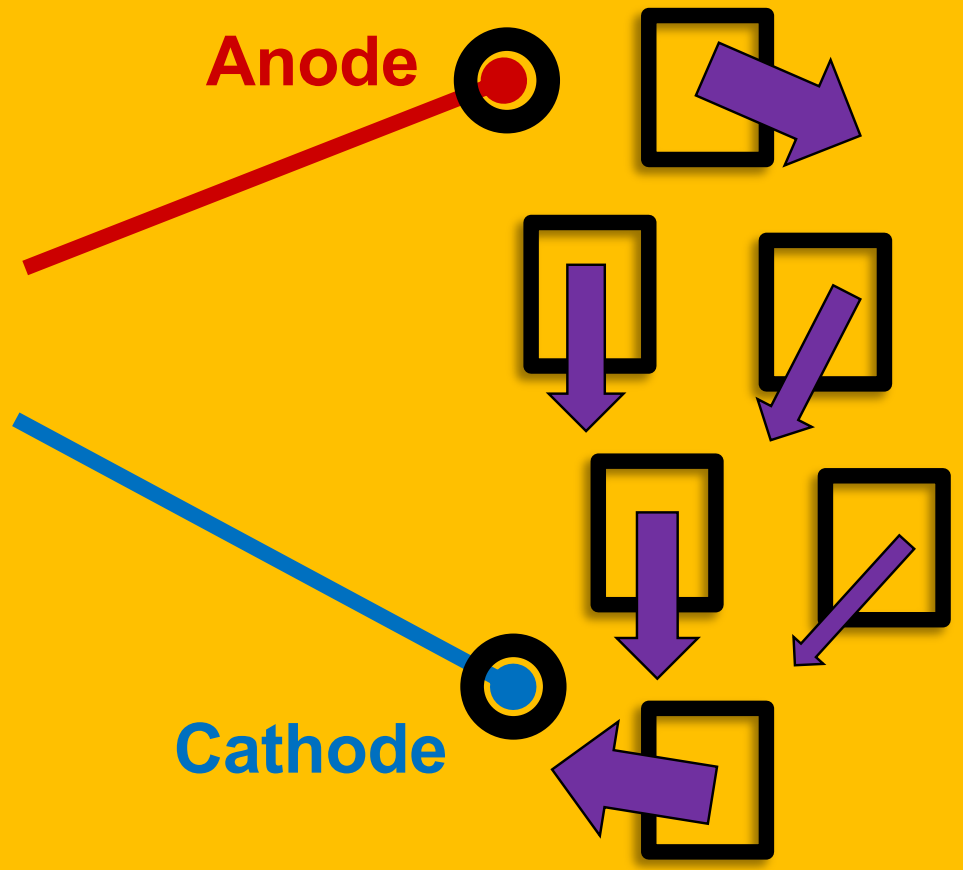
For example, an electrode has an area of 1 cm^2 with 1 mA of current passed through it.
What is the electrode Current Density*?



1 mA current / 1 cm^2
area = 1 mA / cm2

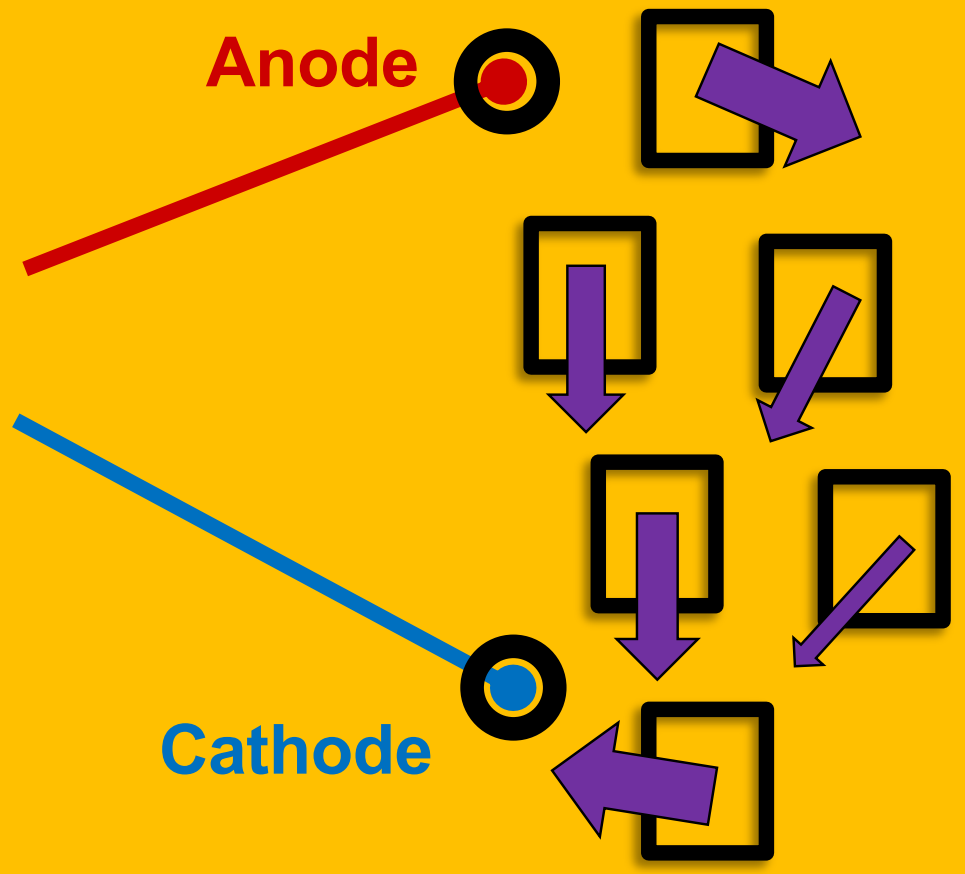
*Assume uniform current density on the electrode surface (no hot spots)

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



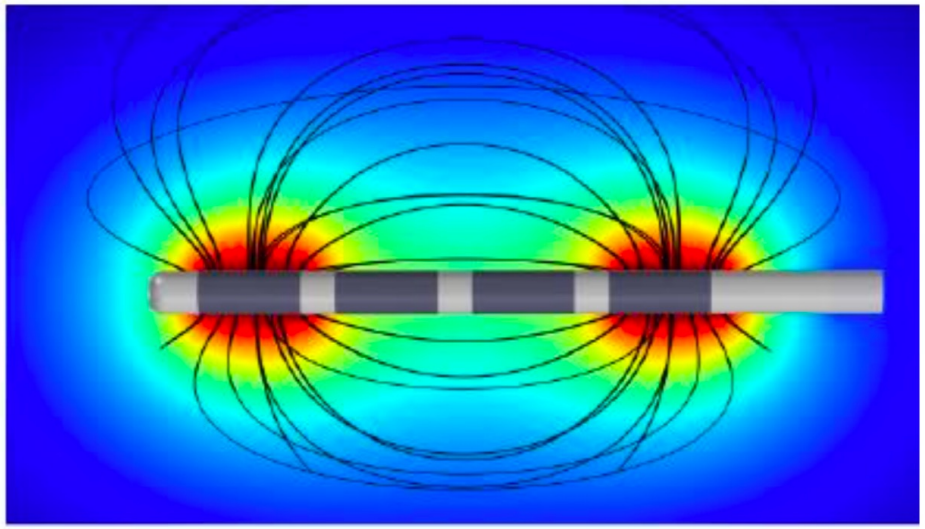
Current Density has a magnitude in each location, but it also has a direction

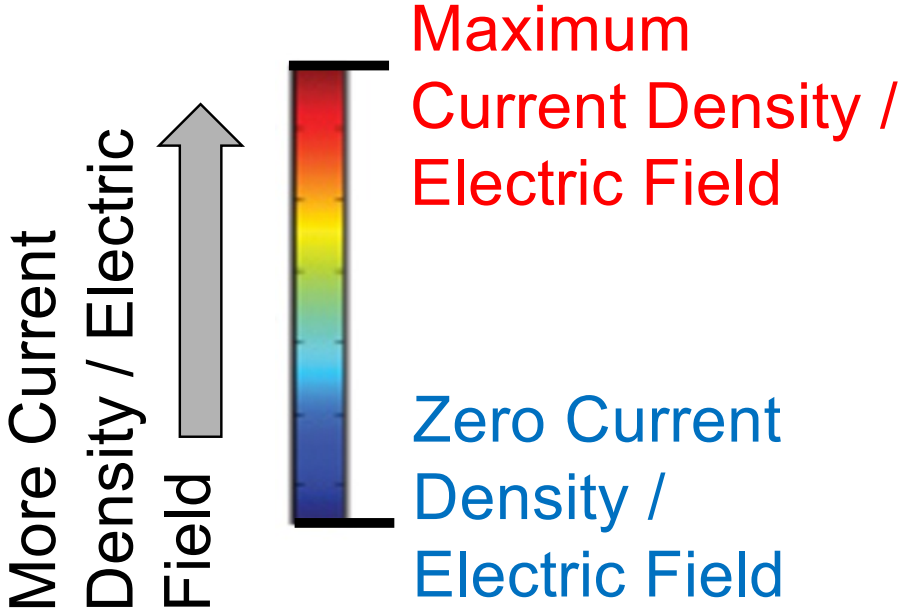
Current Density is related to **Electric Field** by a simple equation.

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.

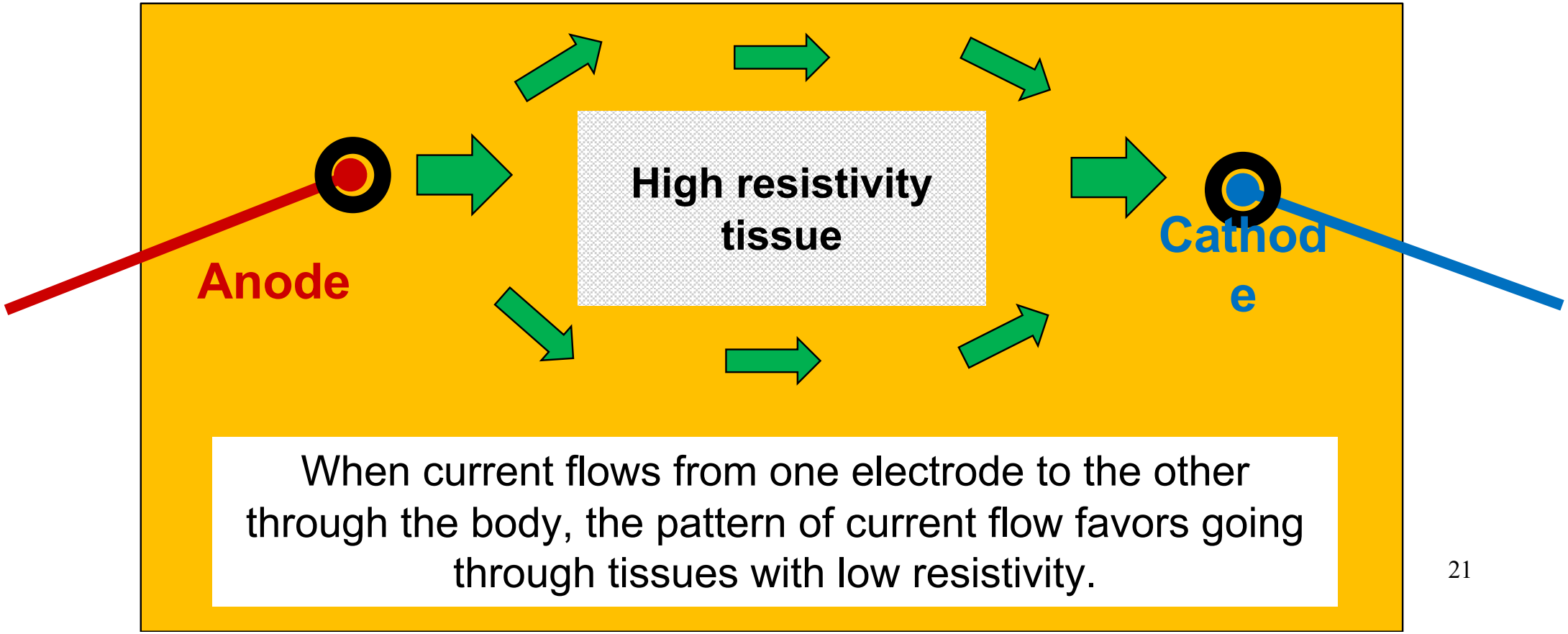




Resistivity is a property of tissue.

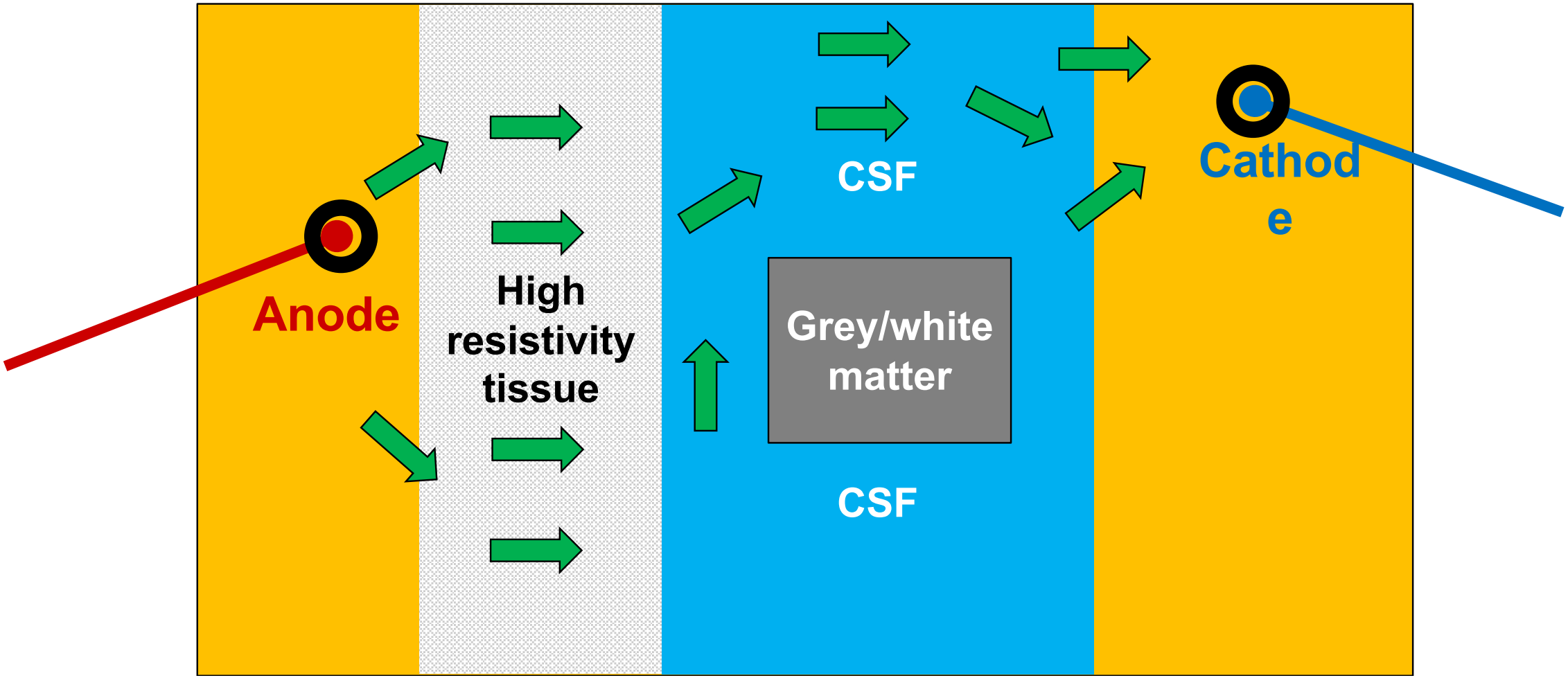
(units of ohm meter)

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



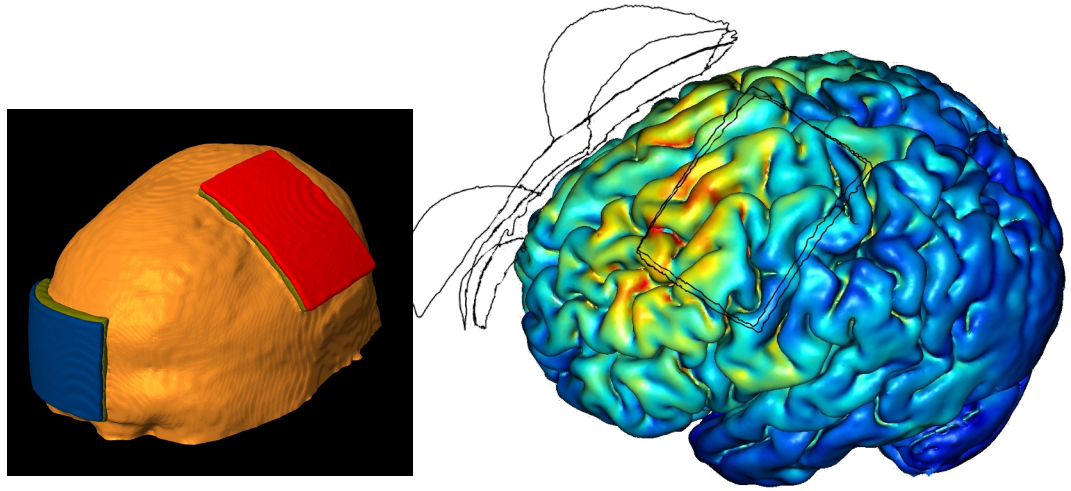
When current flows from one electrode to the other through the body, the pattern of current flow favors going through tissues with low resistivity.

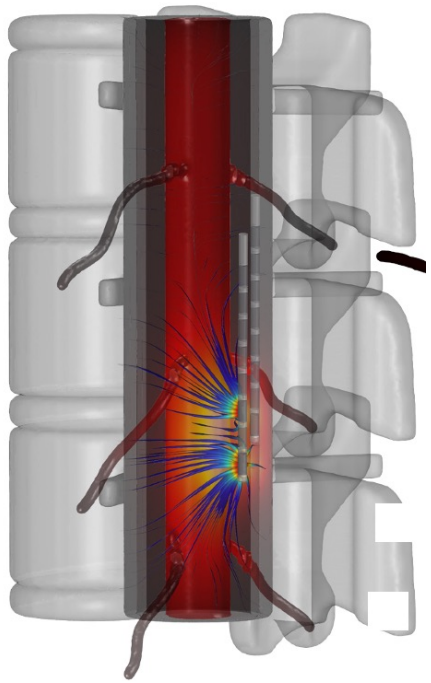
Details of body anatomy and associated tissue **resistivity** can lead to **current patterns** that are hard to guess.



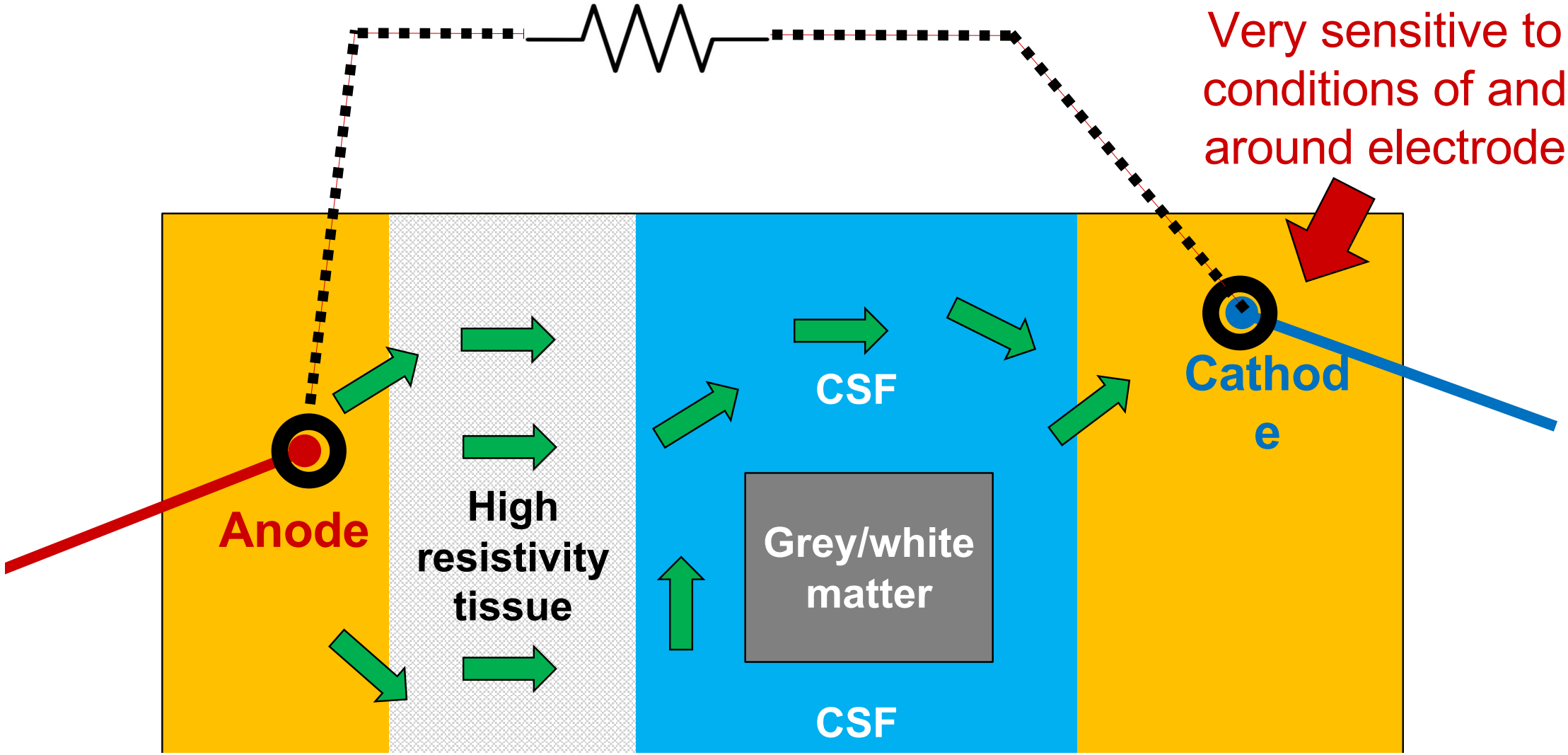
Computational models predict the (complex) pattern of current flow through tissue.

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





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.

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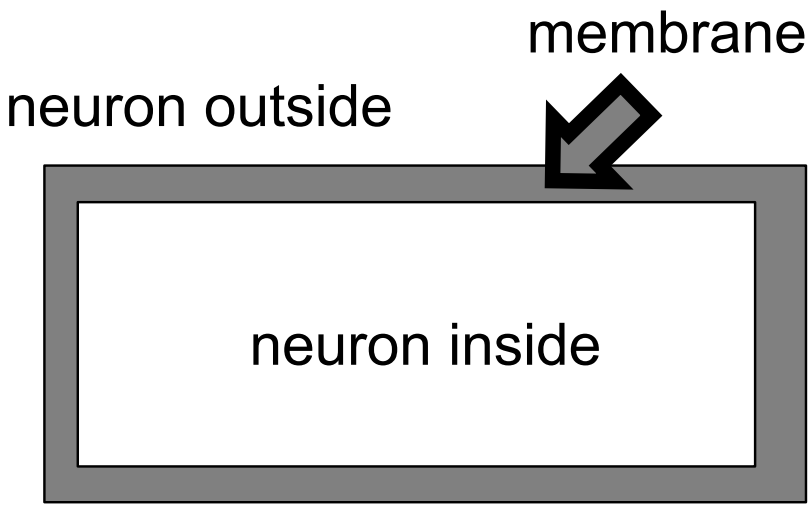
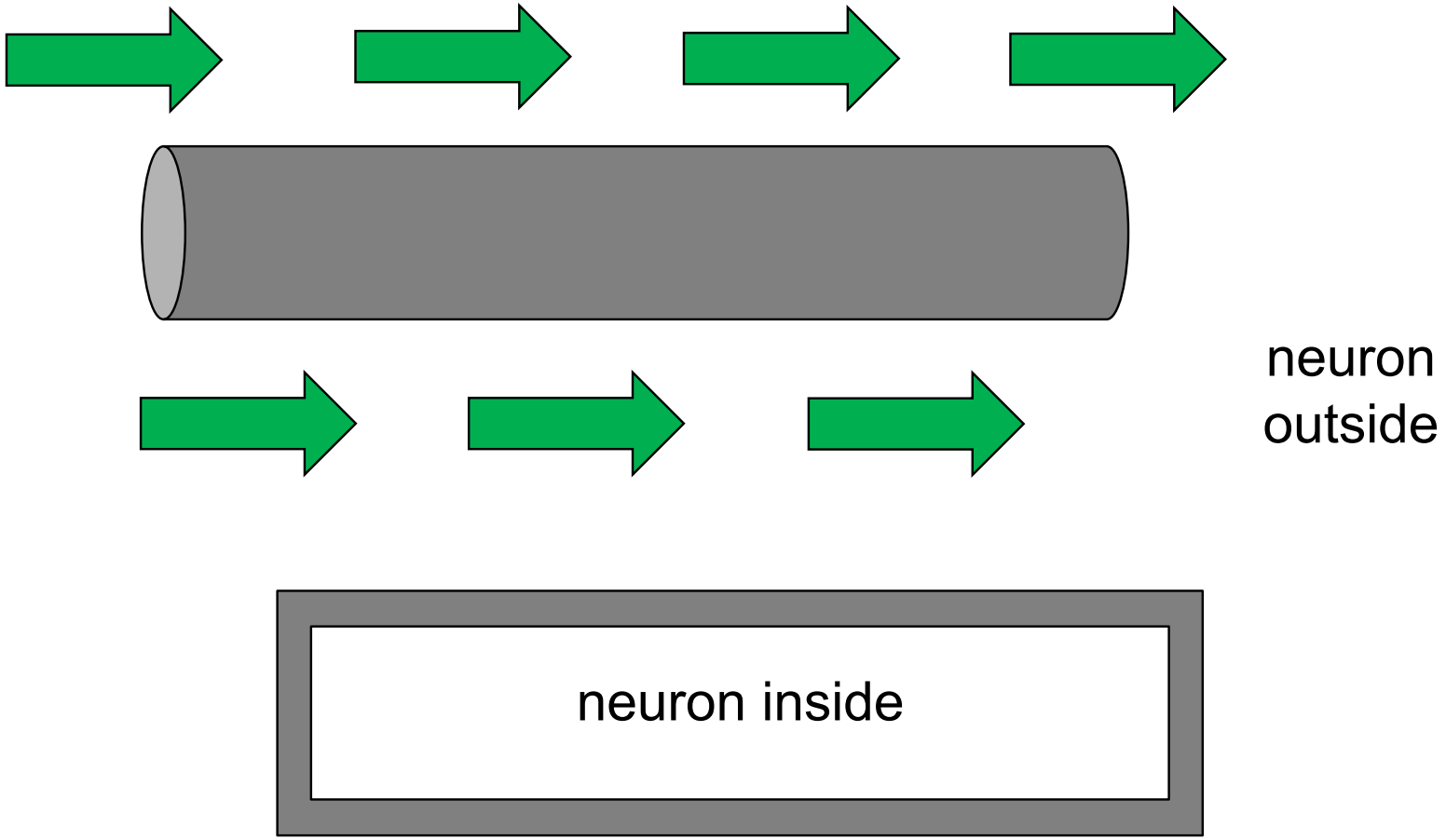
Lets assume our neuron is a tube. The tube has a shell which is the membrane.

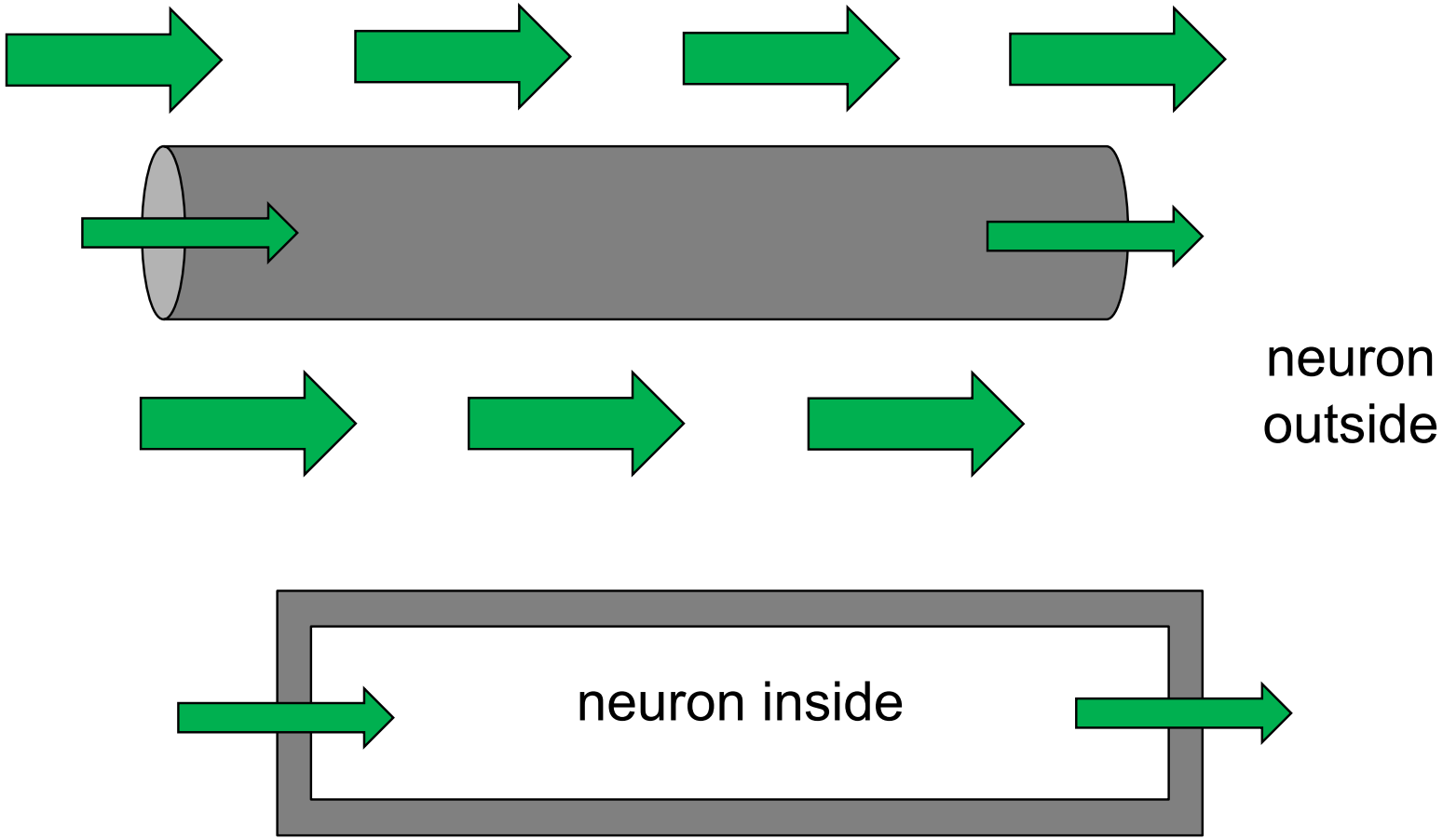
Cross section of tube neurons:



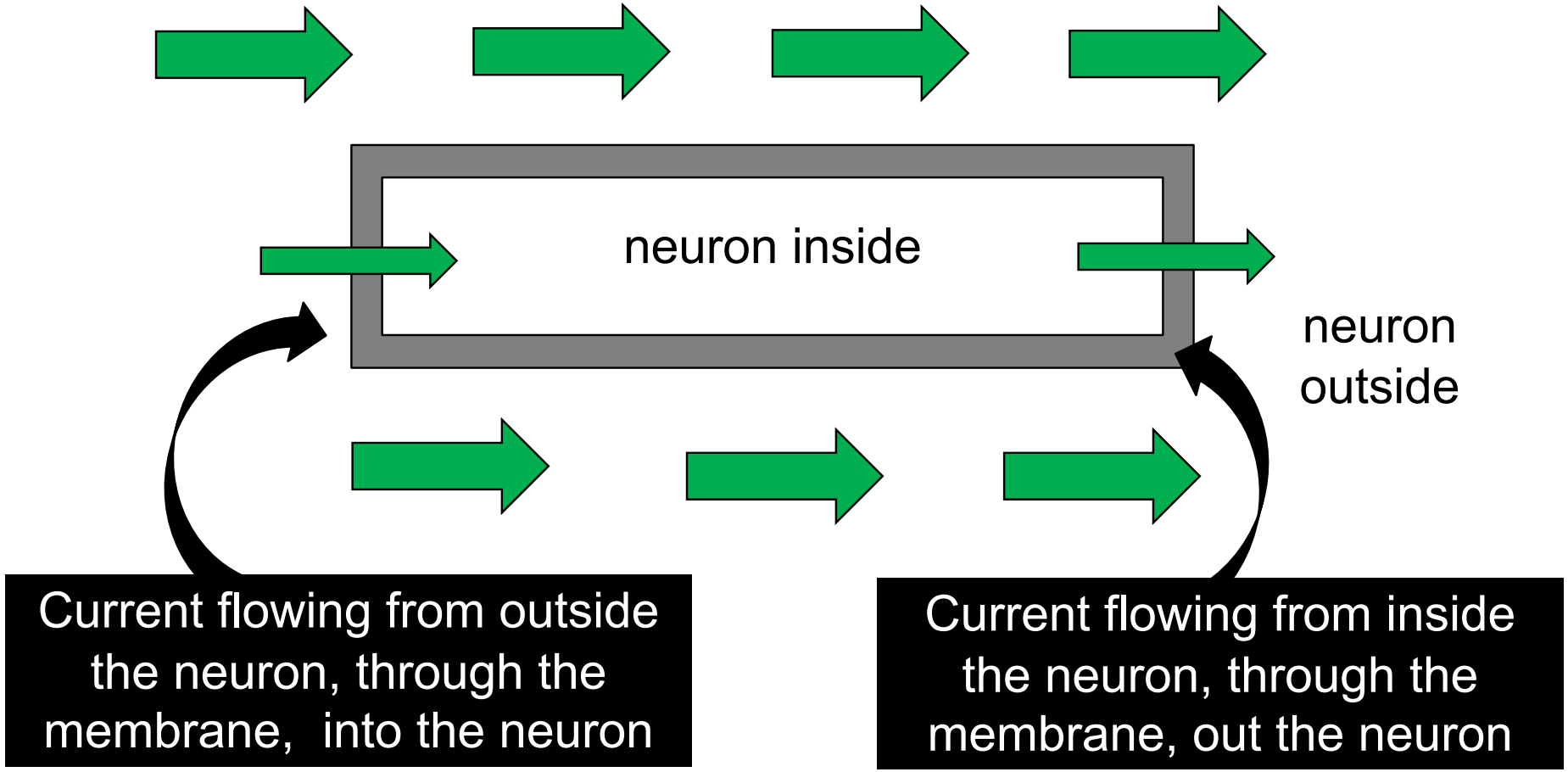
Current flow is generated around the neuron. There is a current density (or electric field) in the extracellular space around the neuron.



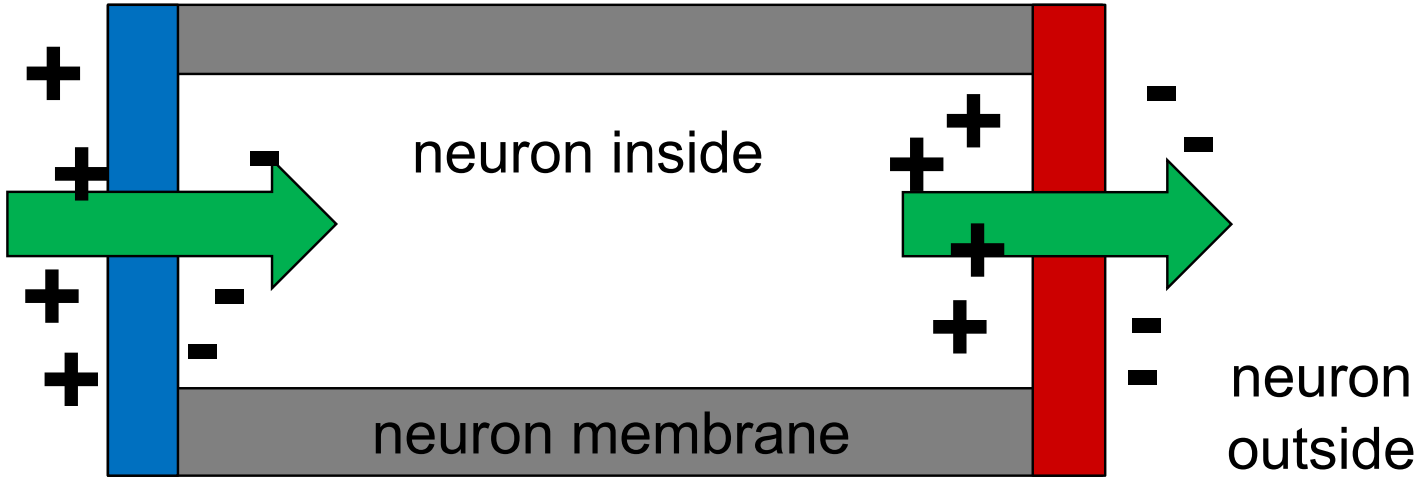
Most of the current generated outside the neuron flows around the neuron.
But some crosses through the neuron.



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**.



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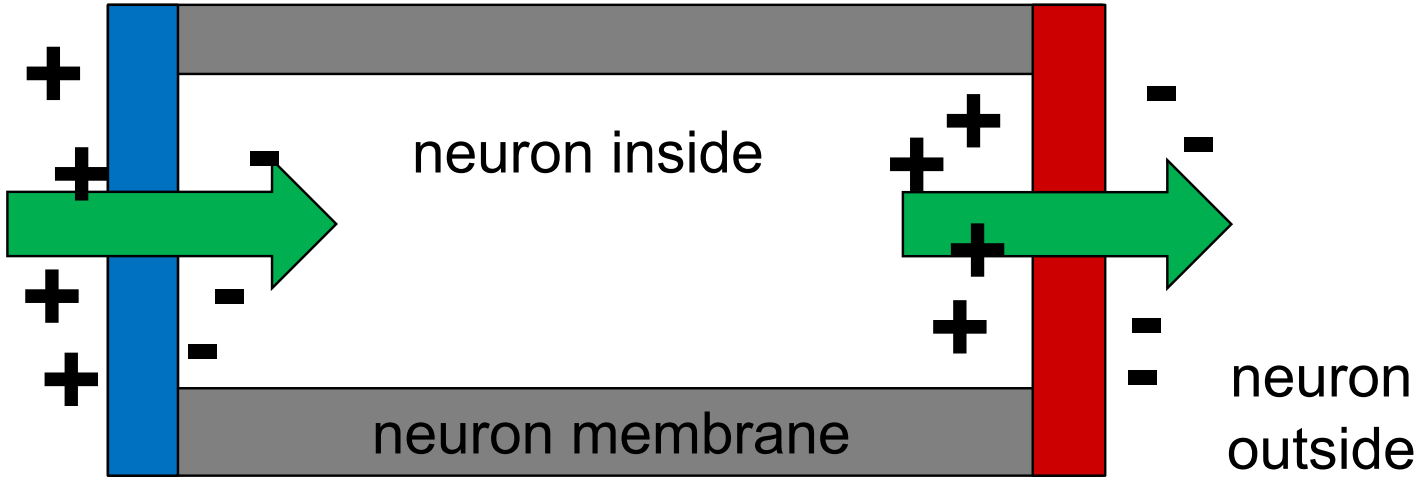
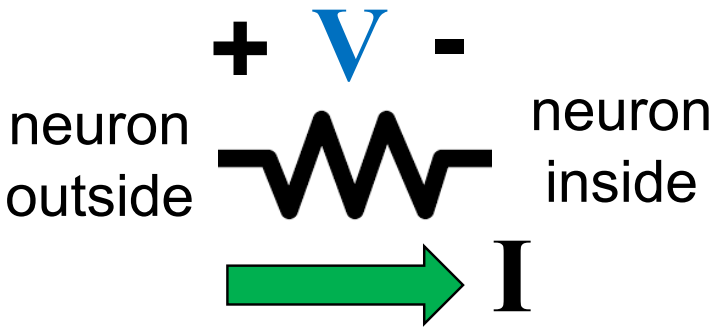
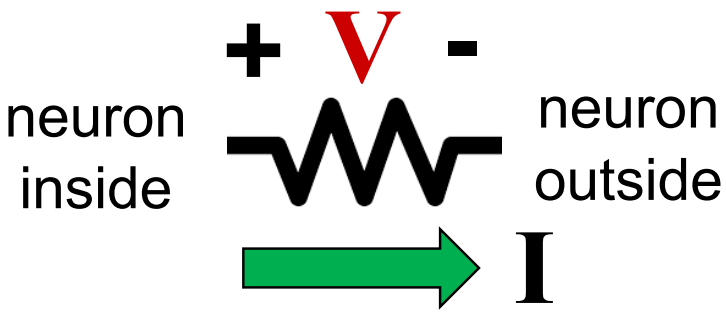
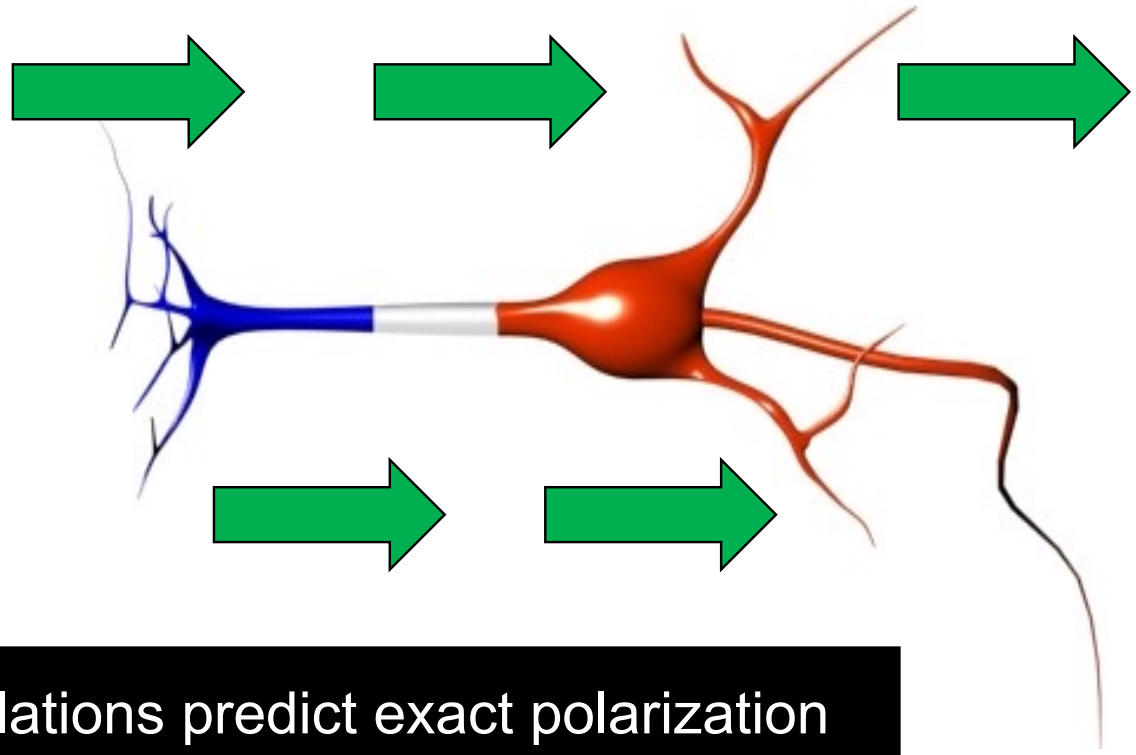


The direction of polarization is consistent with Ohms law



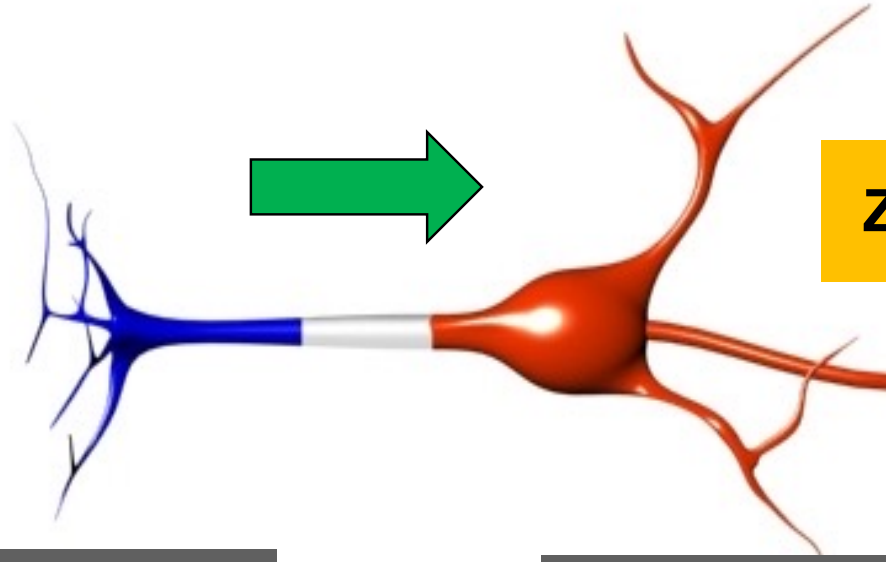


The idea of current flowing into the neurons **hyperpolarizing** and current flowing out of the membrane **depolarizing** extends to more realistic neurons shapes.



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.



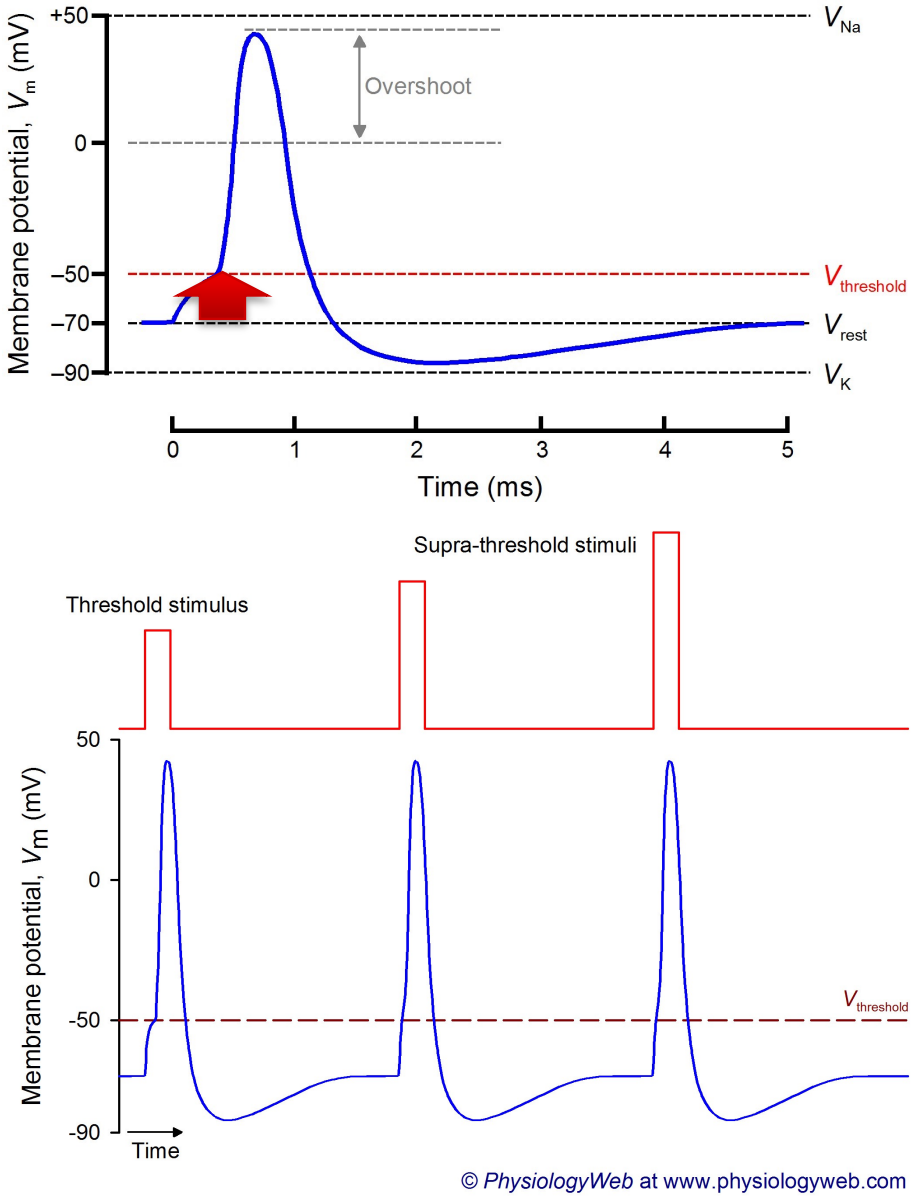
Zero sum??

-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



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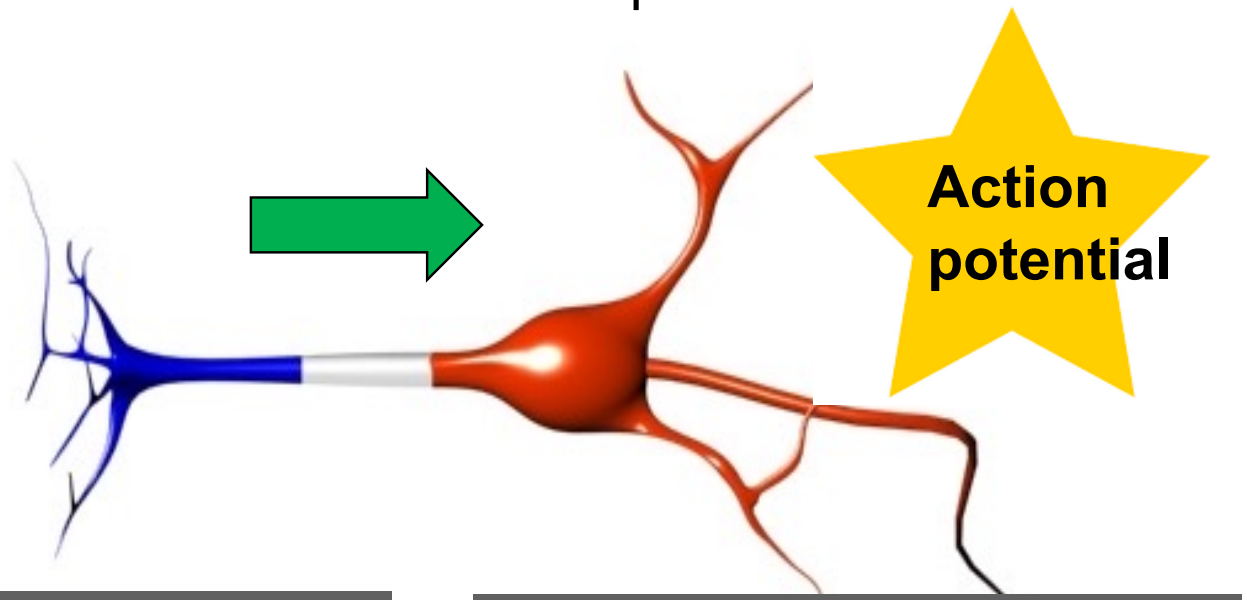
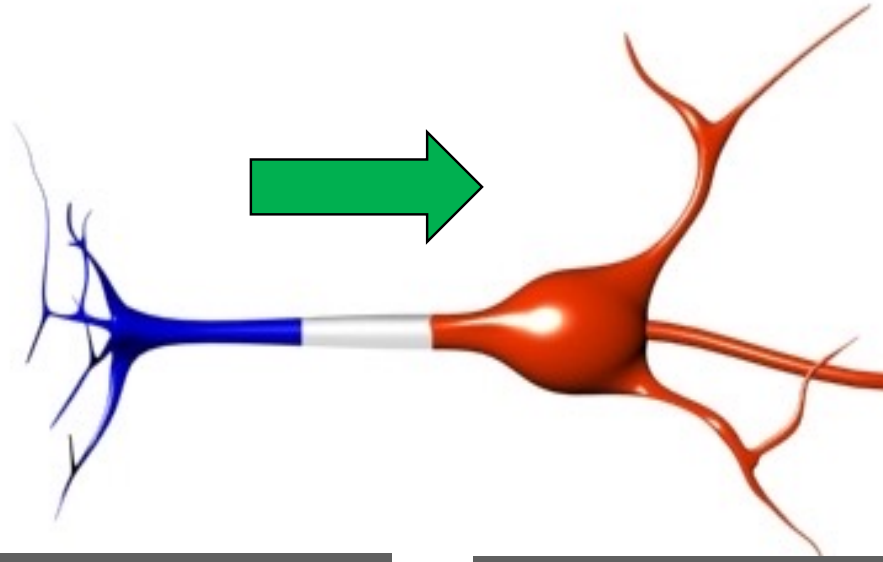


-20 mV hyper-polarization: membrane potential goes from -70 mV to -90 mV

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

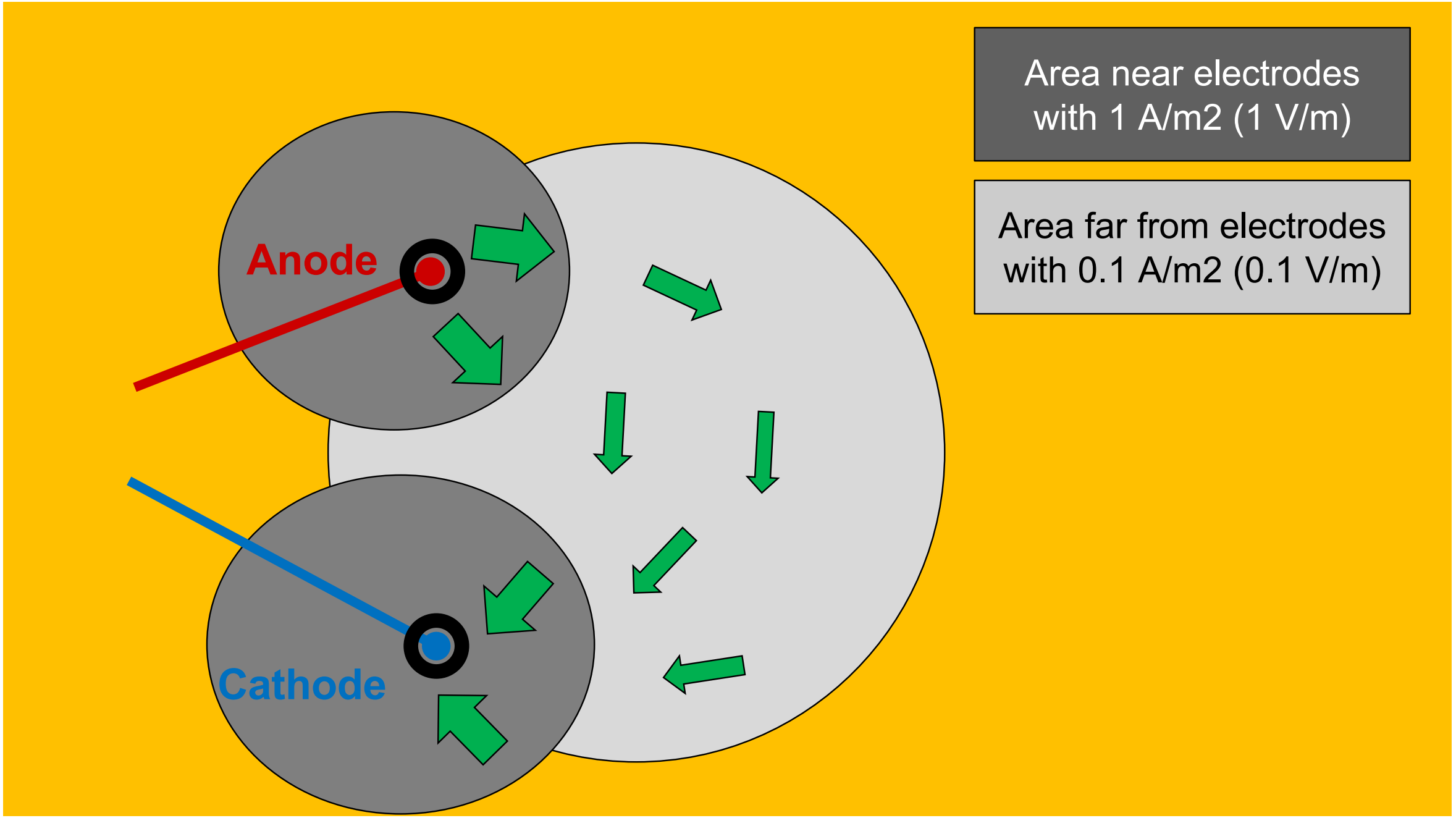
For example: A stimulation device generates **Current Density** around a neuron of 0.1 mA/m^2 (or an Electric field of 0.1 V/m). The results is -2 mV **hyperpolarization** in some membrane parts (compartment) of the neuron, and +2 mV **depolarization** other membrane parts.

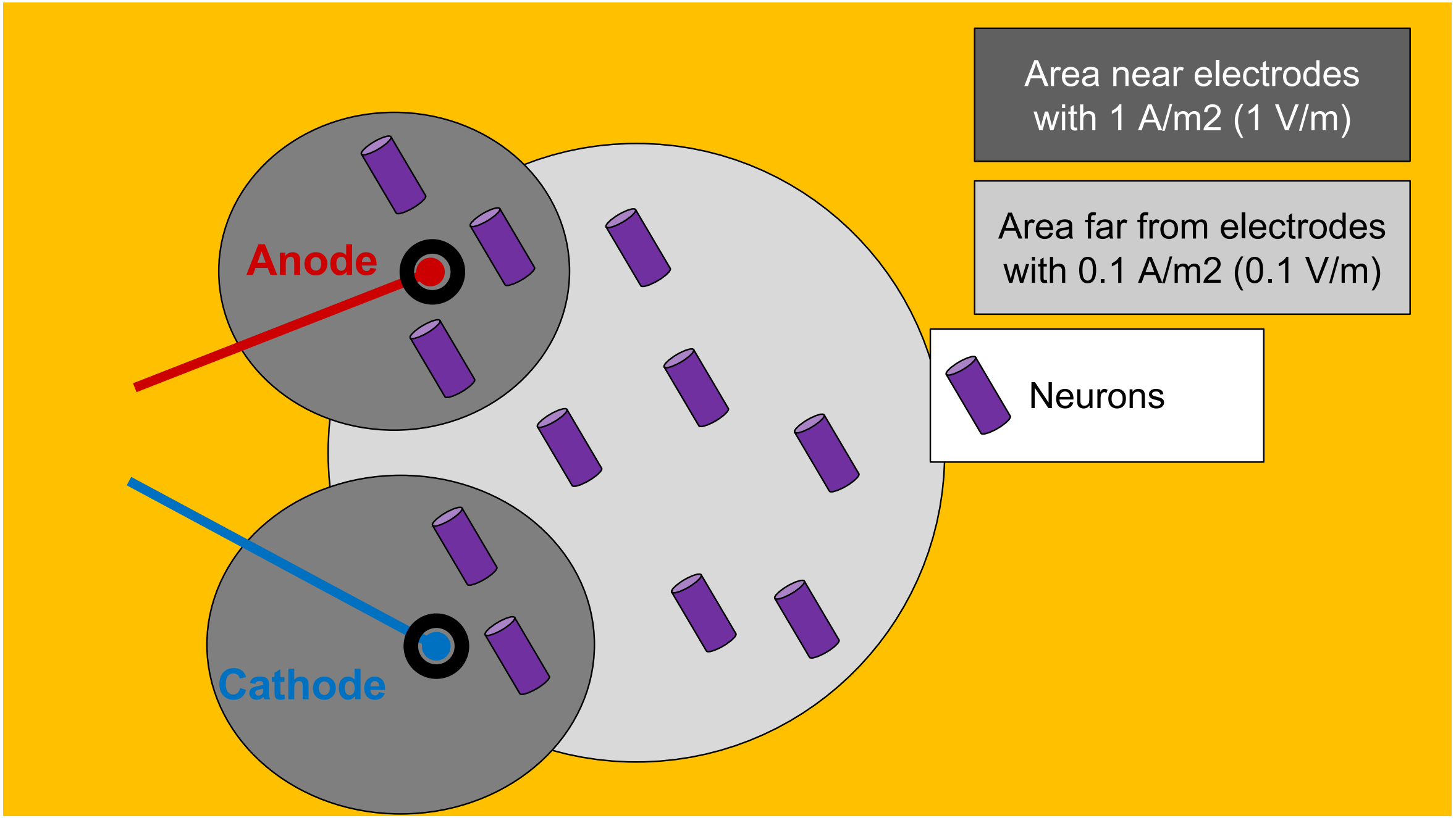


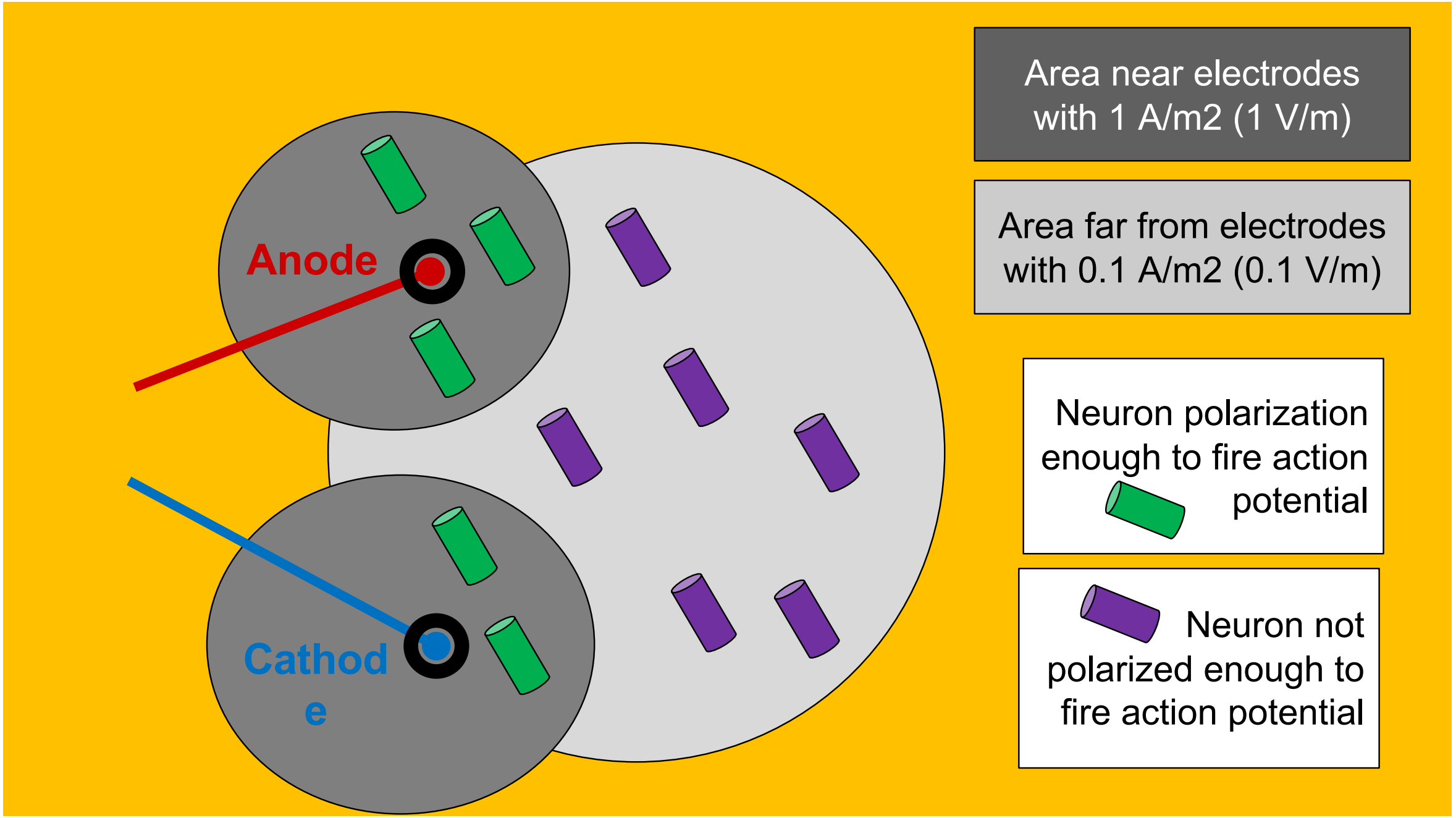
NO Action potential

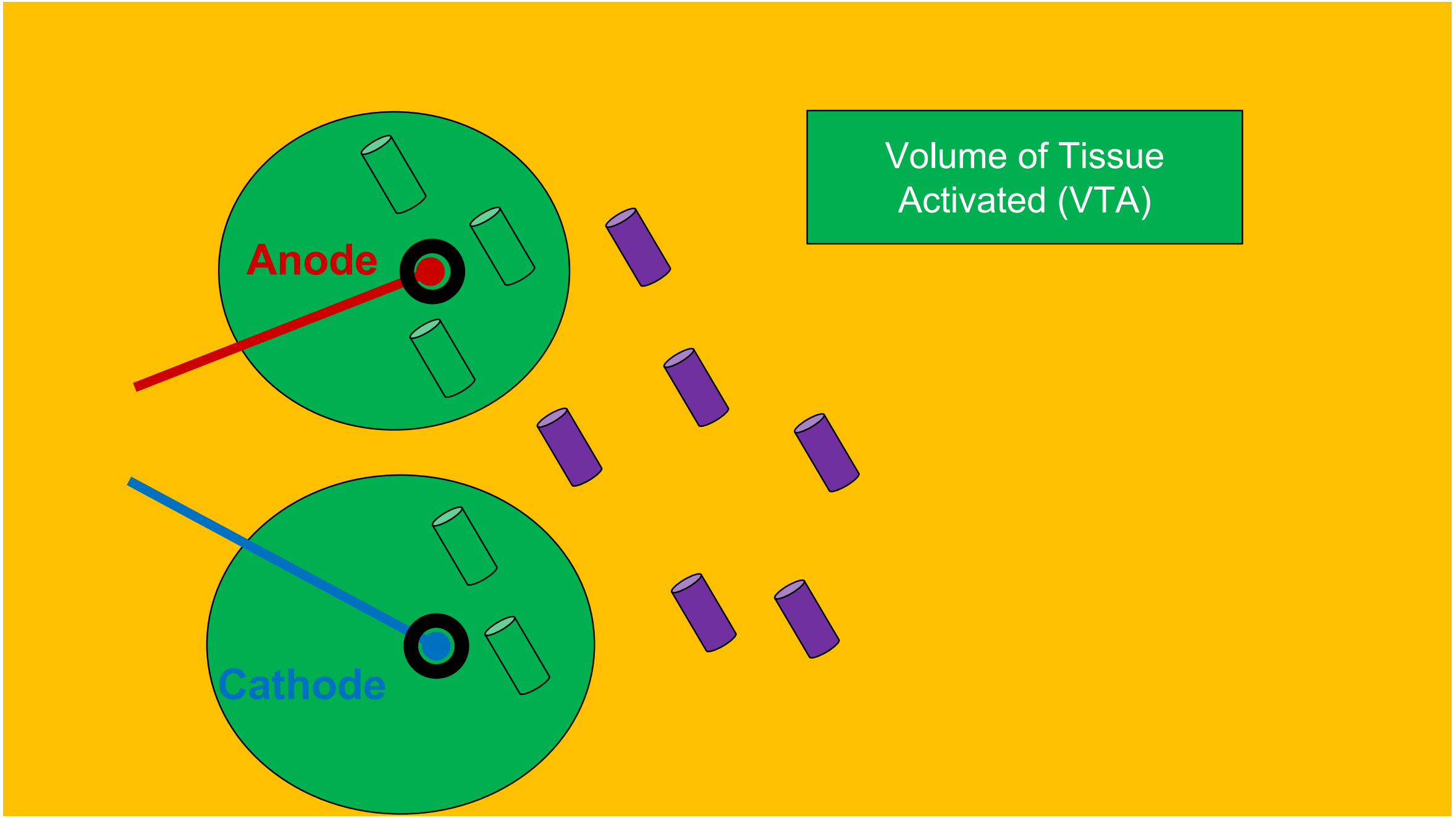
-2 mV hyper-polarization: membrane potential goes from -70 mV to -72 mV

+2 mV de-polarization: membrane potential goes from -70 mV to -68 mV

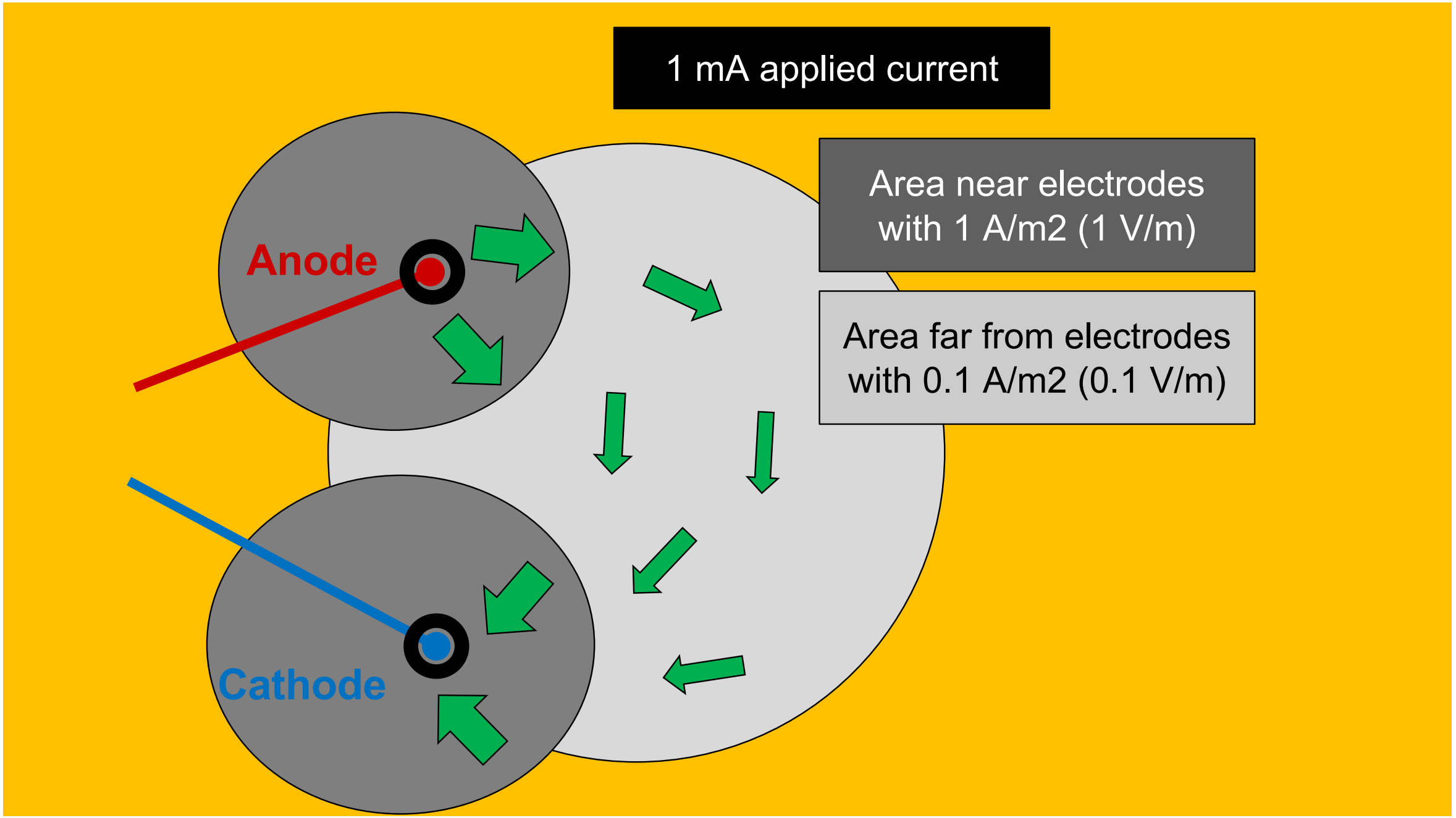

Anode
Cathode
Area near electrodes
with 1 A/m2 (1 V/m)
Area far from electrodes
with 0.1 A/m2 (0.1 V/m)

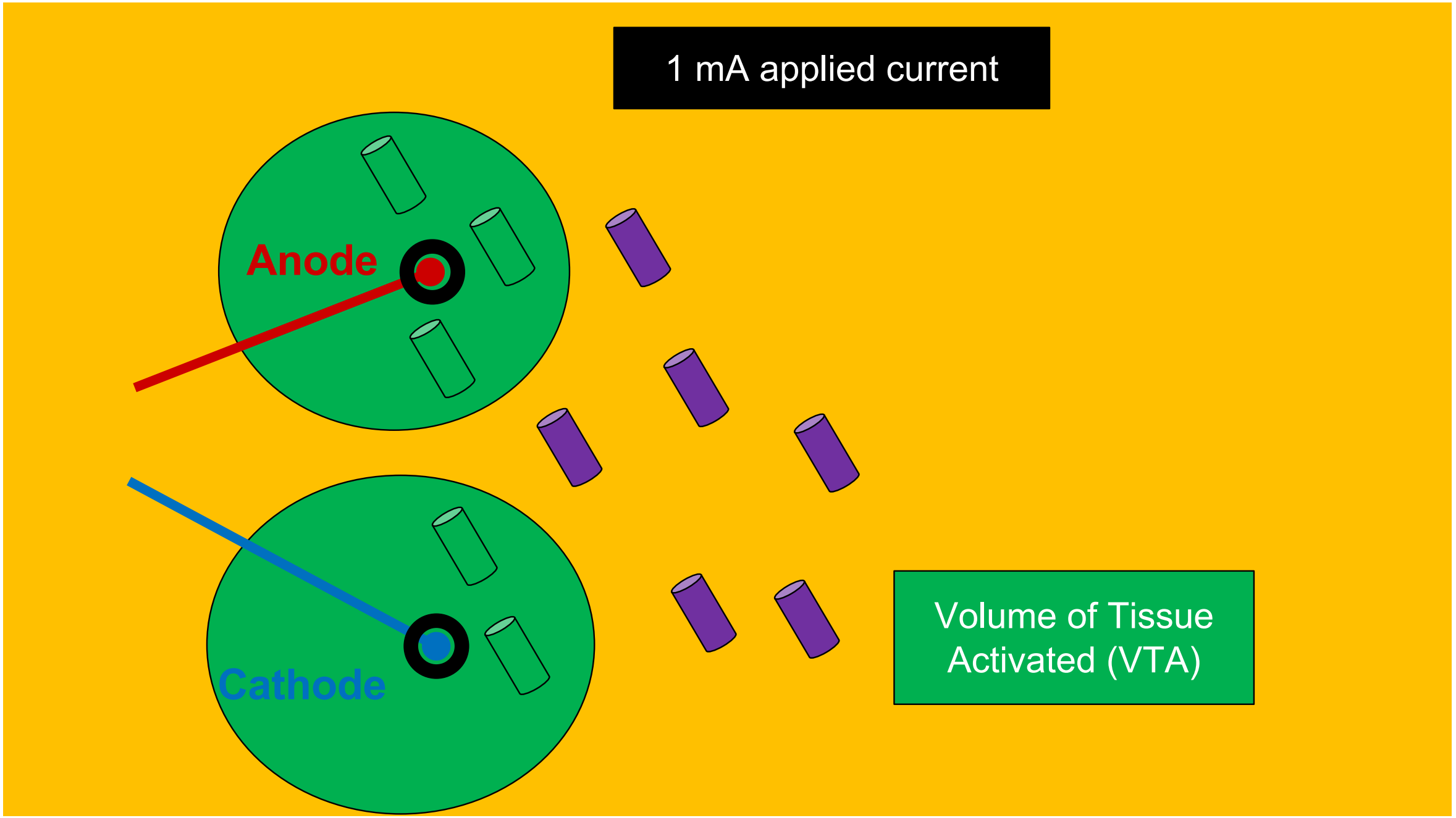

Area near electrodes
with 1 A/m2 (1 V/m)
Area far from electrodes
with 0.1 A/m2 (0.1 V/m)
Neurons
Anode
Cathode

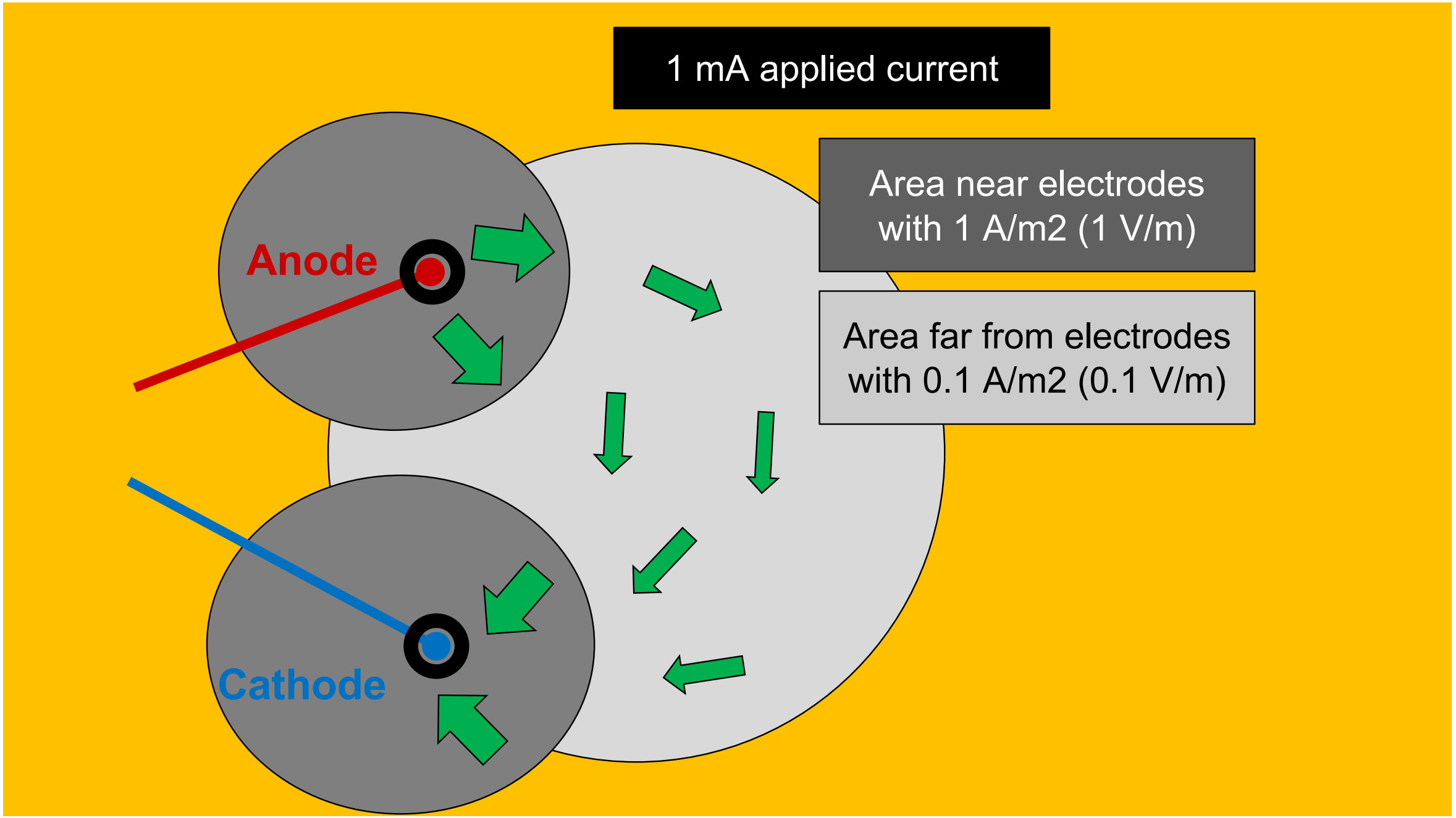

Anode
Cathode
Area near electrodes with 1 A/m2 (1 V/m)
Area far from electrodes with 0.1 A/m2 (0.1 V/m)
Neuron polarization enough to fire action potential
Neuron not polarized enough to fire action potential

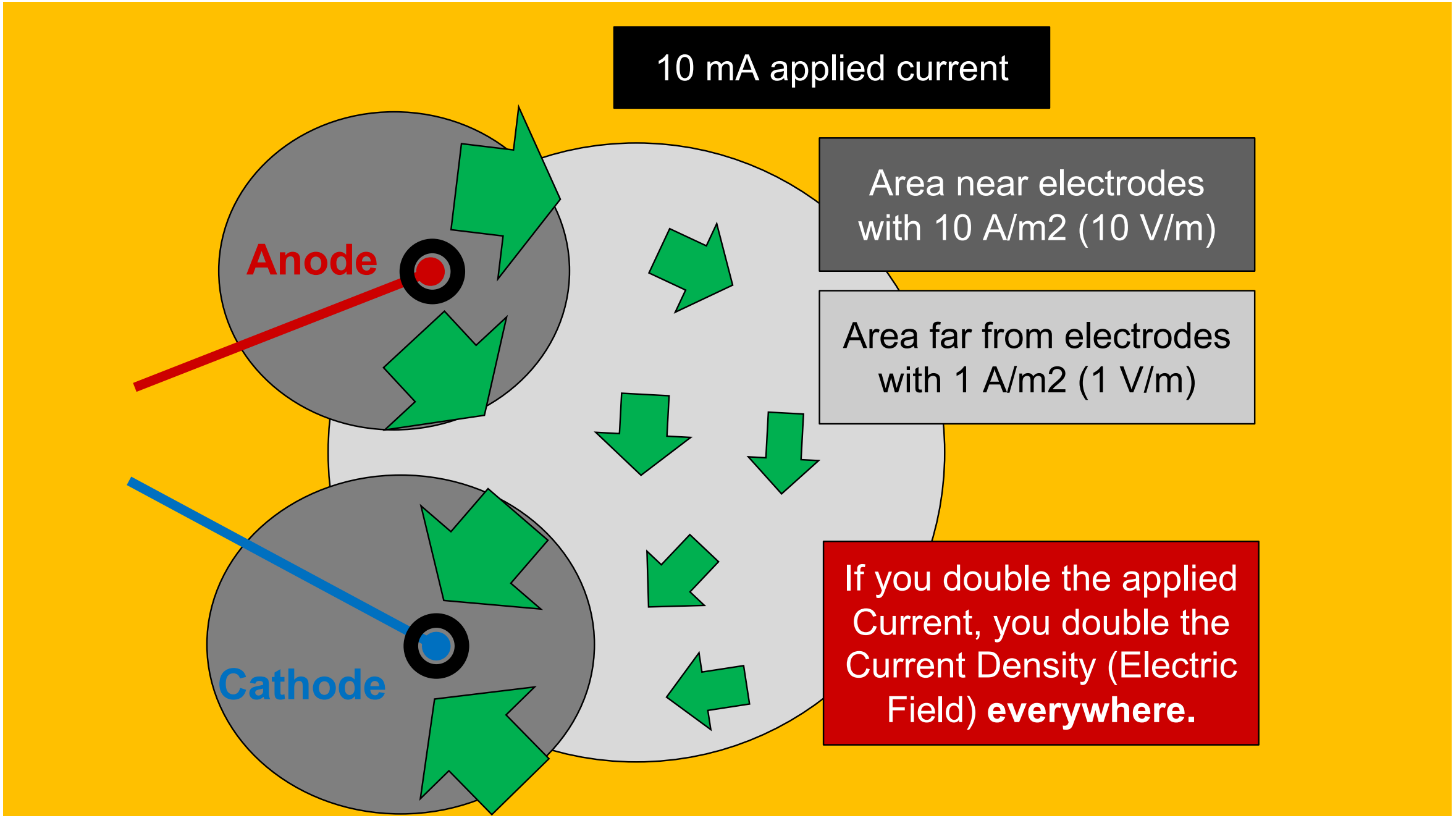

Anode
Cathode
Volume of Tissue Activated (VTA)

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

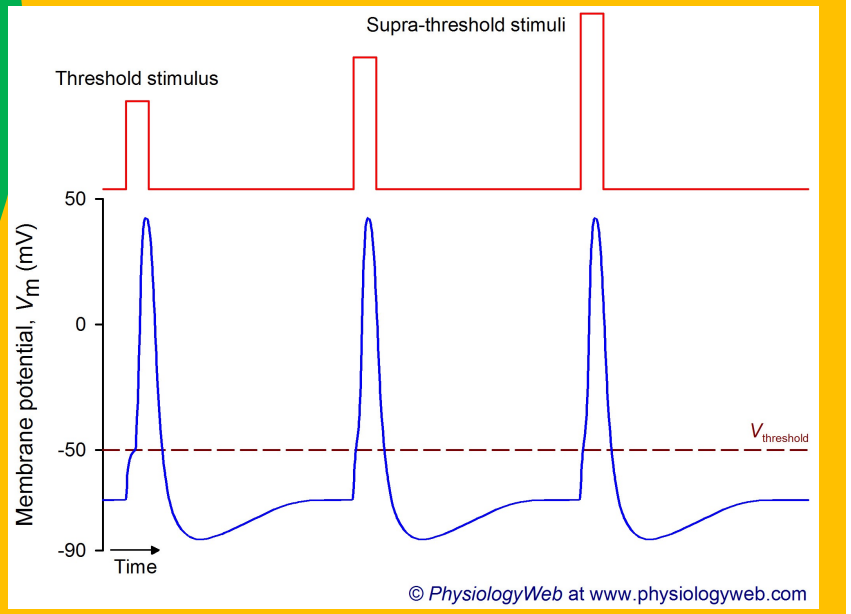
10 mA applied current

Volume of Tissue Activated (VTA)

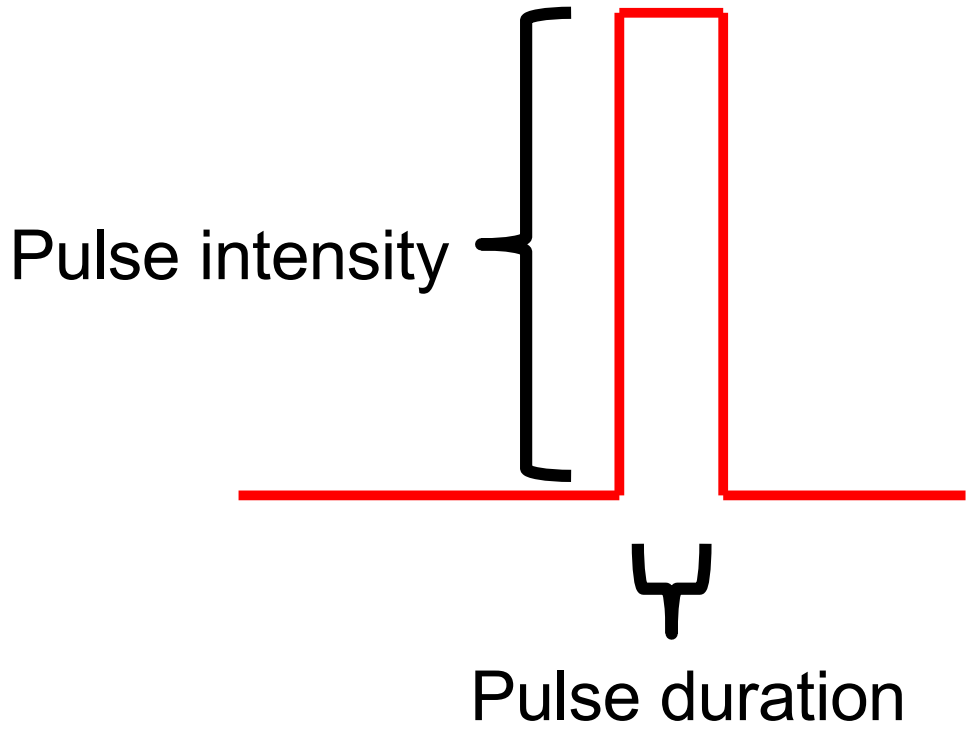
Anode

Cathode

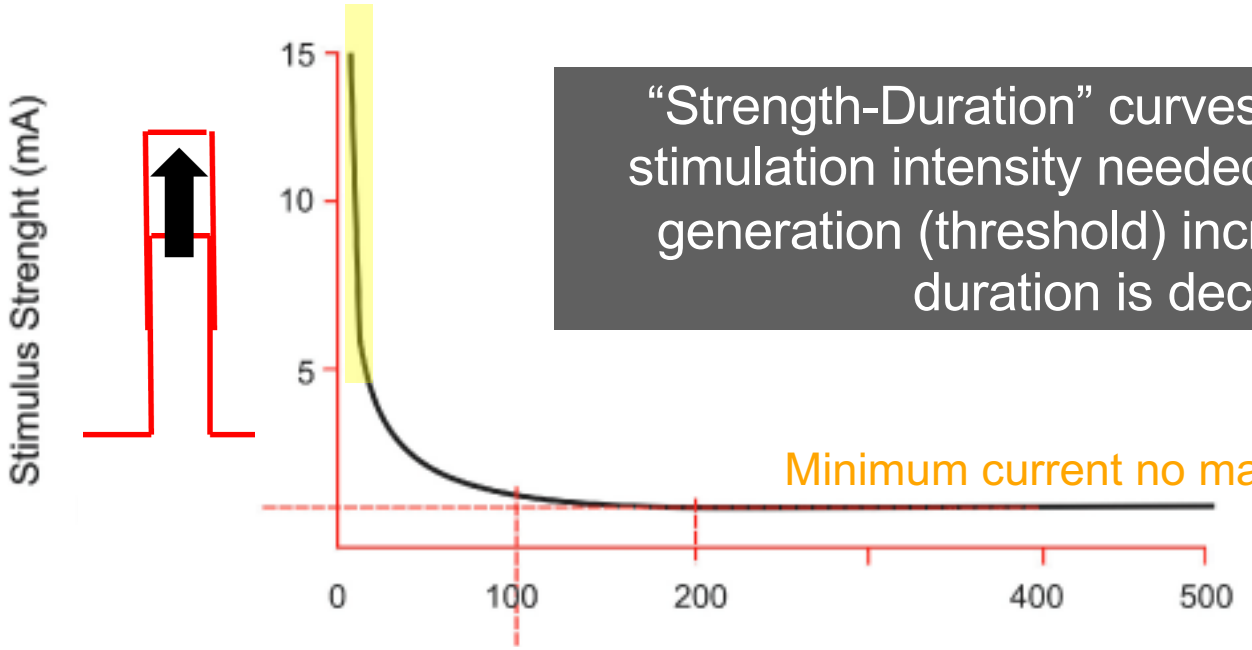
Supra-threshold is threshold



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

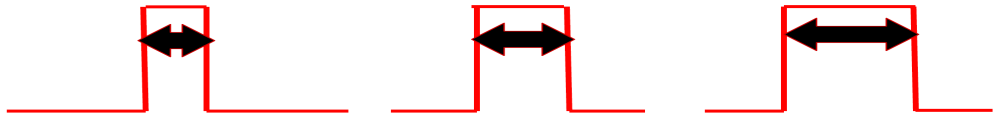


Duration of stimulation pulse (in units of **ms** or **us**)



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

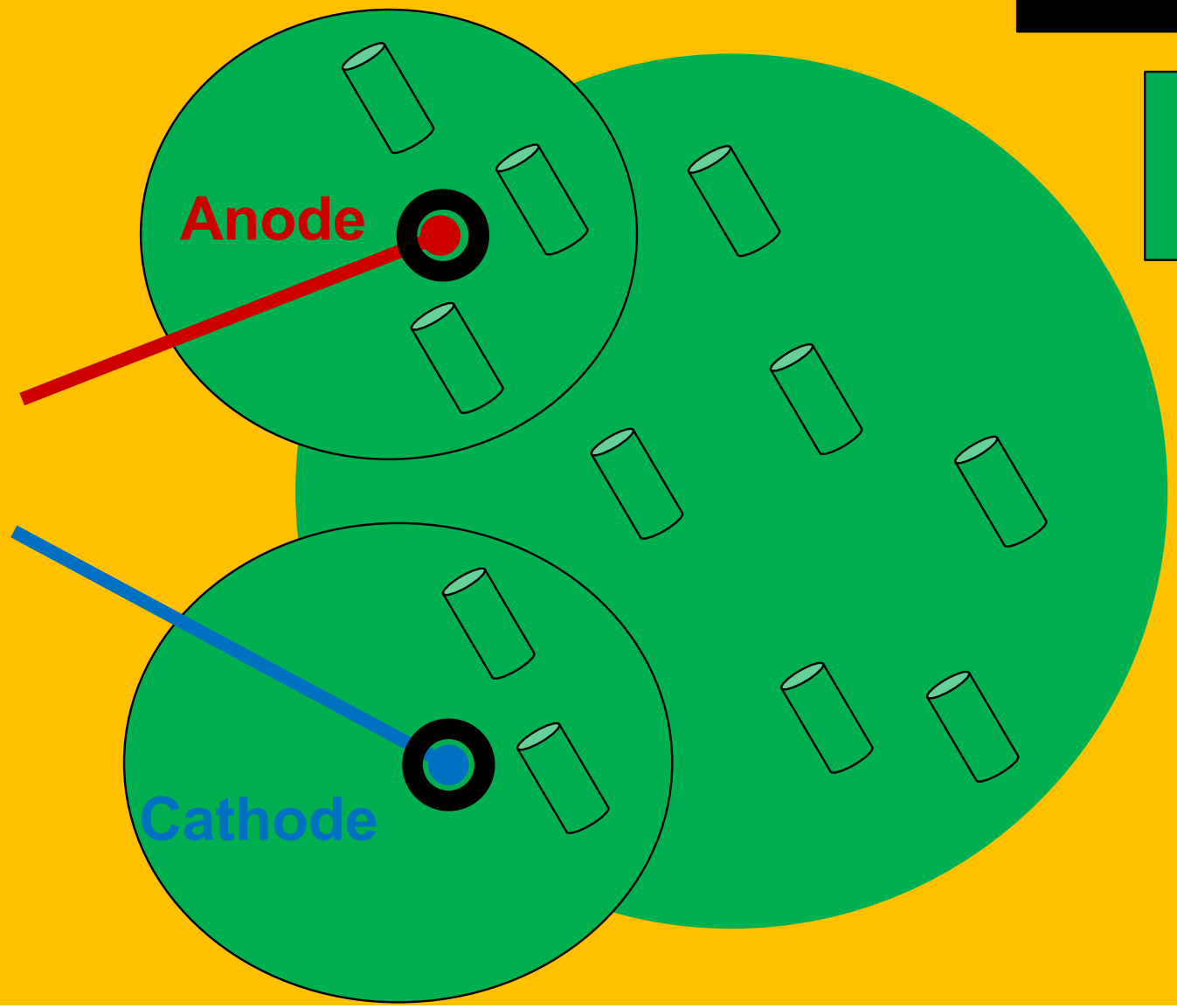
Minimum current no matter how long the pulse



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.

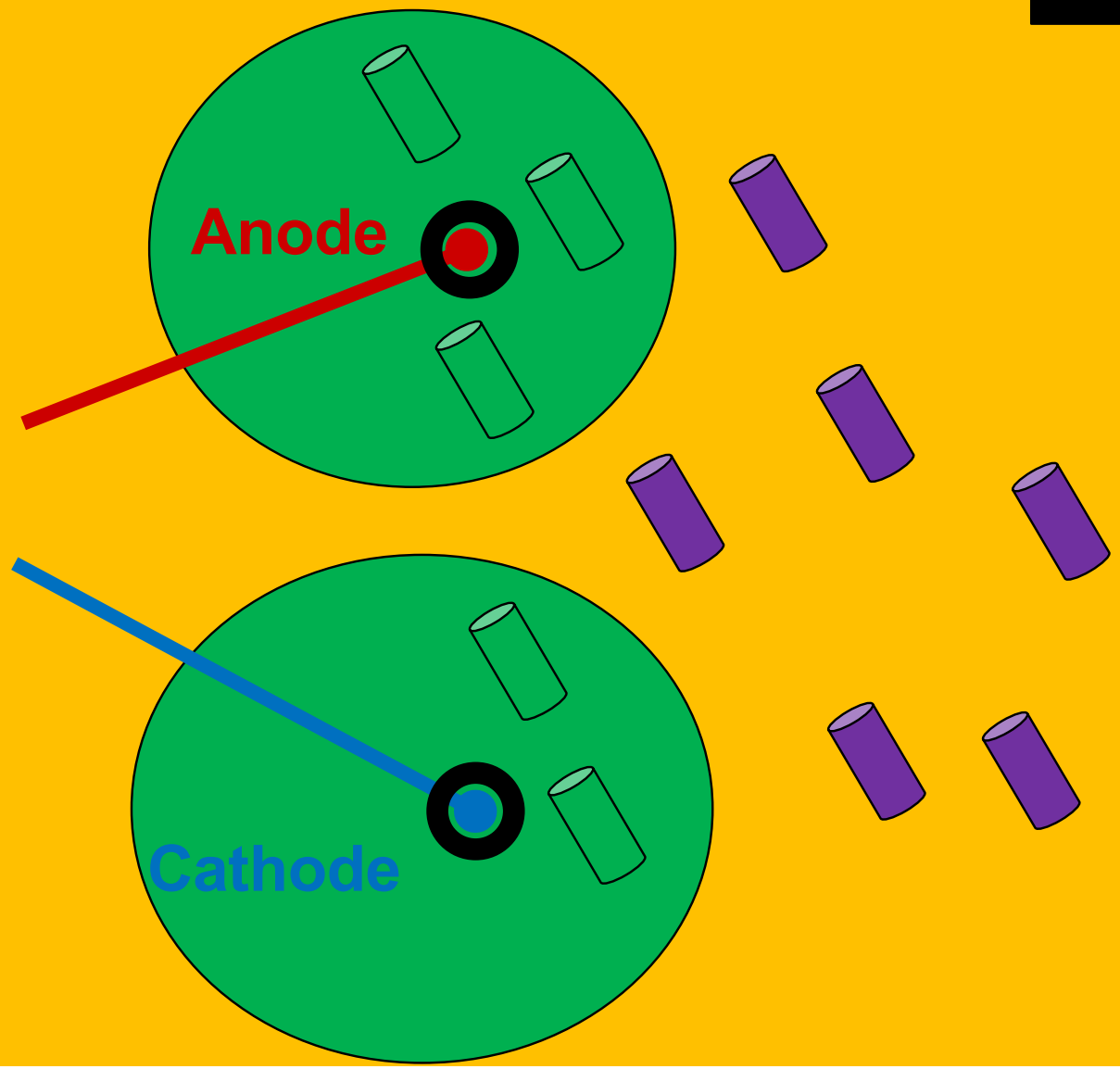
10 mA applied current, with 1 mS pulse duration



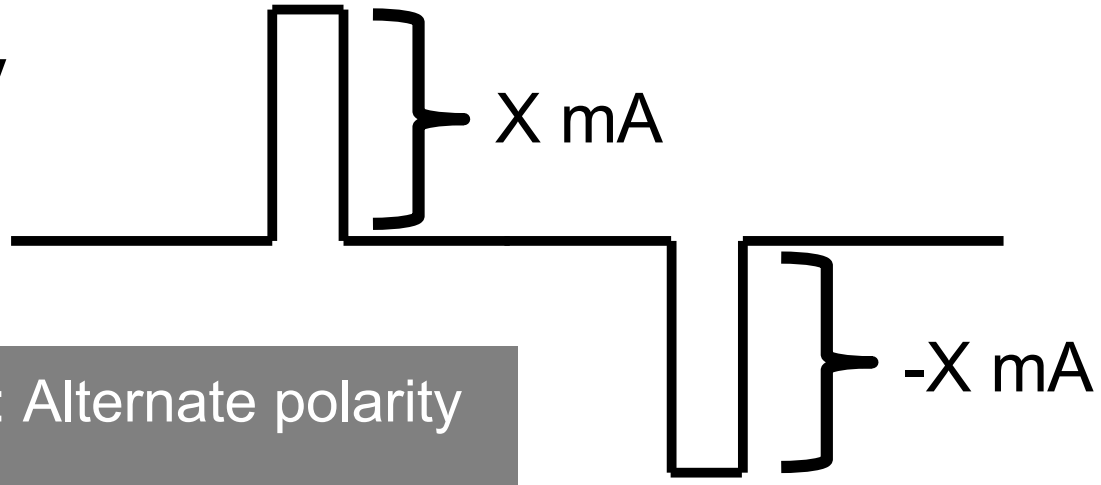
Volume of Tissue Activated (VTA)

10 mA applied current, with 0.1 mS pulse duration

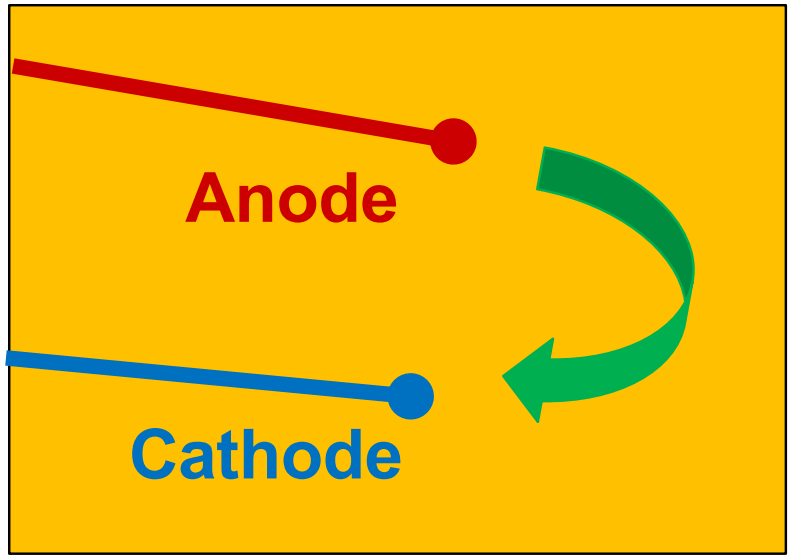
Volume of Tissue Activated (VTA)

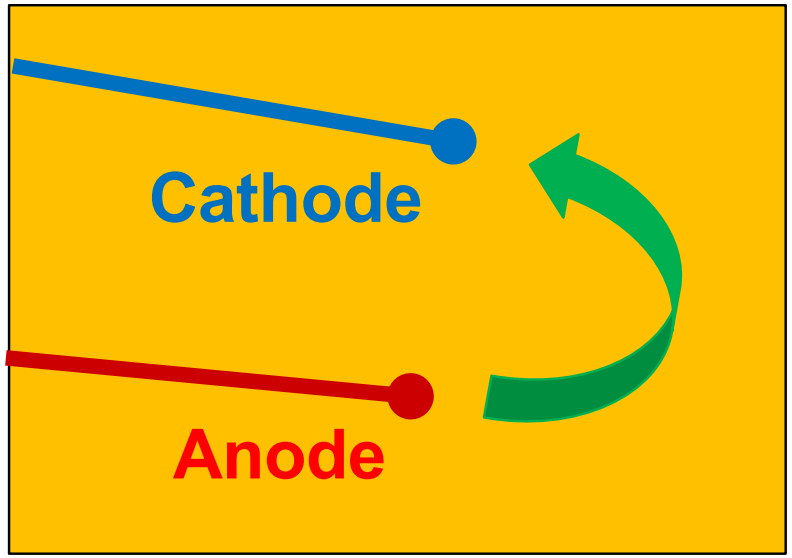


Pulse **polarity**

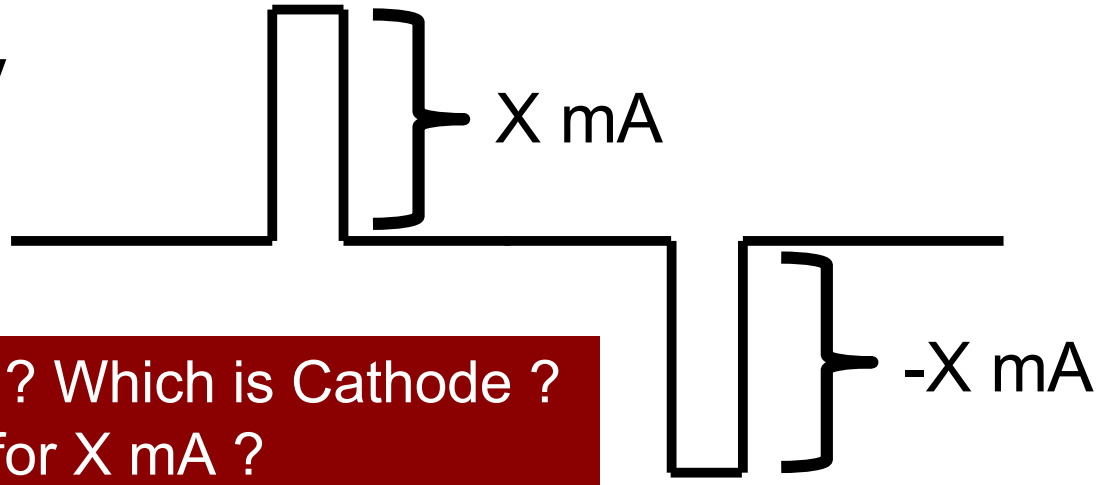


Biphasic stimulation: Alternate polarity pulses are provided

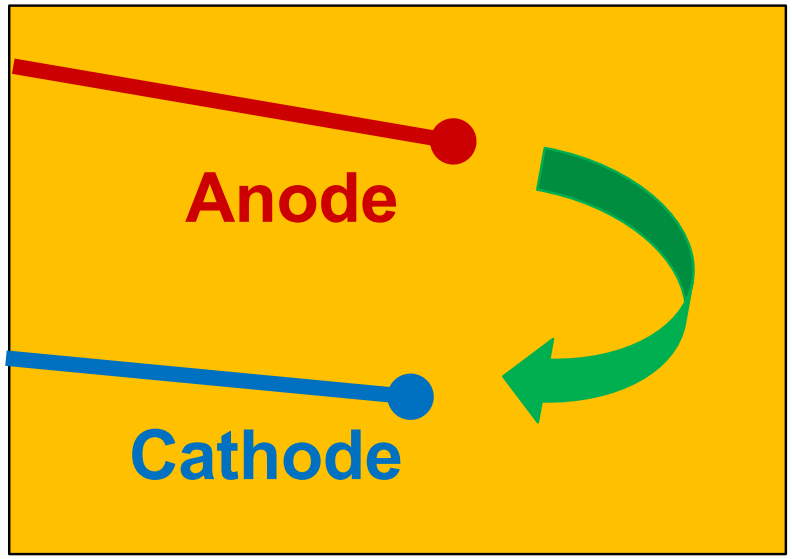


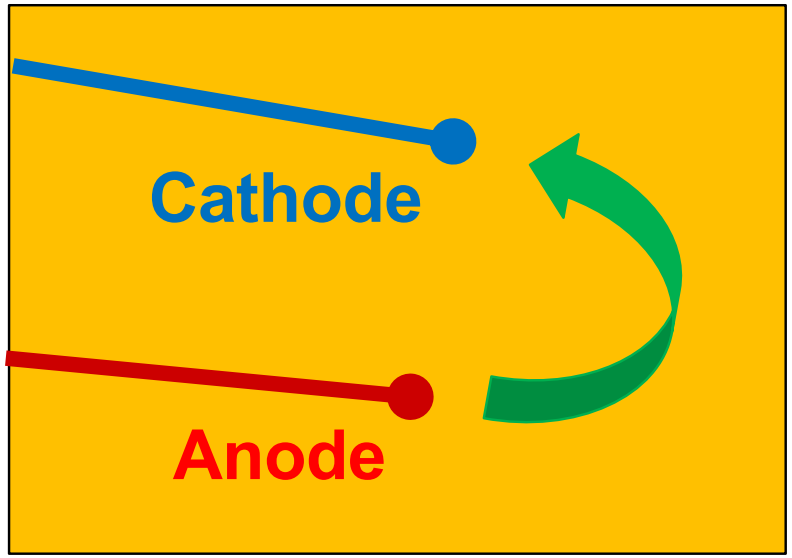


Pulse **polarity**

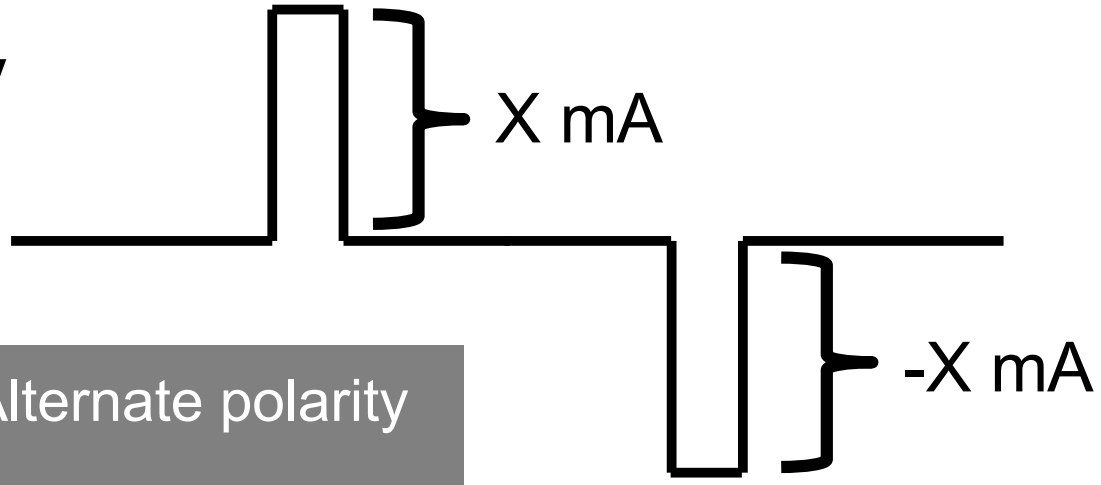


Which electrode is the Anode ? Which is Cathode ?
Which way does current flow for X mA ?
Which way does current flow for -X mA ?

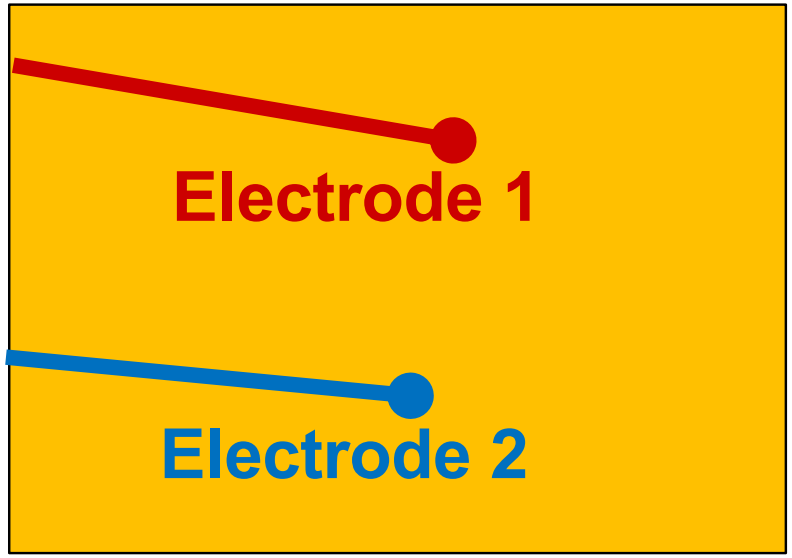




Pulse **polarity**



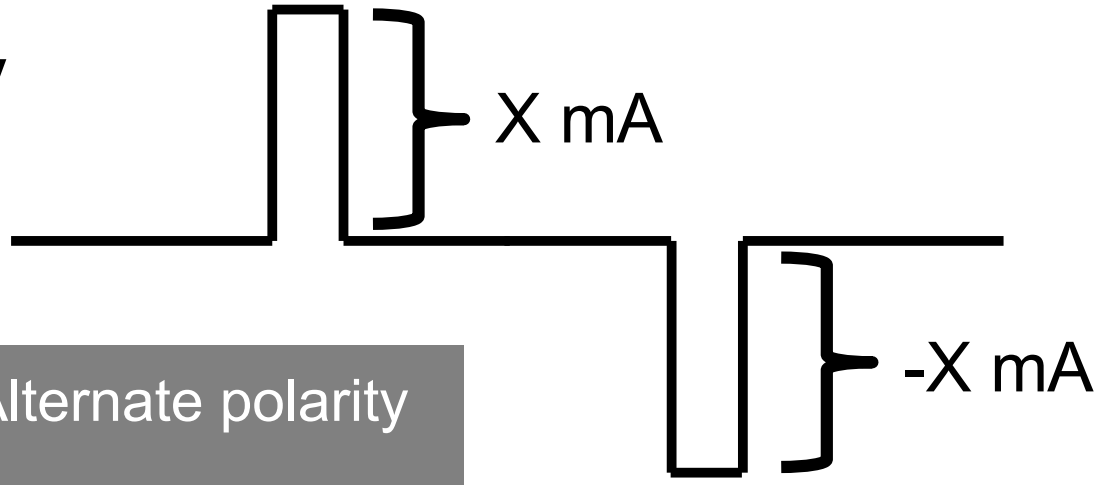
Biphasic stimulation: Alternate polarity pulses are provided



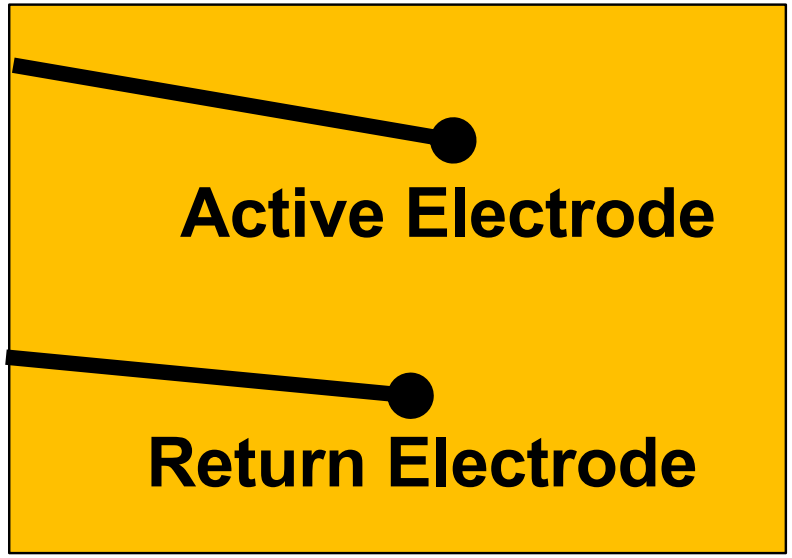
Define stimulation **Polarity** (direction of current flow) relative to one electrode.

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.
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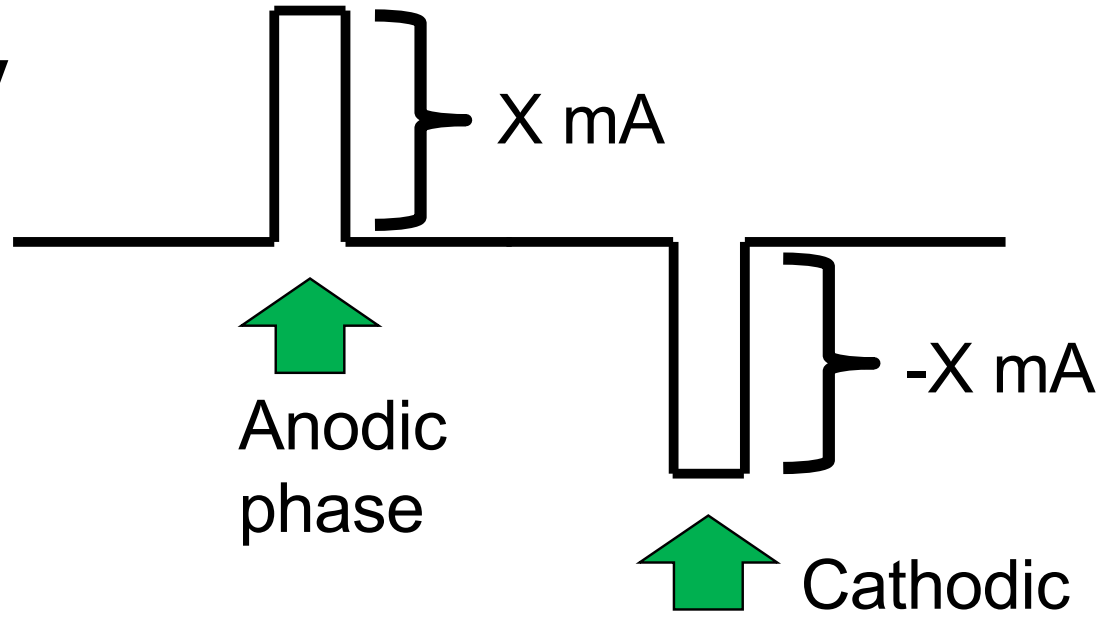
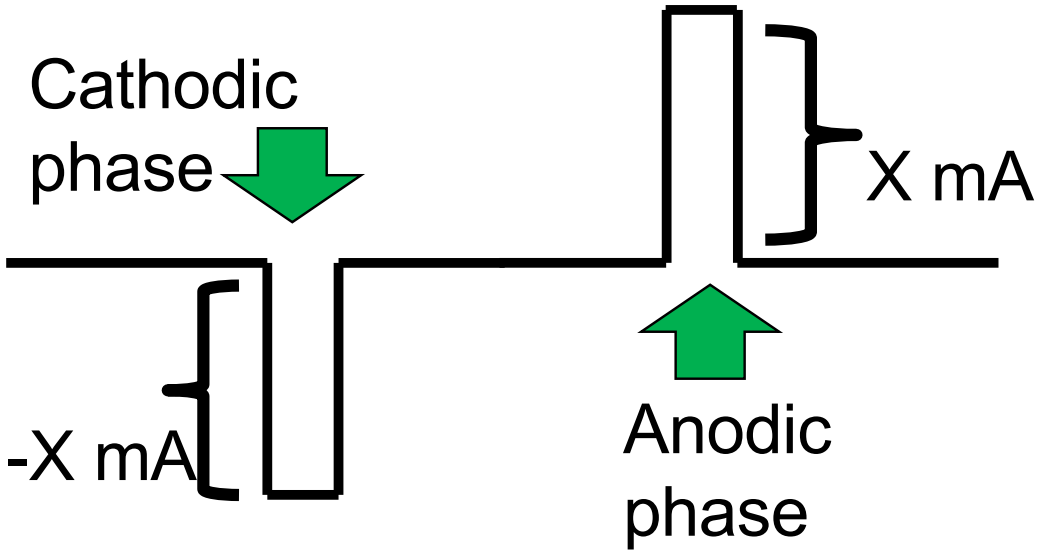
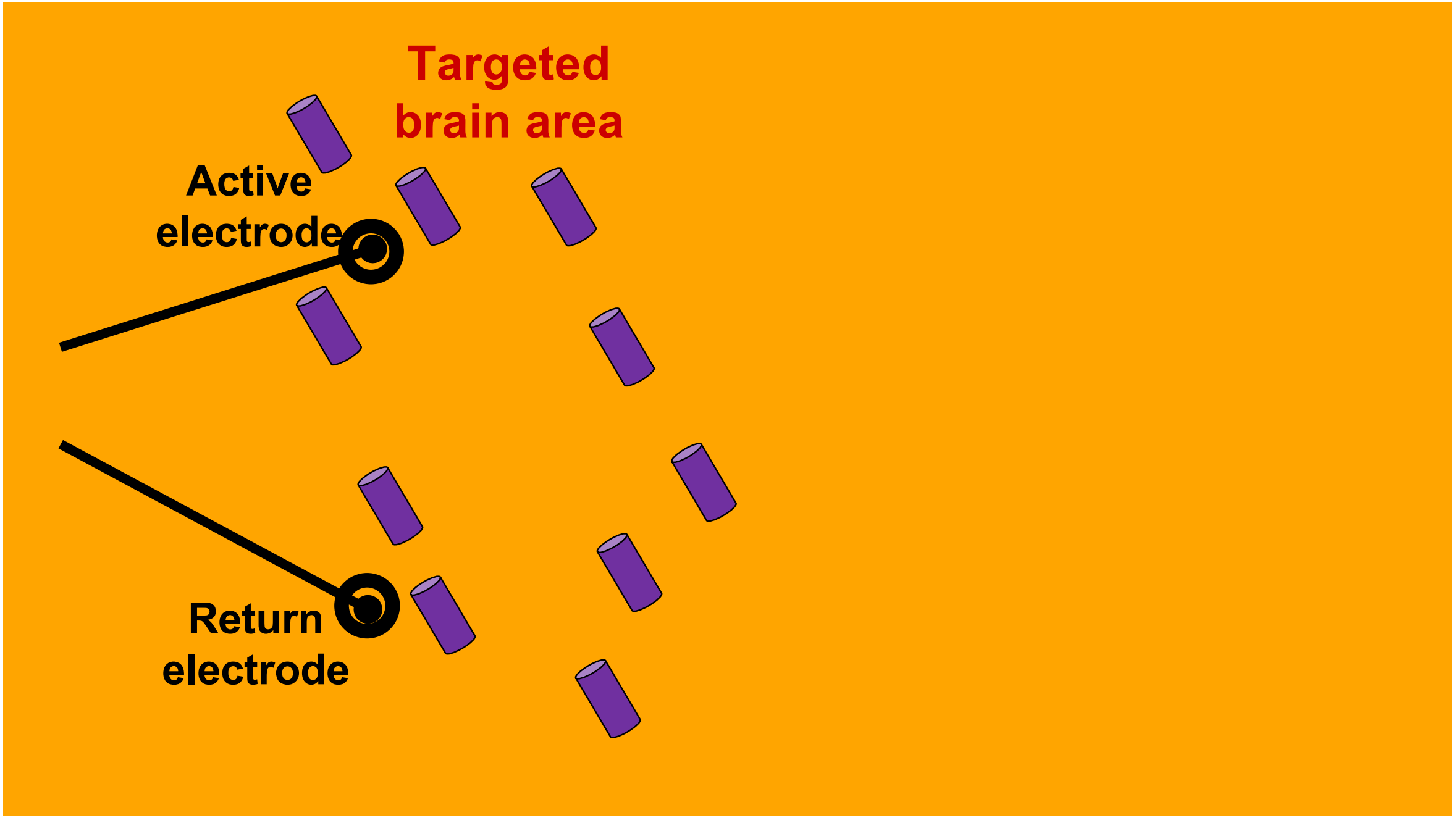
Pulse **polarity**

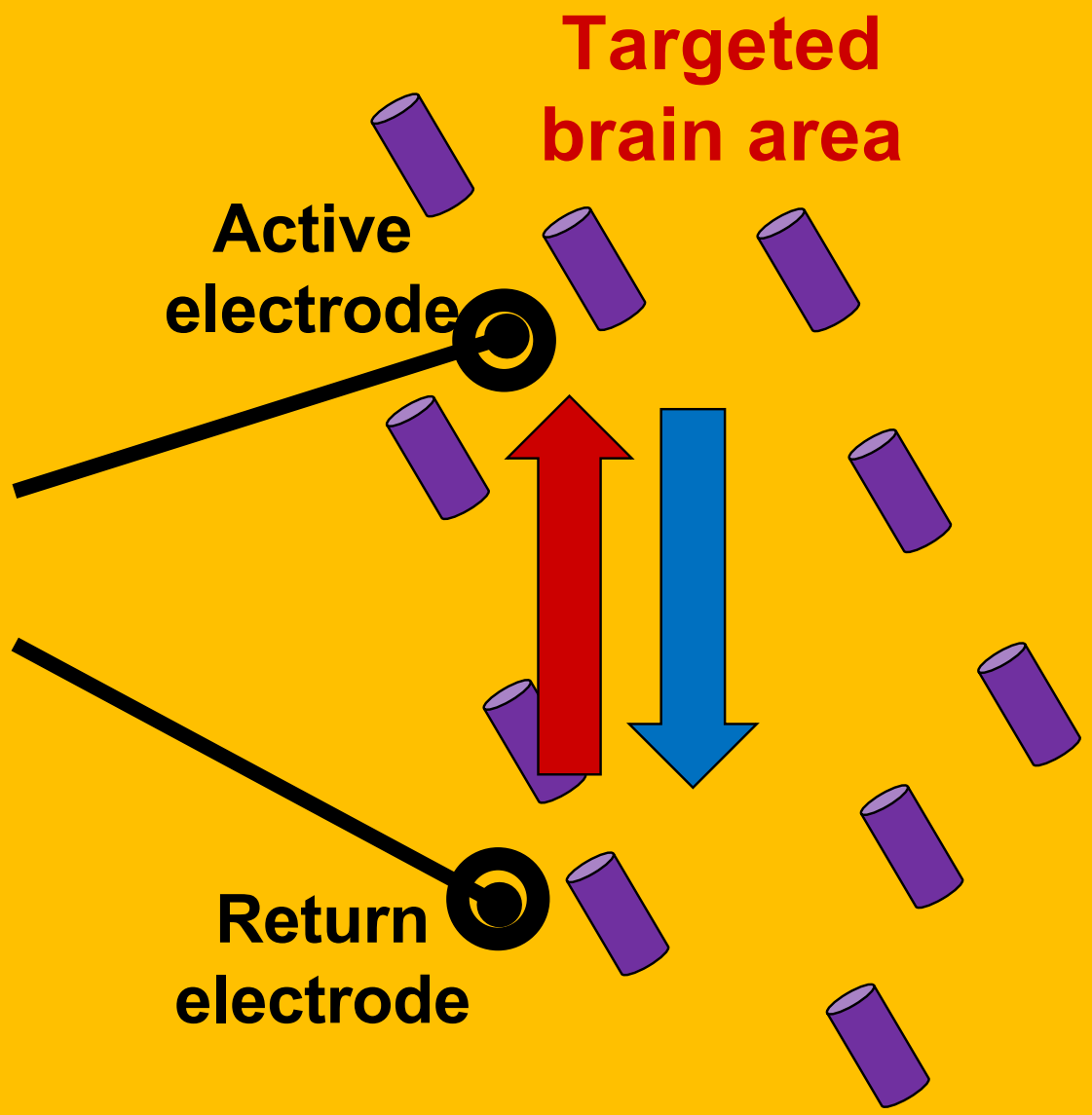


All invasive device use **Biphasic** stimulation.



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


Targeted
brain area
Active
electrode
Return
electrode



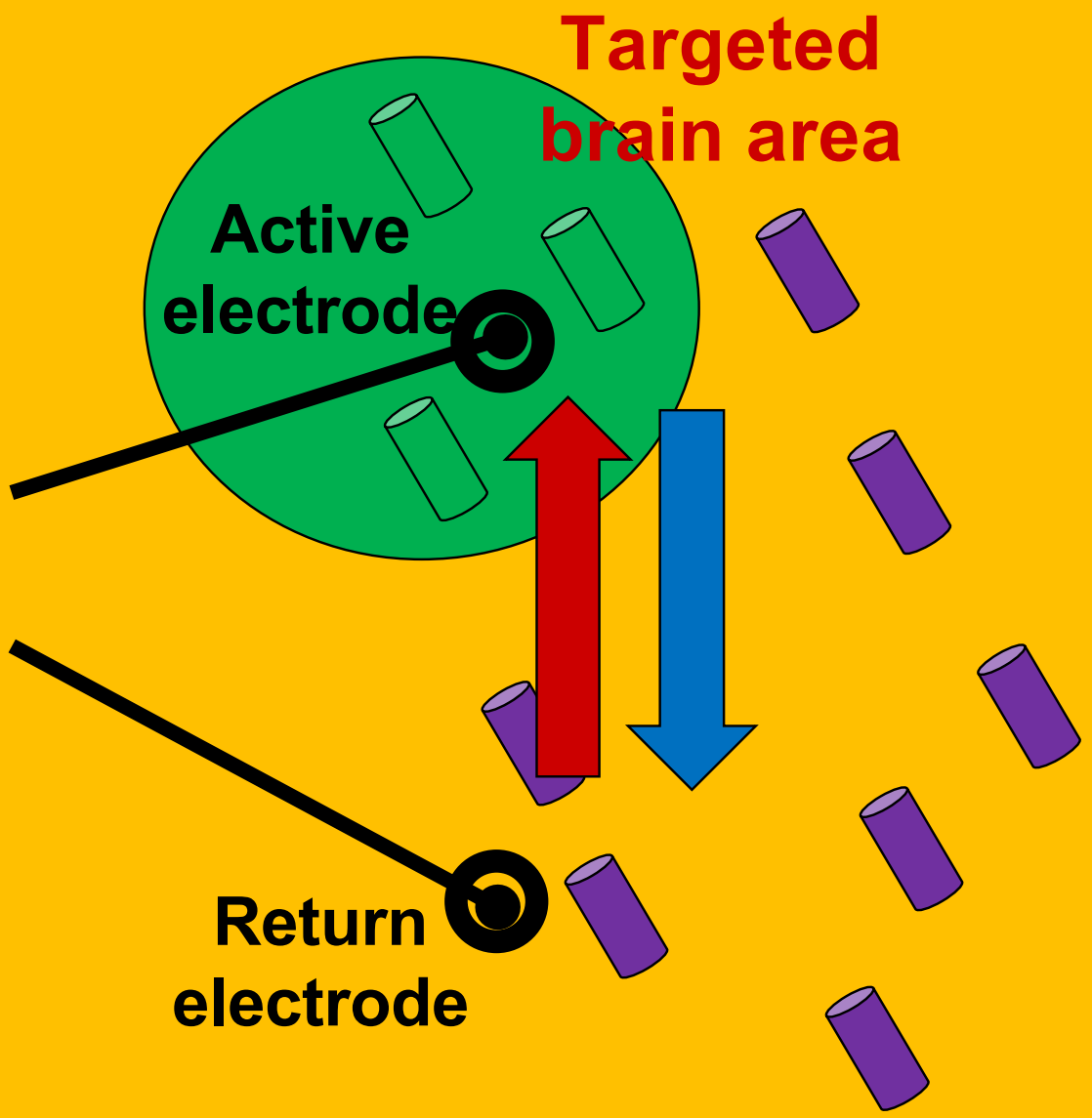
Cathodic phase

Anodic phase

Biphasic stimulation:

-1 mA applied current,
1 ms pulse duration

1 mA applied current,
1 ms pulse duration



Biphasic stimulation:

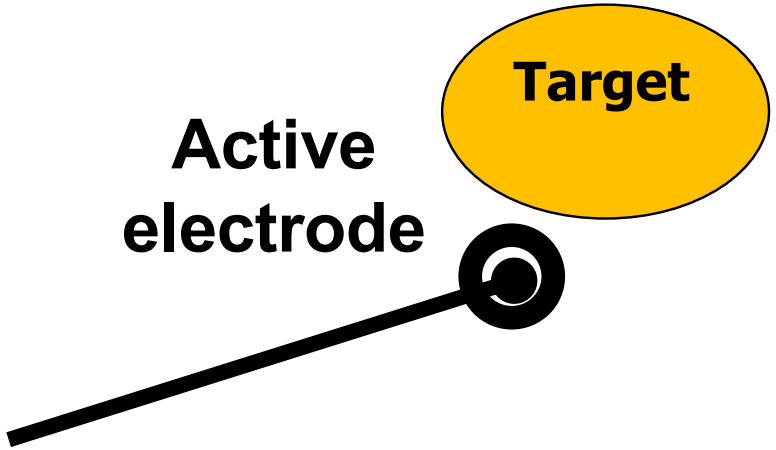
Cathodic phase

-1 mA applied current, 1 ms pulse duration

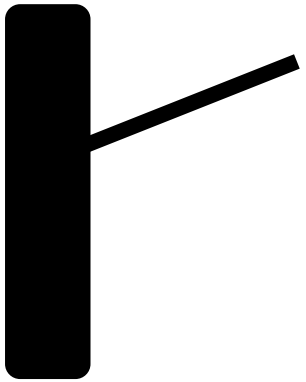
Anodic phase

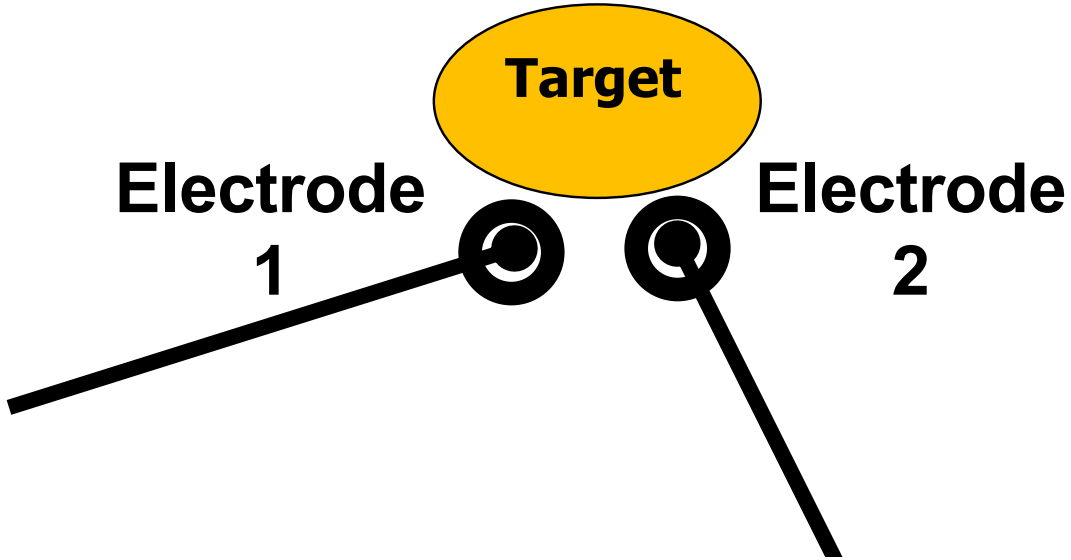
1 mA applied current, 1 ms pulse duration

Volume of Tissue Activated (VTA) : All neurons activated across all phases

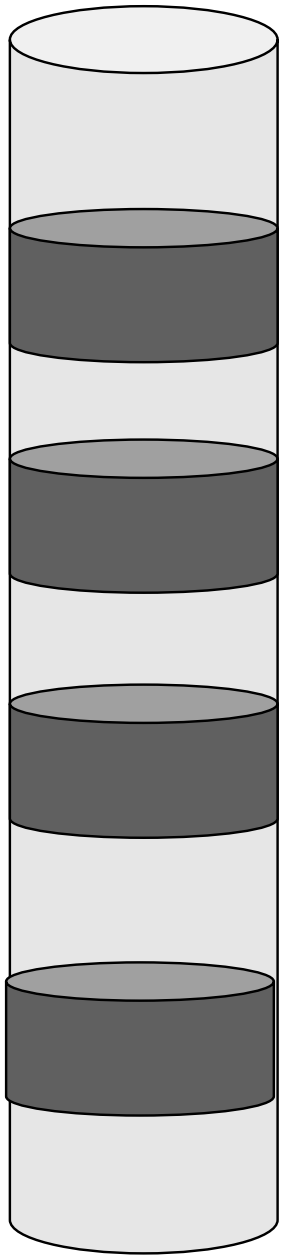


Monopolar Stimulation: When Return electrode is larger and/or farther from Target. (technically still bi-poles).
Waveform: “Biphasic”



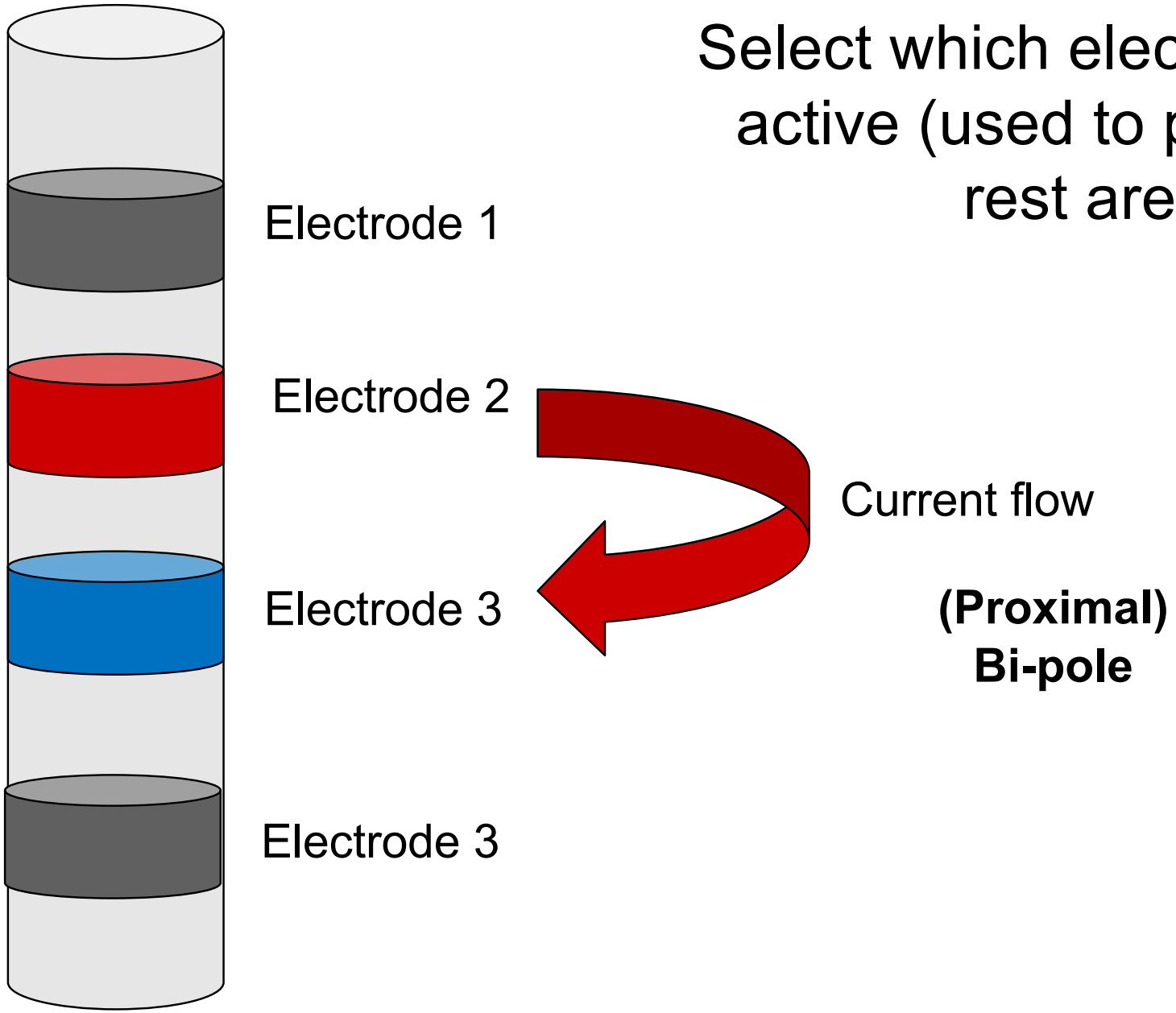


Bipolar Stimulation: When both electrodes are the same size (and proximity to Target)

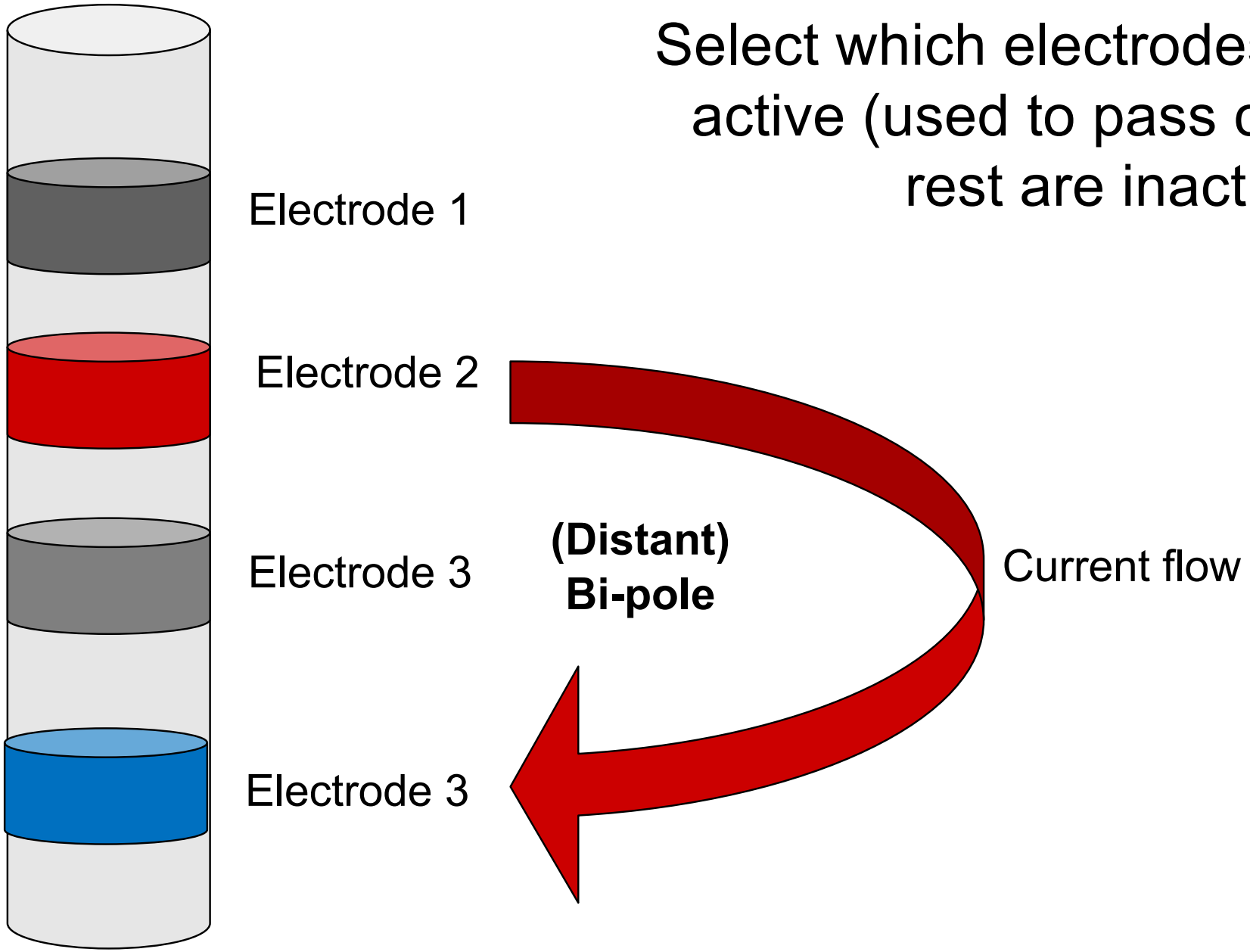


Select which electrodes on lead are active (used to pass current), the rest are inactive.

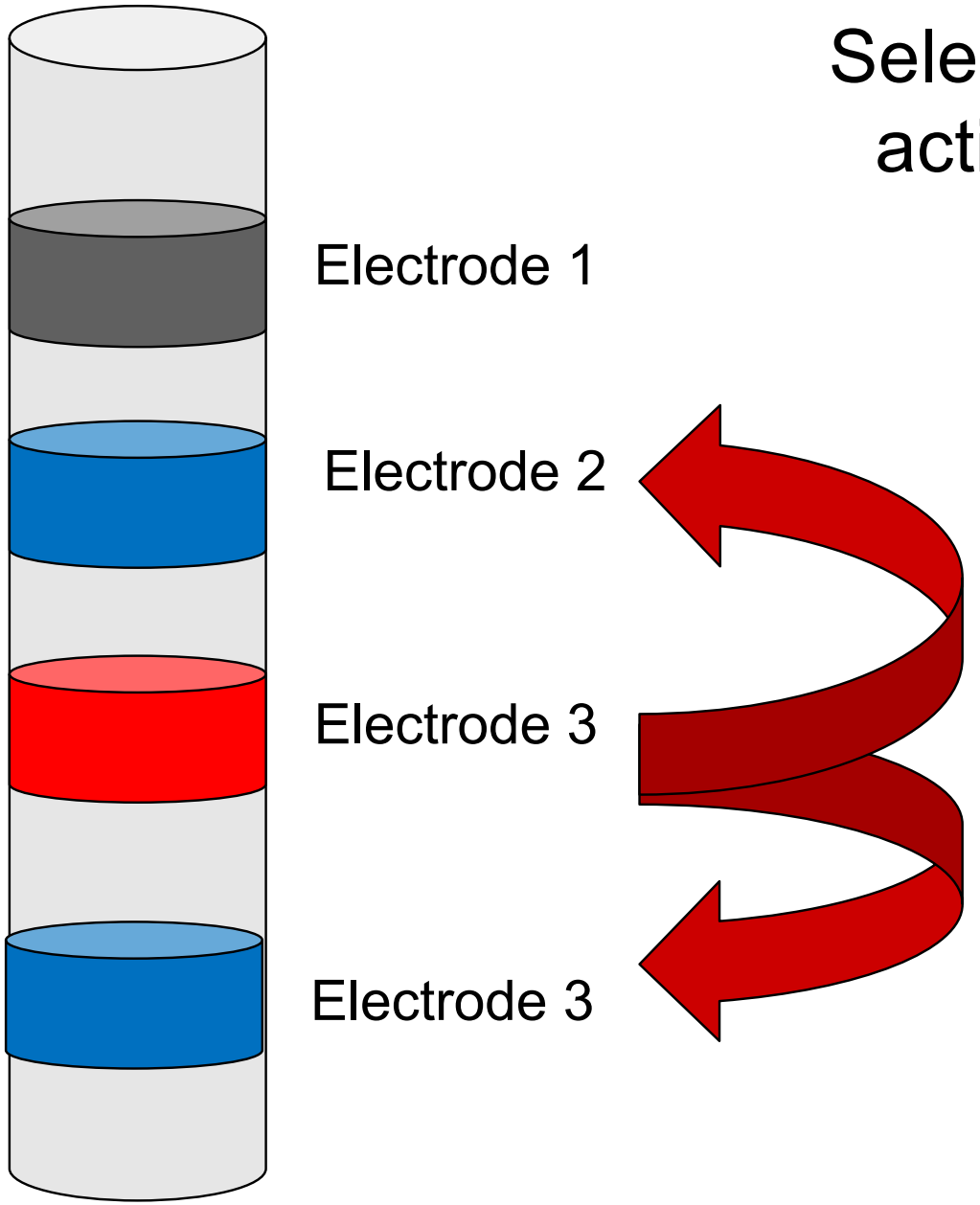
Select which electrodes on lead are active (used to pass current), the rest are inactive.



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

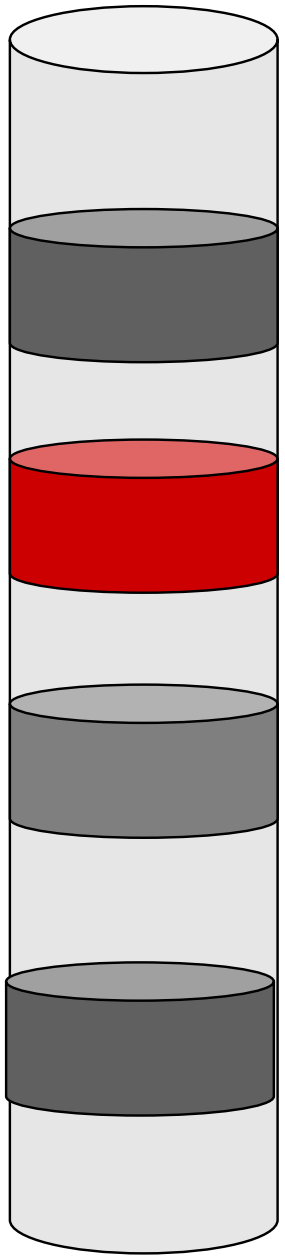


Select which electrodes on lead are active (used to pass current), the rest are inactive.



“Guarded” Tri-pole

Current flow



Electrode 1

Electrode 2

Electrode 3

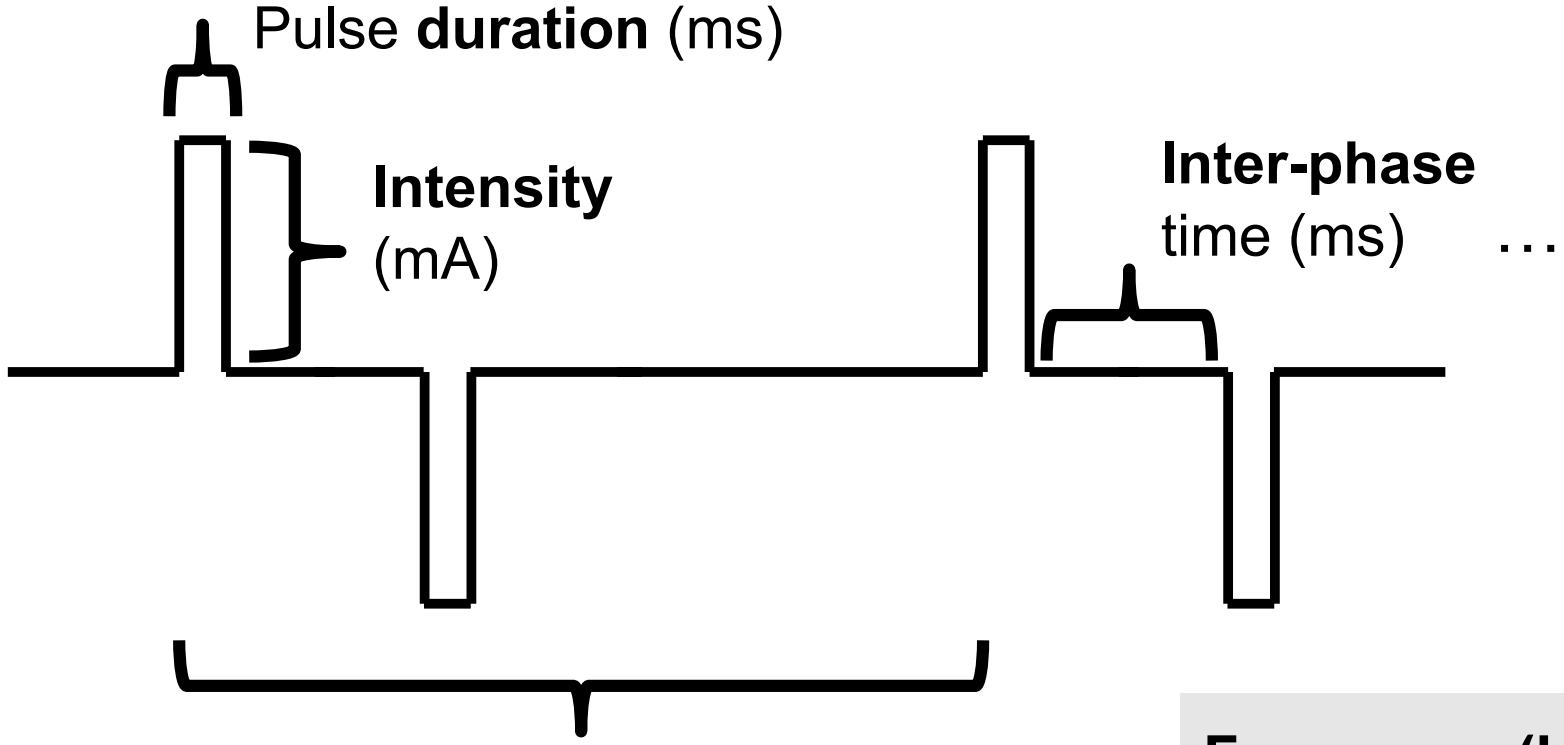
Electrode 3

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

Current flow

Monopolar

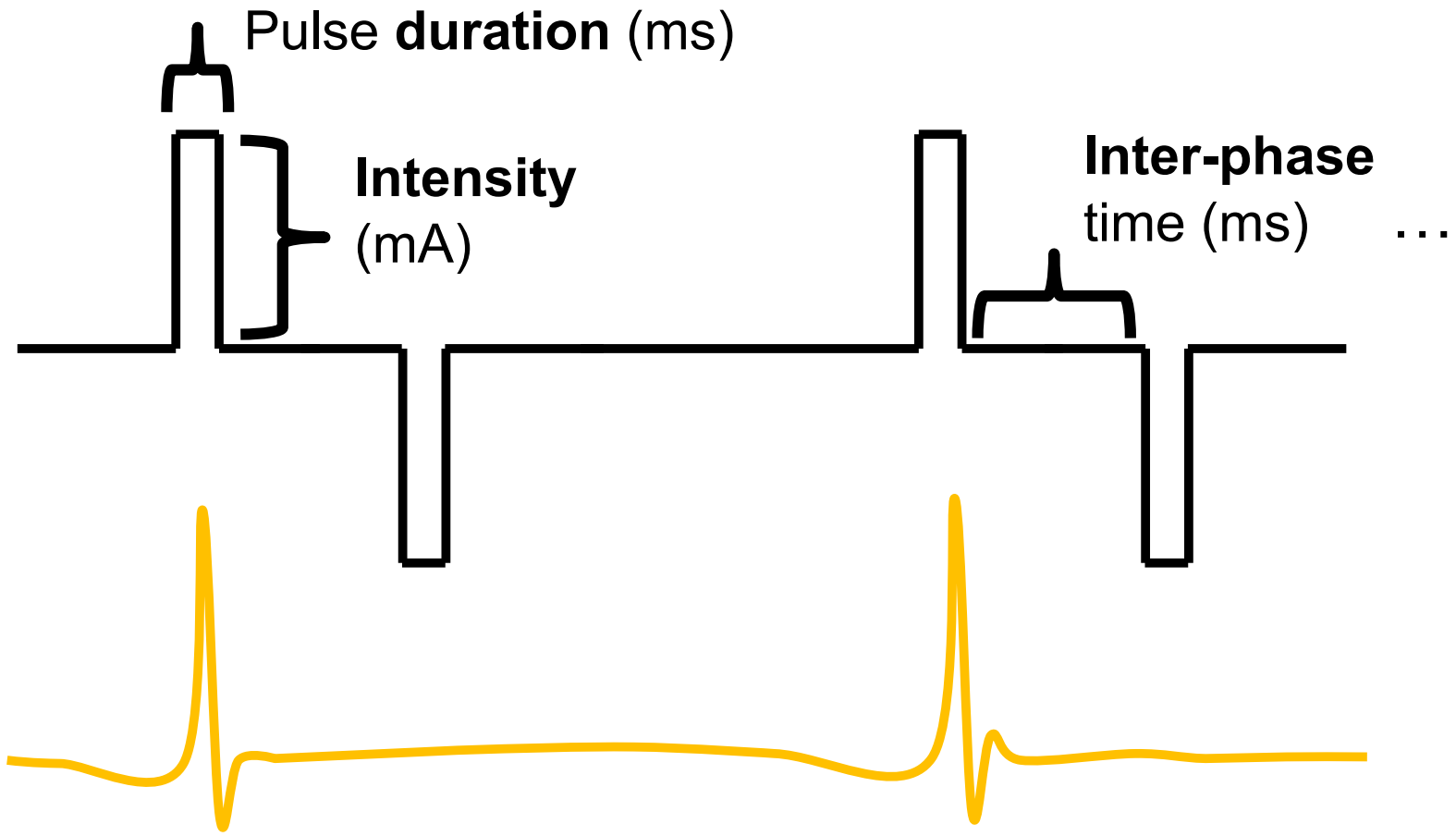
Stimulation is provided in pulse pairs (of opposite polarity) repeated at a **Pulse Period**



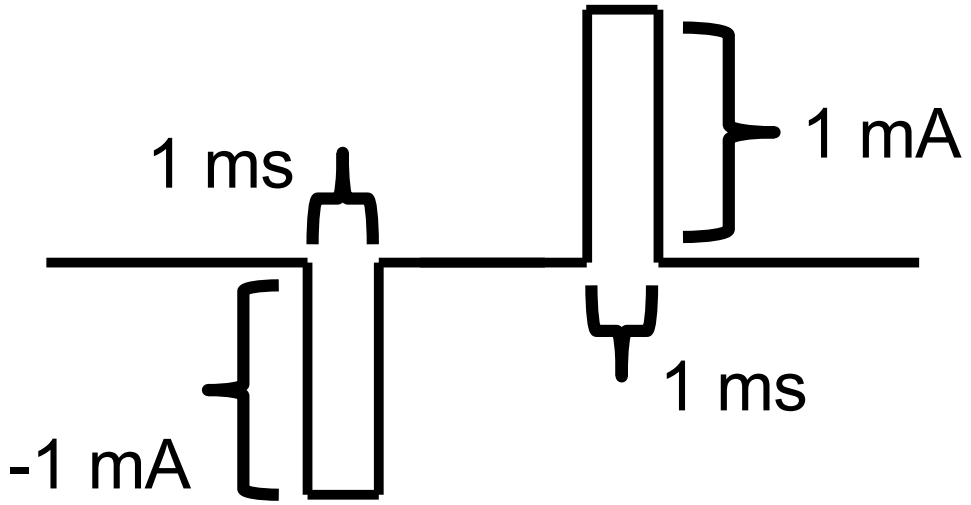
Pulse period (ms): Time from start of the leading pulse (given phase) to the next leading pulse (same phase)

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

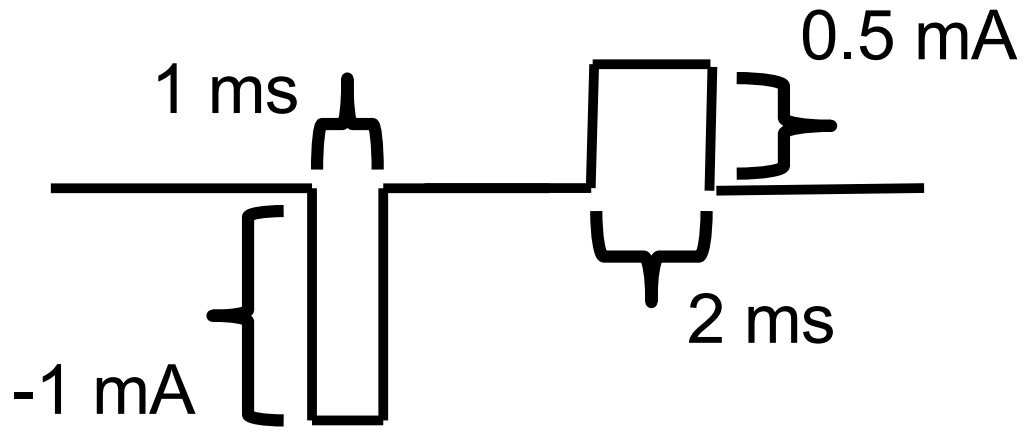
Stimulation is provided in pulse pairs (of opposite polarity) repeated at a **Pulse Period**



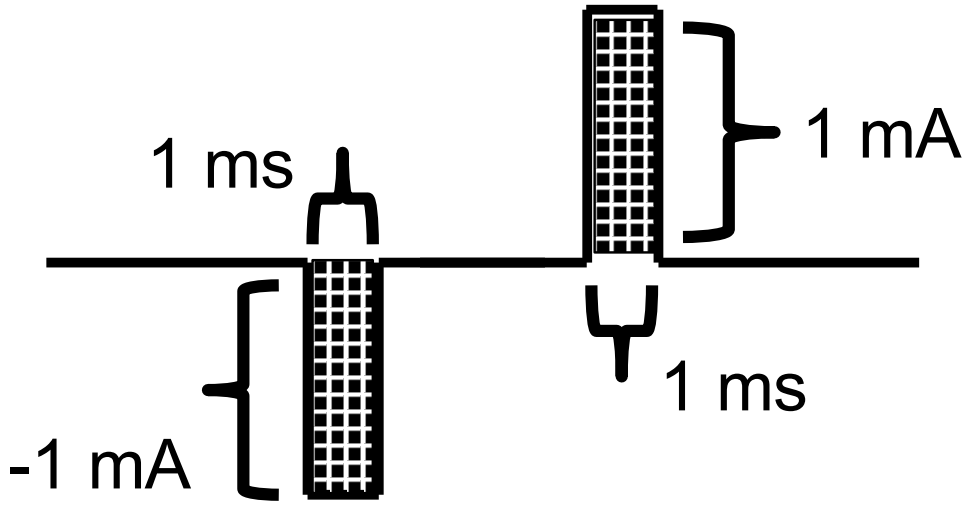
Action potentials may be triggered by just one phase, so at the stimulation ”frequency”.



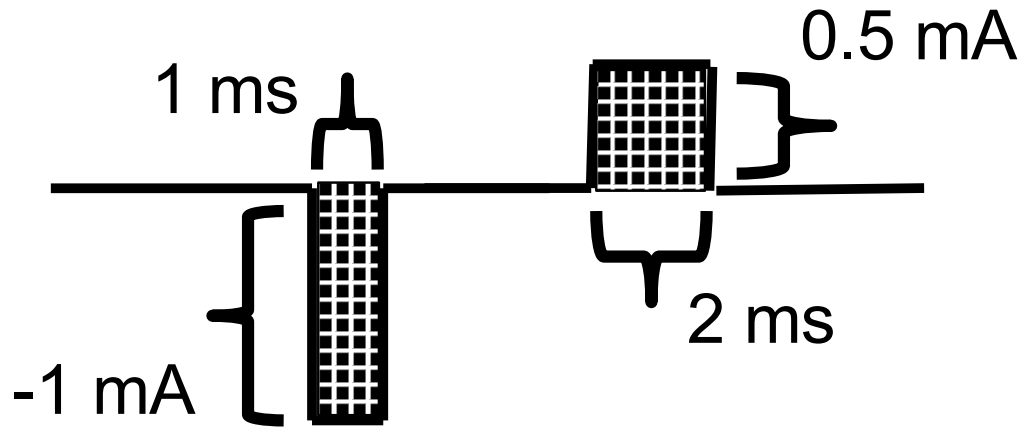
Symmetric biphasic stimulation: When the two pulse phases have the same duration and magnitude



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



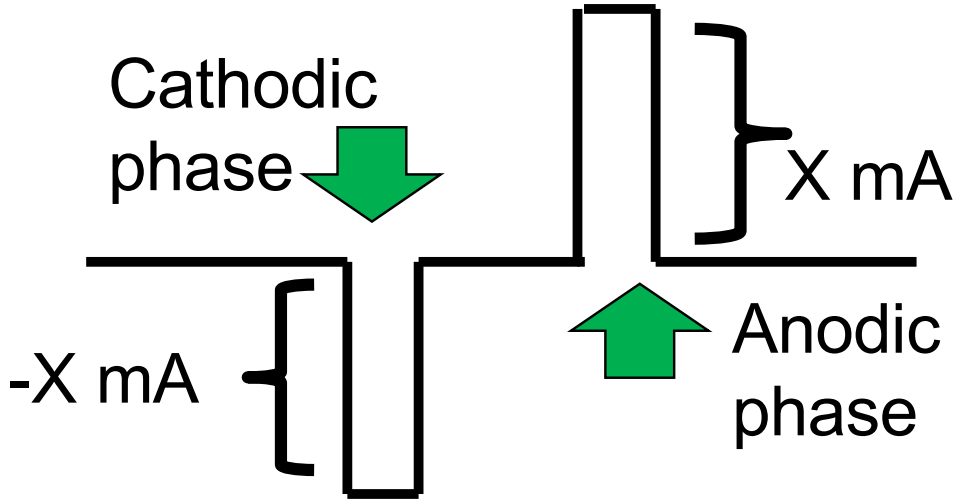
Symmetric biphasic stimulation: When the two pulse phases have the same duration and magnitude



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

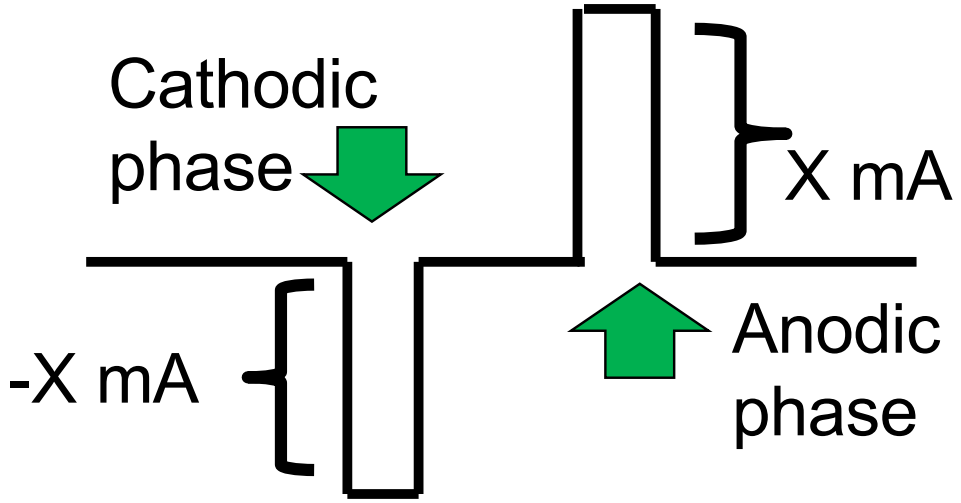
But invasive stimulation always **Charge Balanced**: Charge of the two phases add to zero.

Why **biphasic stimulation?**

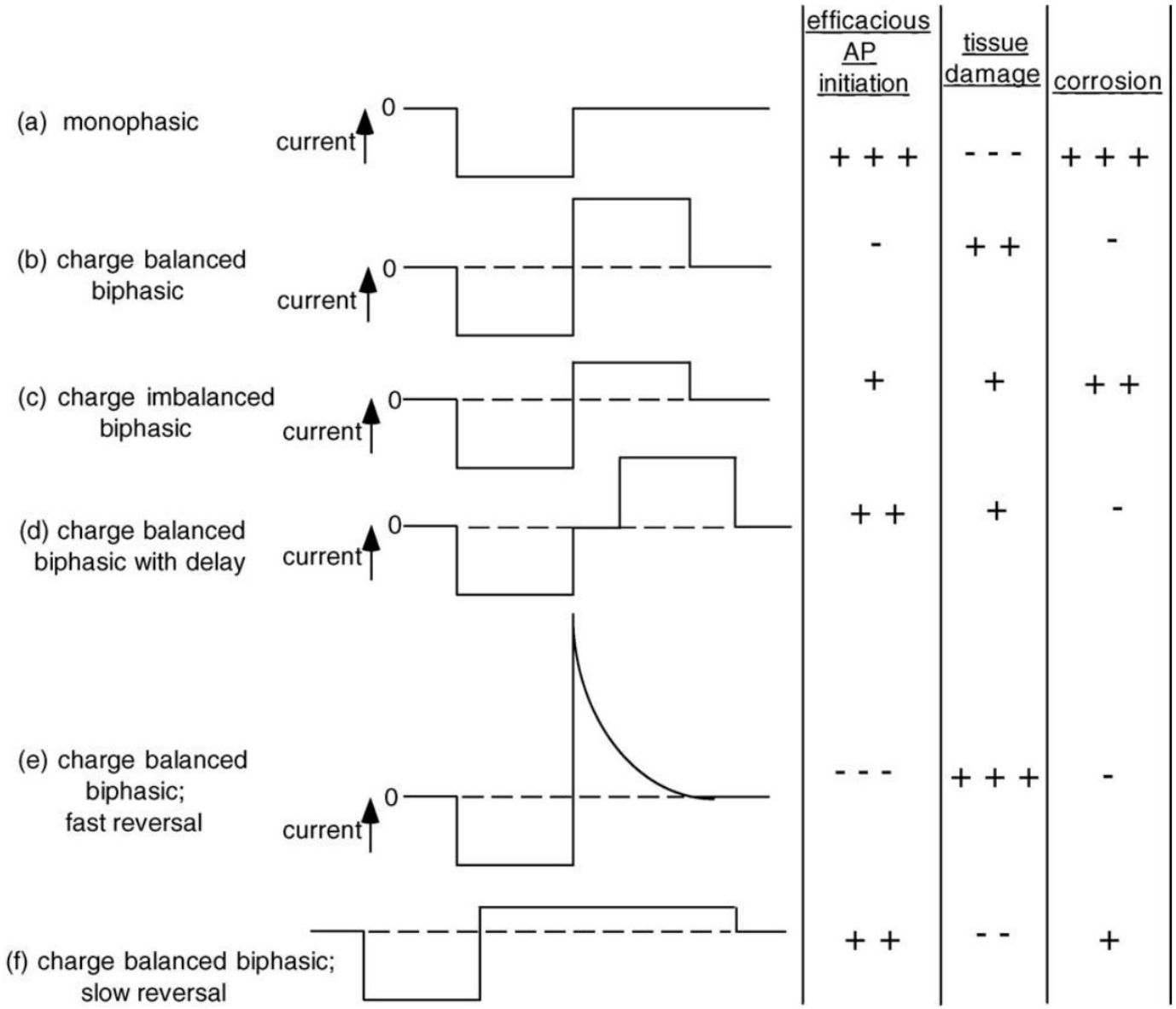


- Only one phase (usually the leading cathodic phase) responsible for stimulation
  e.g. 100 Hz stimulation will actually have 200 pulses per second (100 anodic and 100 cathodic) but is intended to produce action potentials at 100 Hz
- **Biphasic** may increase or decrease current threshold compared 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.


efficacious AP initiation
tissue damage
corrosion
(a) monophasic
current
0
+ + +
- - -
+ + +
(b) charge balanced biphasic
current
0
-
+ +
-
(c) charge imbalanced biphasic
current
0
+
+
+ +
(d) charge balanced biphasic with delay
current
0
+ +
+
-
(e) charge balanced biphasic; fast reversal
current
0
- - -
+ + +
-
(f) charge balanced biphasic; slow reversal
+ +
- -
+

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. Always charged balanced)

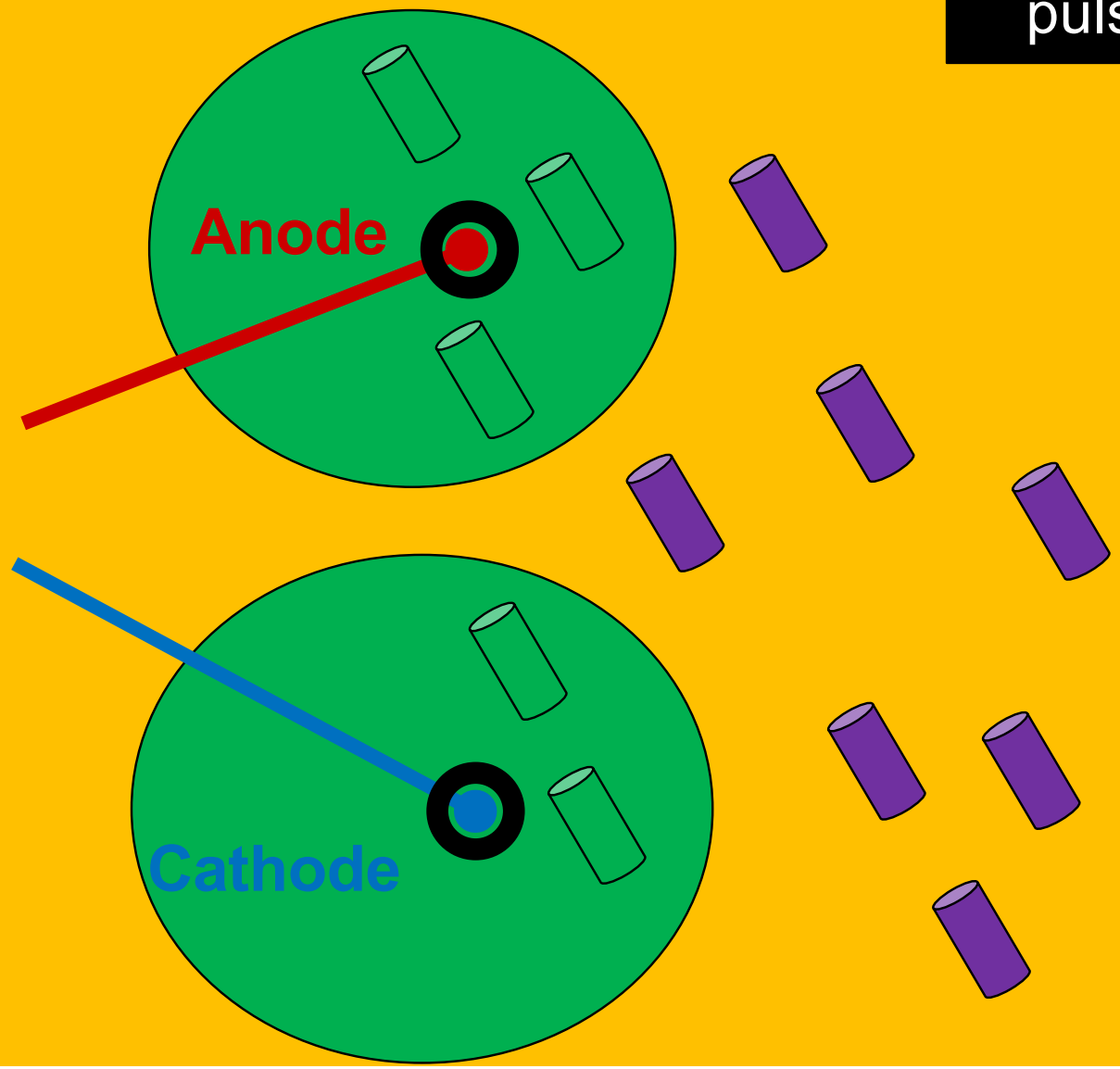
- Two devices with the same dose will have identical effects on the same body. Reporting dose underpins reproducibility. Summary metrics or terms (eg. “pulse density”, “kHz”, “Burst”…) don’t replace need to fully account for dose.
- Dose may be adjusted (e.g., based on patient response / biomarkers).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

Part 3: Three things that change everything.

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

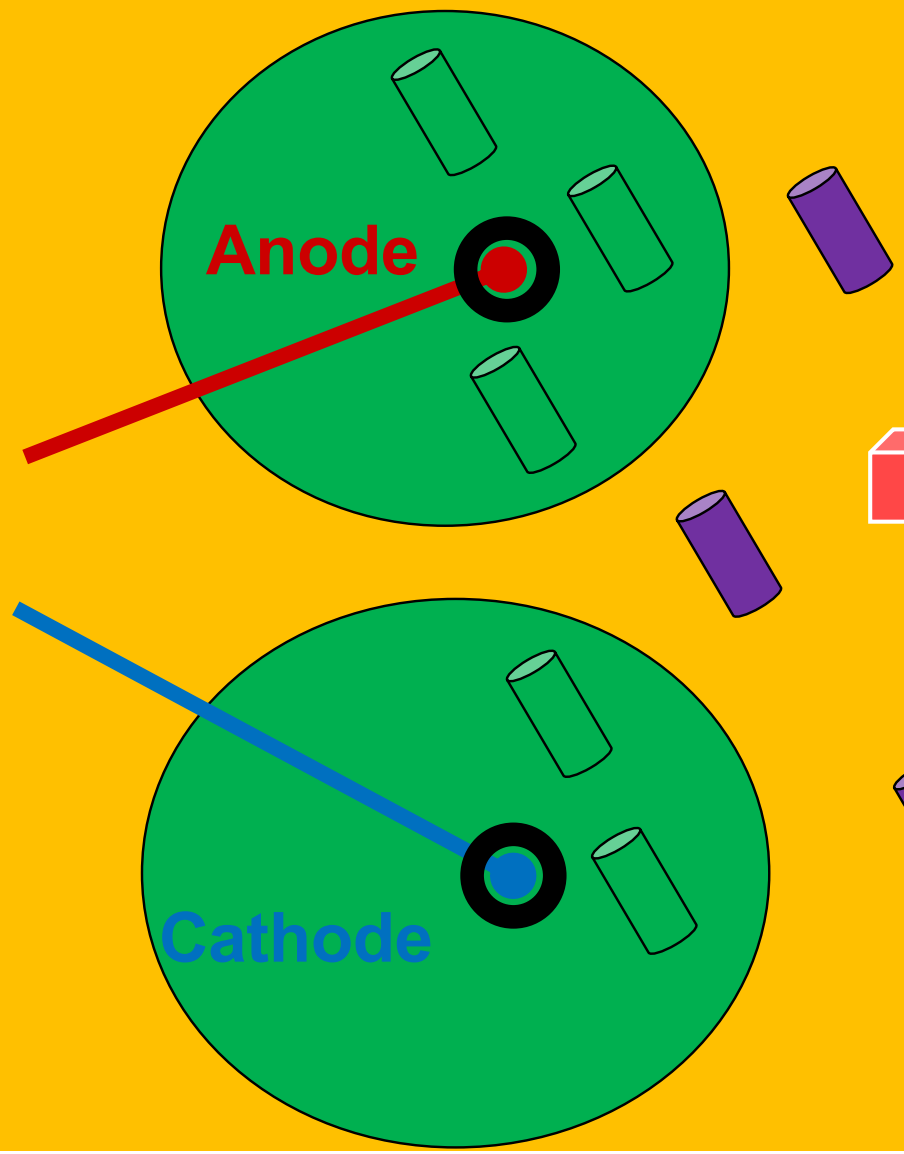
X mA applied current, with Y mS pulse duration, Z timing pattern

Volume of Tissue Activated (VTA)



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

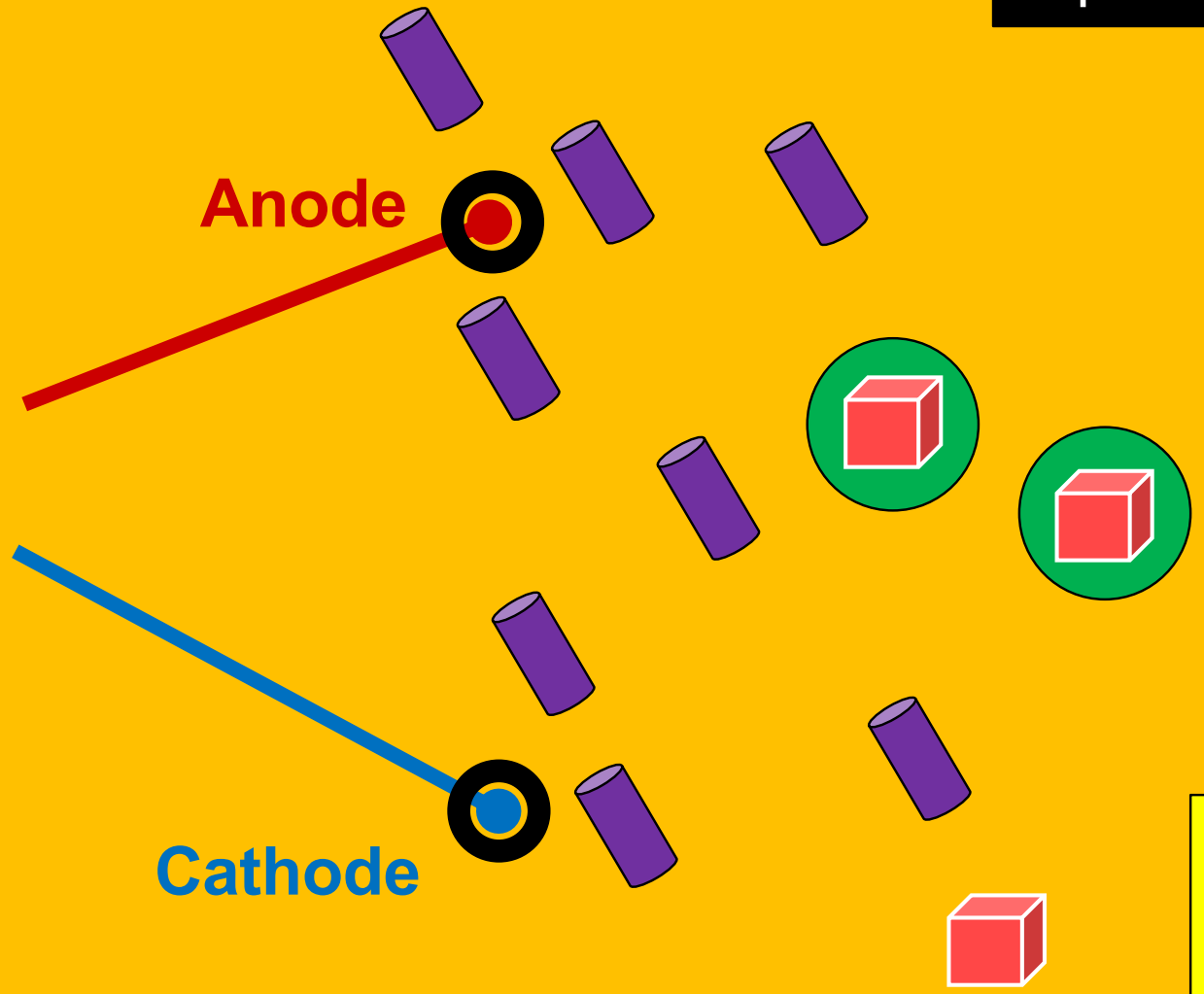
Volume of Tissue Activated (VTA)



Cell type 1

Cell type 2

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



Cells activated

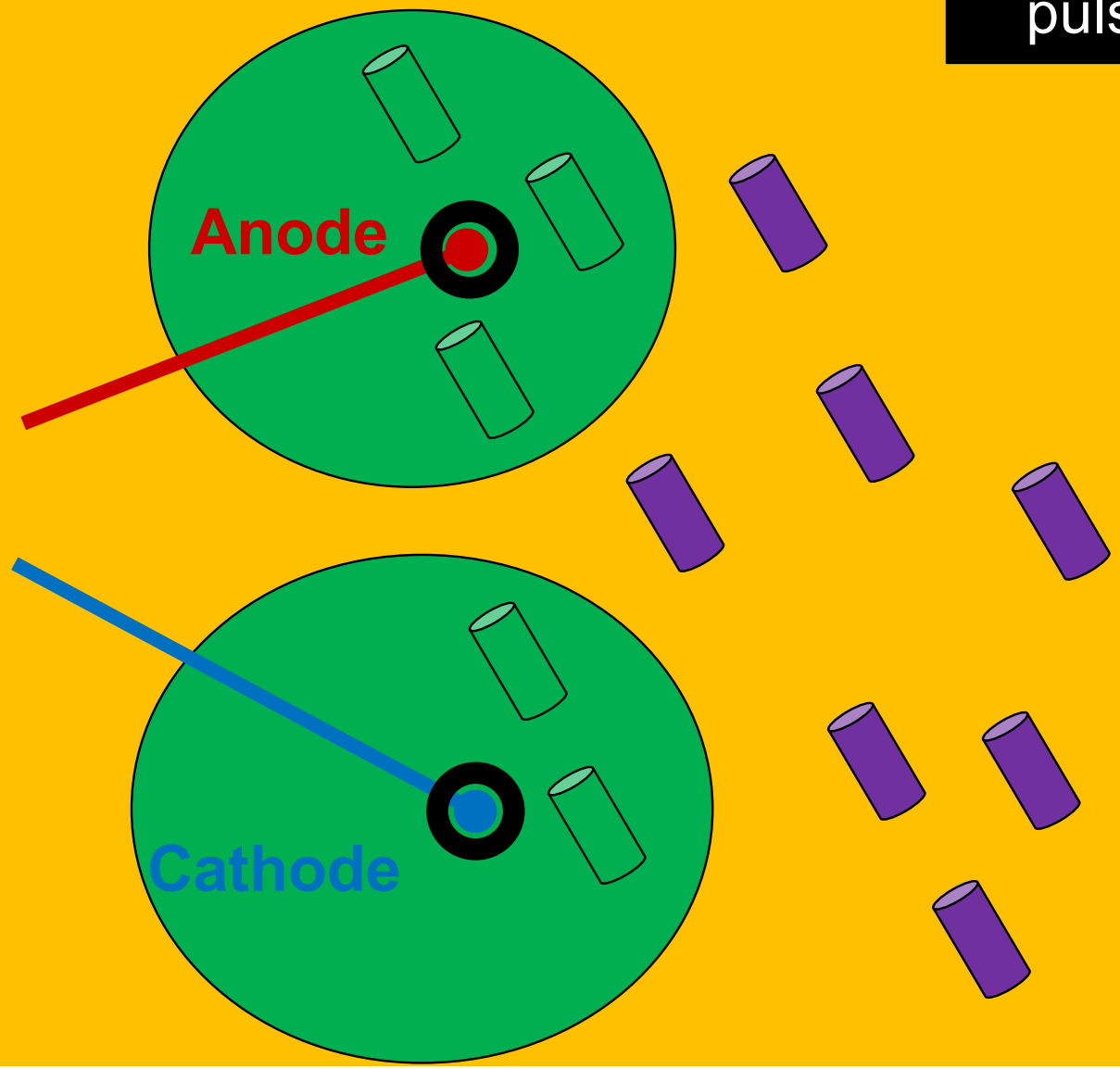
Cell type 1

Cell type 2

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

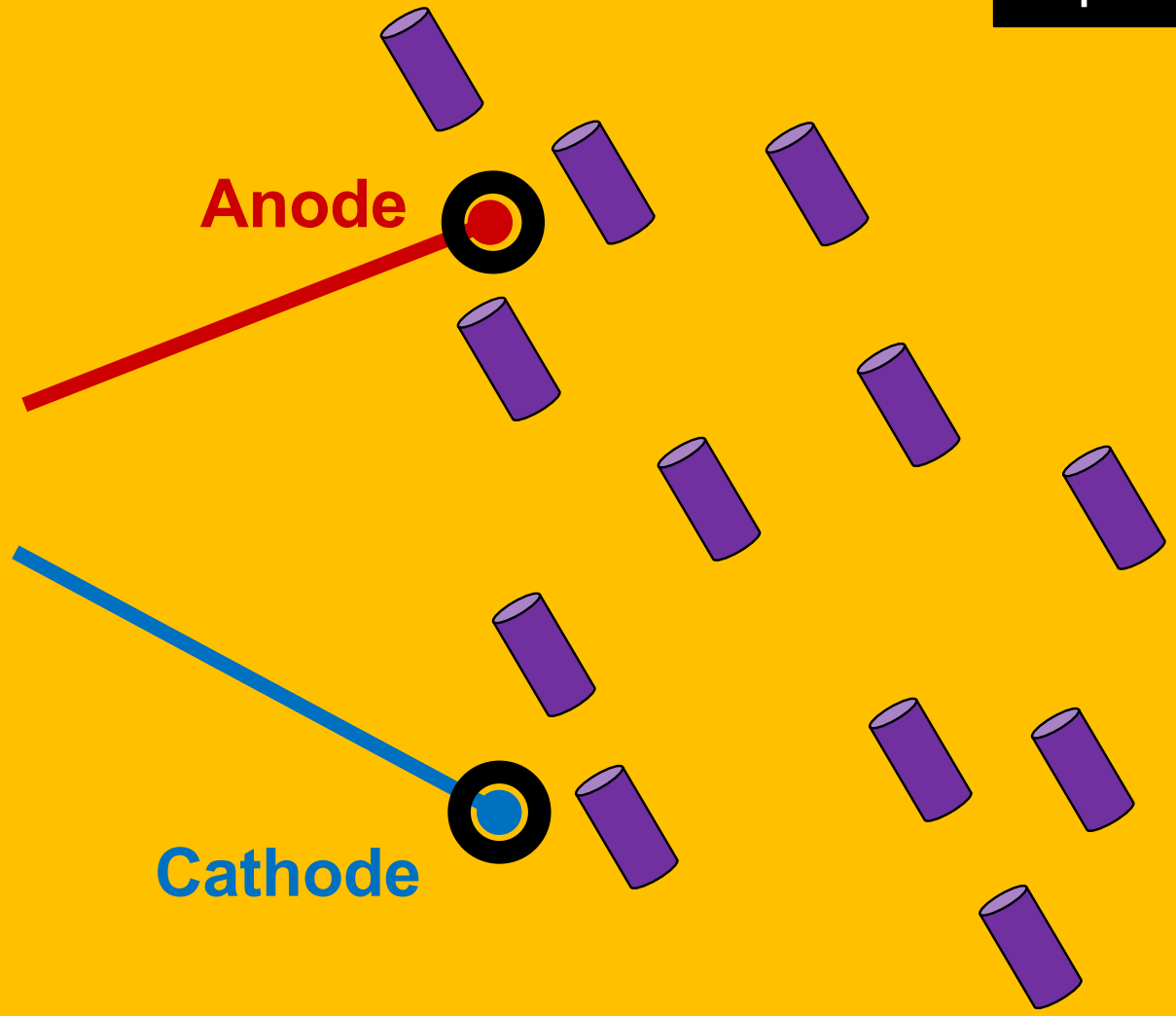
X mA applied current, with Y mS pulse duration, Z timing pattern

Volume of Tissue Activated (VTA)



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

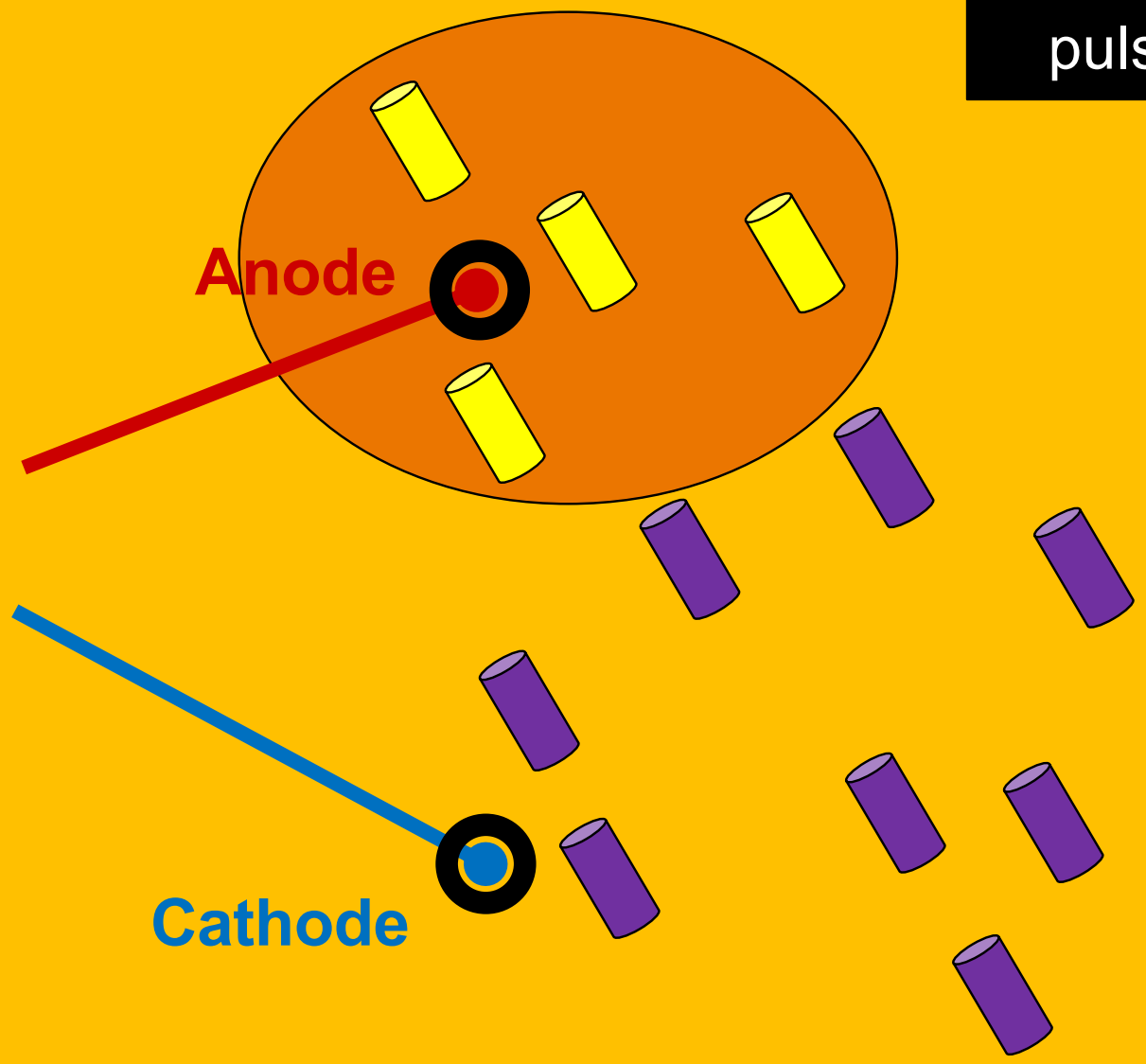
Volume of Tissue Activated (VTA)



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

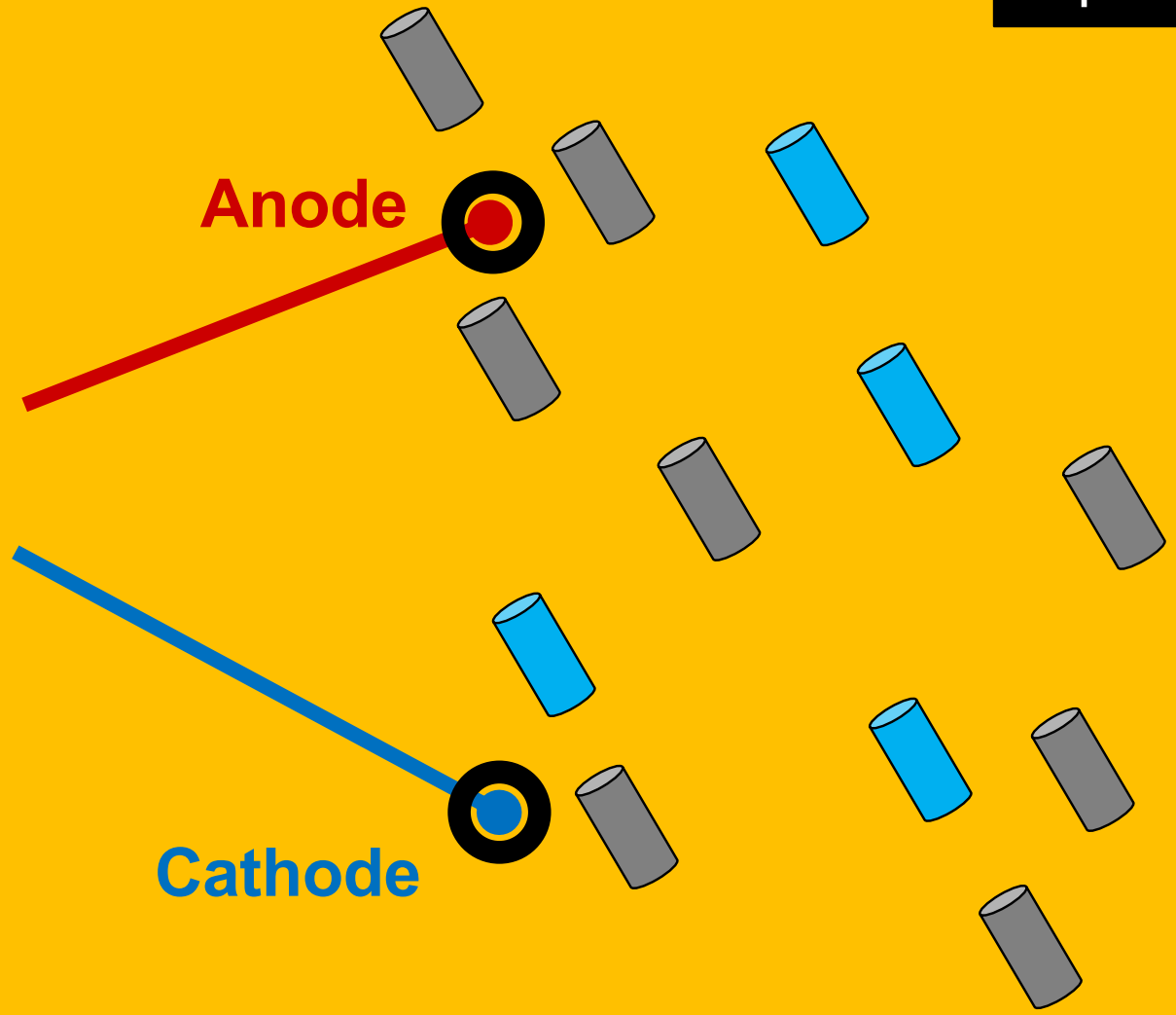


Volume of Tissue Modulated

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

“Sub-threshold” change in neuronal activity.

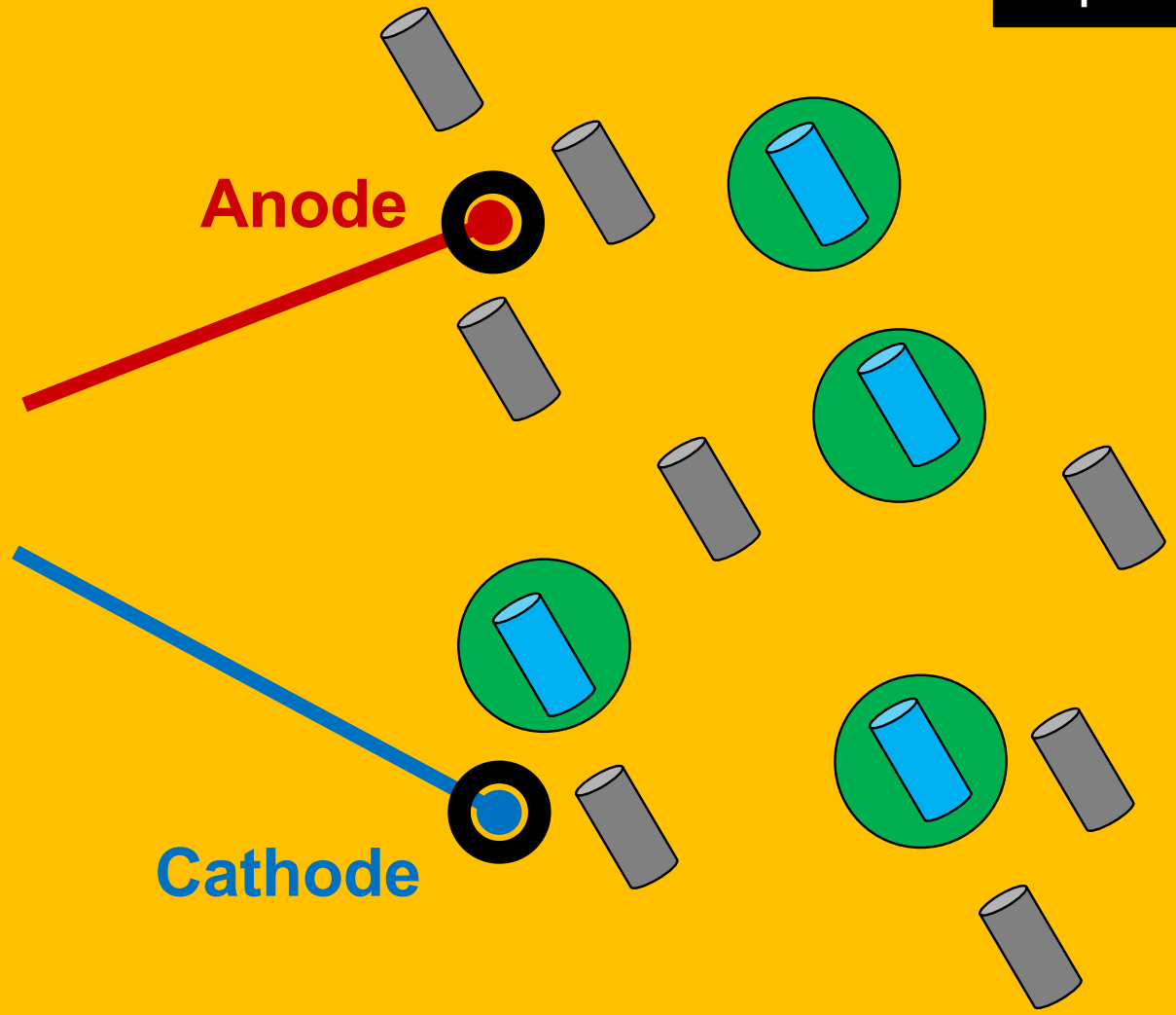
X mA applied current, with Y mS pulse duration, Z timing pattern



Neurons active at the moment.

Neurons not active at the moment.

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



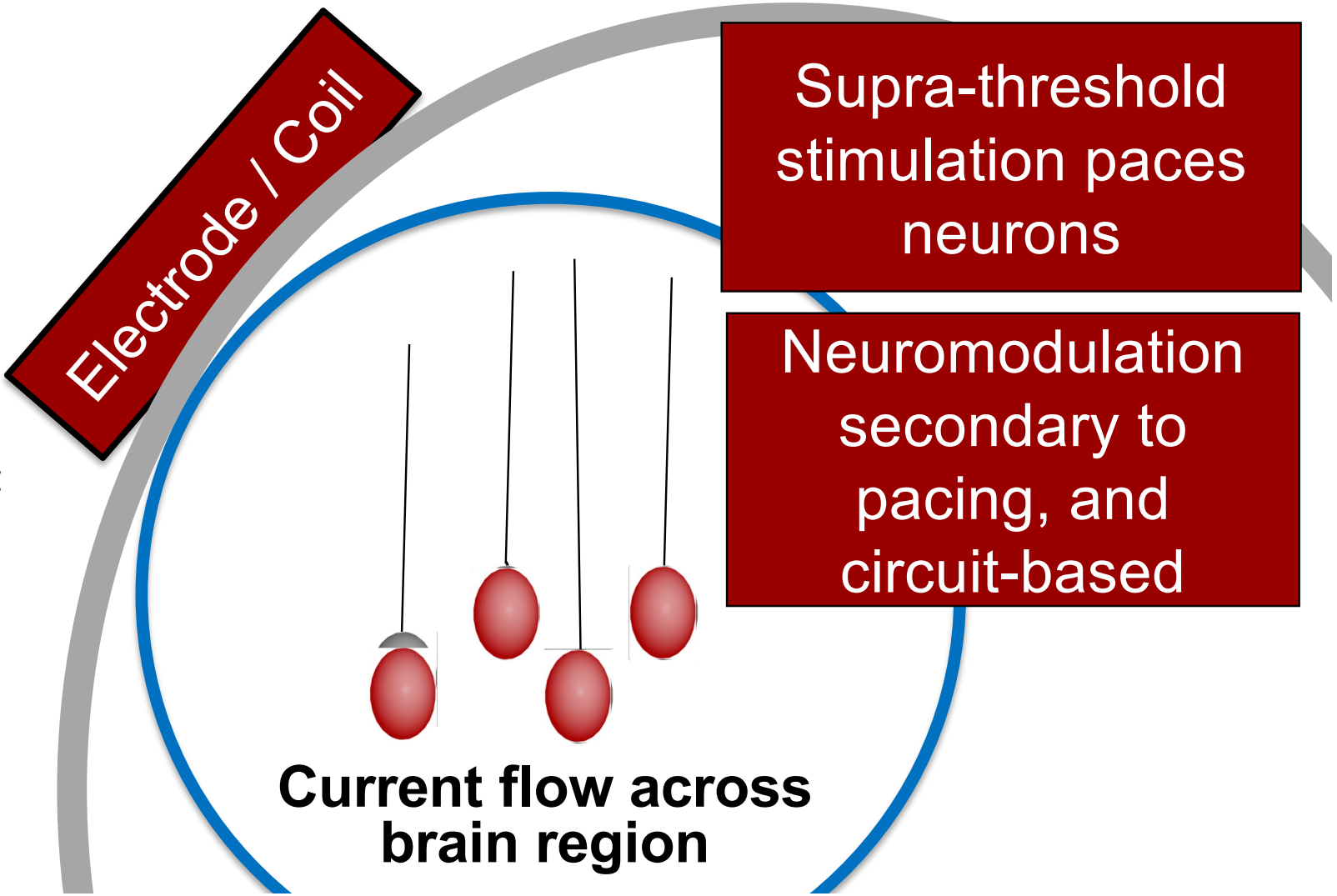
Cells activated based on ongoing active state.

Neurons active at the moment.

Neurons not active at the moment.

From Anatomical Targeting to Functional Targeting

Supra-threshold stimulation (TES, TMS, ECT…)

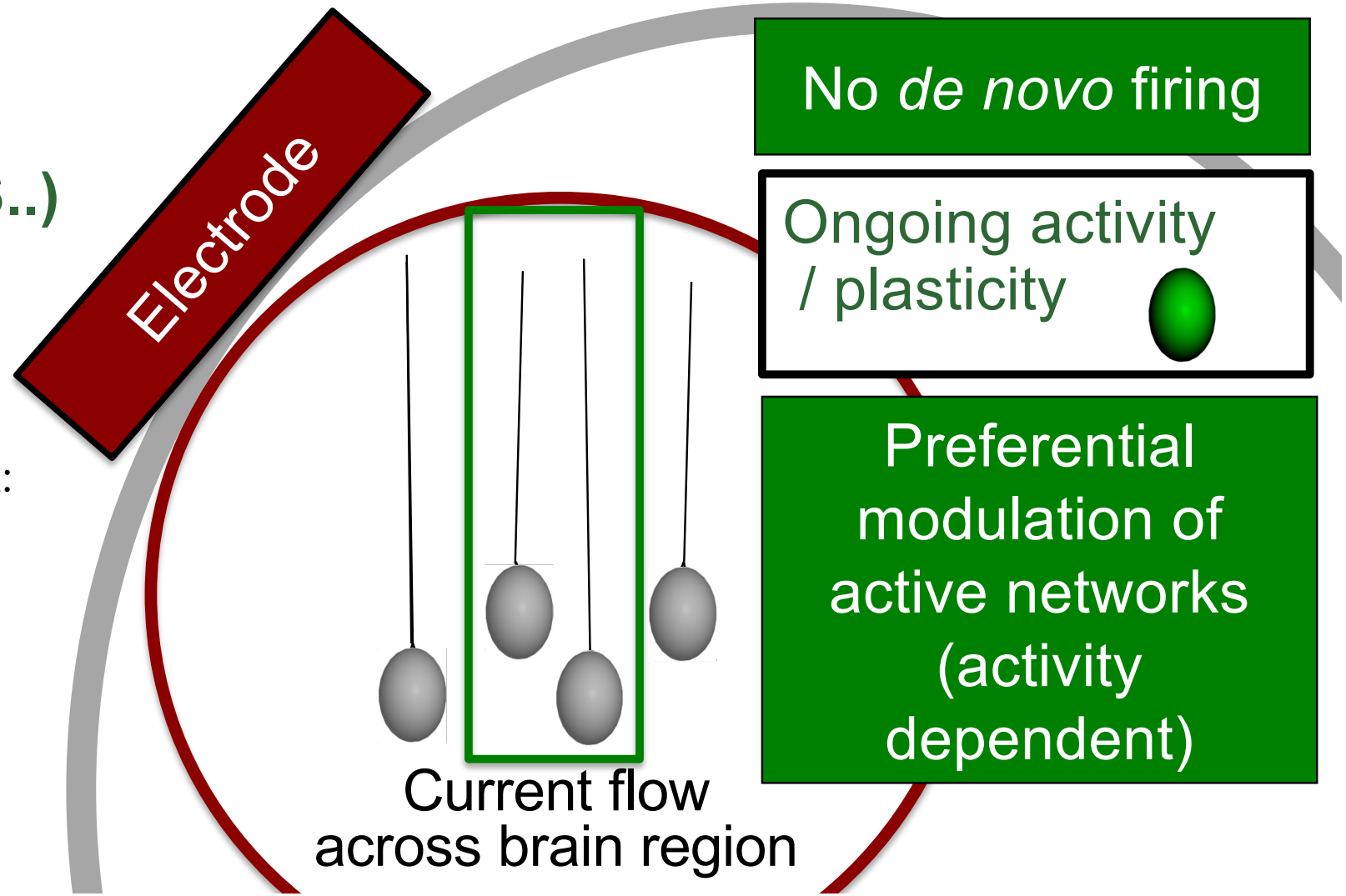


Jackson et al. Animal models of transcranial DC stimulation: Methods and mechanisms. *J Physiol* 2016

Bikson et al. Effects DC electric fields on excitability in rat hippocampal slices in vitro. *J Physiol* 2014

From Anatomical Targeting to Functional Targeting..

Sub-threshold stimulation (tDCS, tACS, tRNS..)



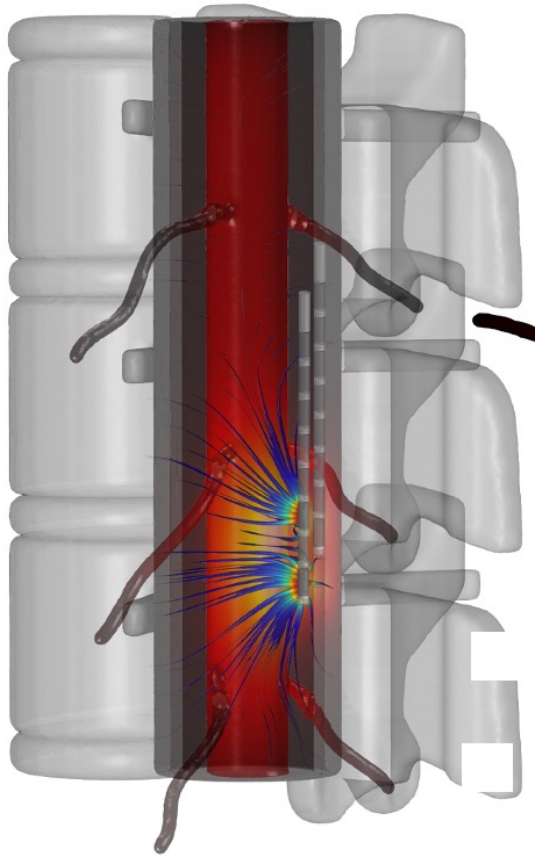
Jackson et al. Animal models of transcranial DC stimulation: Methods and mechanisms. *J Physiol* 2016

Bikson et al. Effects DC electric fields on excitability in rat hippocampal slices in vitro. *J Physiol* 2014

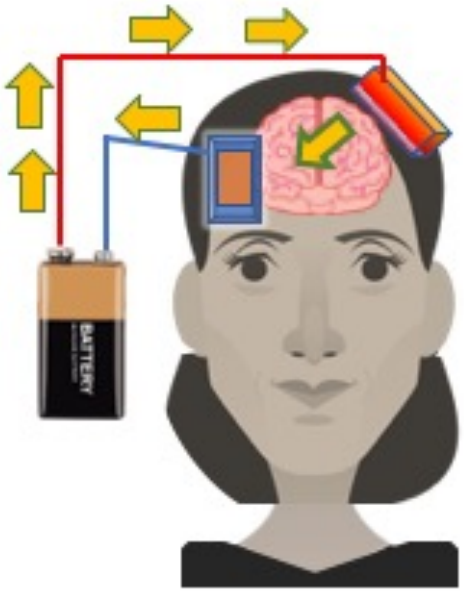
A simple introduction to how neuromodulation devices work.

Oct 18, 2023

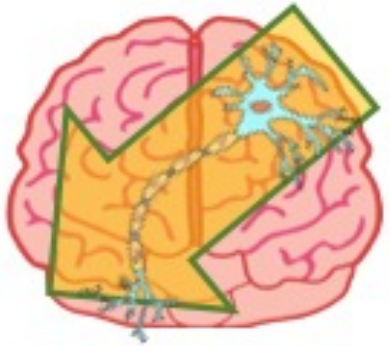
Marom Bikson



1 Direction of current flow from device across head and brain



transcranial
Direct
Current
Stimulation



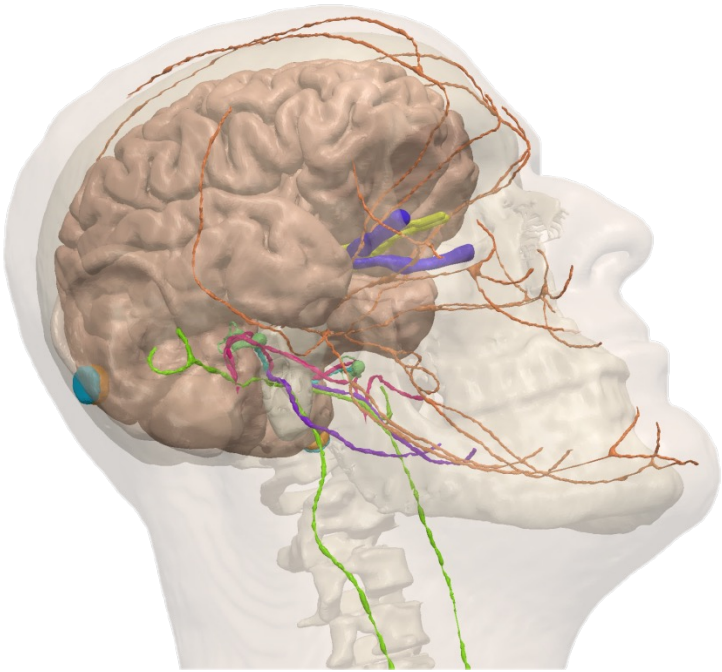
2 Modulation of brain cells (neurons) but current flow

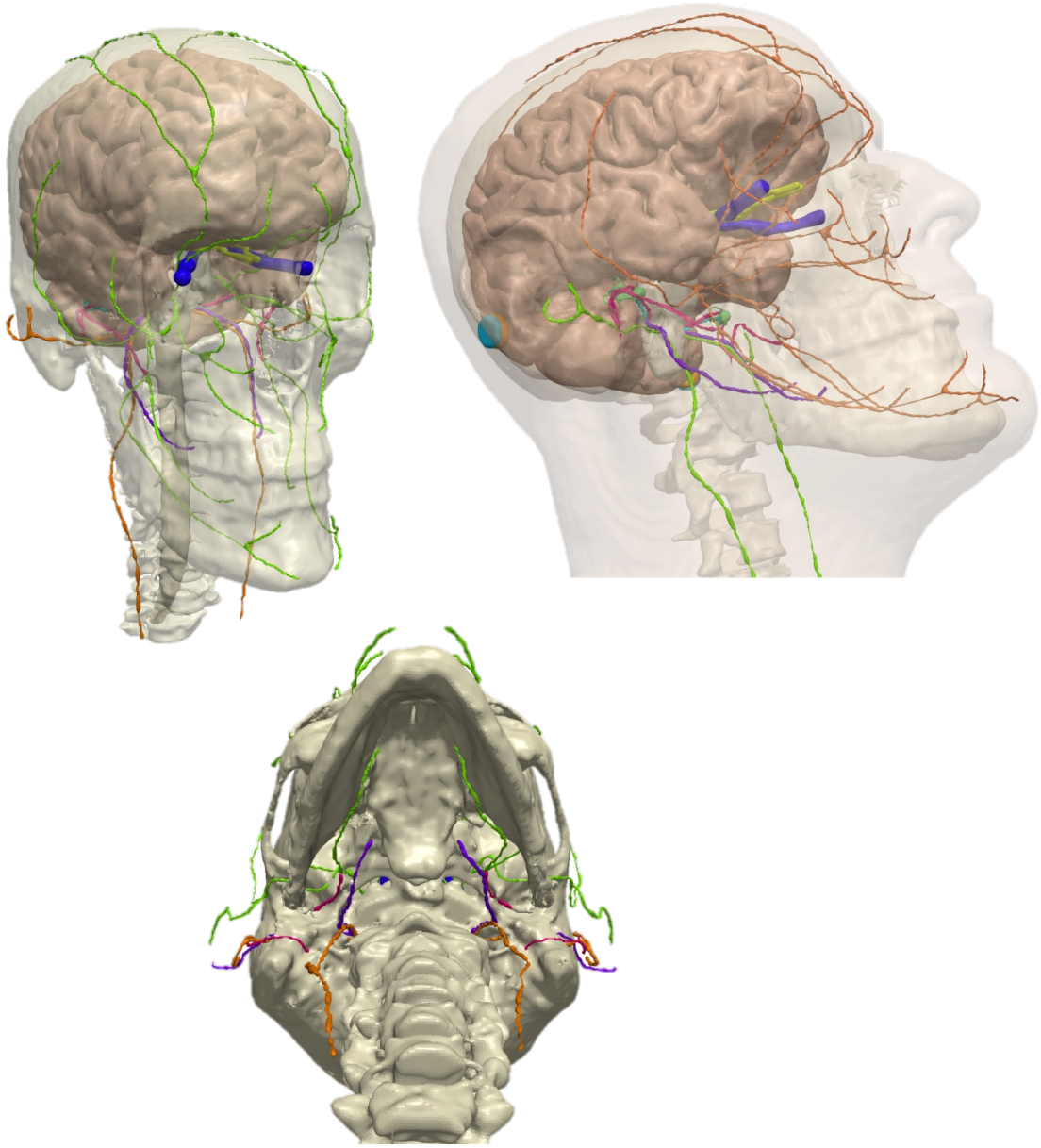
Brain Stimulation 13 (2020) 717–750

Electrical stimulation of cranial nerves in cognition and disease

Devin Adair [a], Dennis Truong [a], Zeinab Esmaeilpour [a], Nigel Gebodh [a], Helen Borges [a], Libby Ho [a], J. Douglas Bremner [b, c], Bashar W. Badran [d], Vitaly Napadow [e], Vincent P. Clark [f, g, h], Marom Bikson [a, **]

- The cranial nerves are the pathways through which environmental information (sensation) is directly communicated to the brain, leading to perception, and giving rise to higher cognition.
- Because cranial nerves modulate brain function, cranial nerve electrical stimulation has applications in the clinical, behavioral, and cognitive domains.
- Among other neuromodulation approaches, cranial nerve stimulation is unique in allowing axon pathway-specific engagement of brain circuits, including thalamocortical networks.
- Cranial nerve stimulation is not simply sensory substitution.





Fiber Type	Cranial Nerves	Function
Special somatic afferent (SSA)	**II** **VIII**	Vision Balance, hearing
Special visceral afferent (SVA)	**I** **VII, IX, X**	Smell Taste
General somatic afferent (GSA)	**V, VII, IX, X**	Proprioception (touch)
General visceral afferent (GVA)	**VII, IX, X**	Sensation from viscera
Special visceral efferent (SVE)	**V, VII, IX, X**	Motor control of the pharyngeal arches
General visceral efferent (GVE)	III, **VII, IX, X**	Autonomic motor and smooth muscles of the gut
General somatic efferent (GSE)	III, IV, VI XII	Motor control of eye muscles Motor control of the tongue