

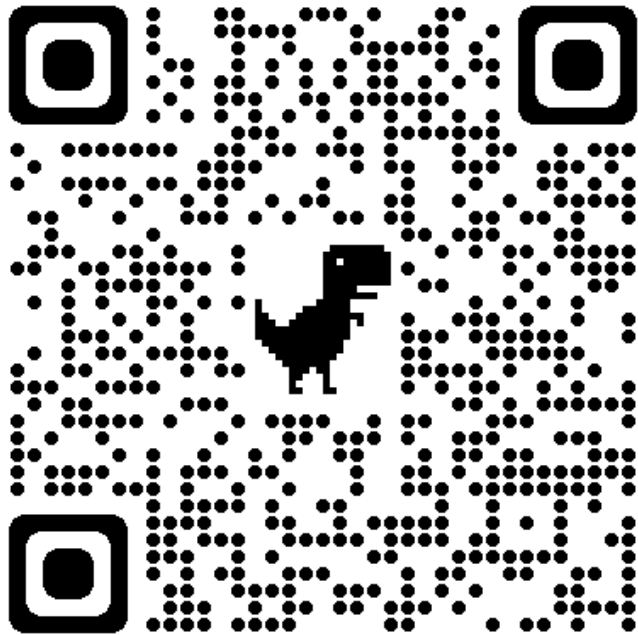
# Neuromodulation Design and Biomarkers

Dec 20, 2023 @Medtronic

Marom Bikson

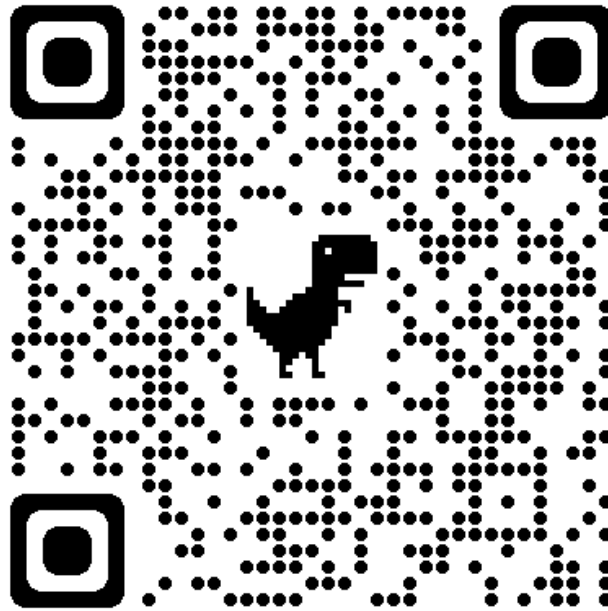
Talk based on monograph of neuromodulation biomarkers

[neuromodec.org/2023/09/neuromodulation-design-and-biomarkers](https://neuromodec.org/2023/09/neuromodulation-design-and-biomarkers)

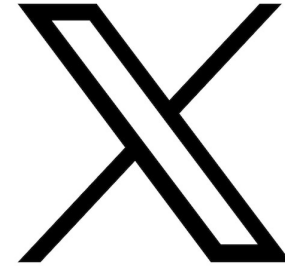


Recoded talk extending ideas to pain neuromodulation

<https://youtu.be/lzmKlnGNkss?si=vX06K9b6ZDjfJO9D>

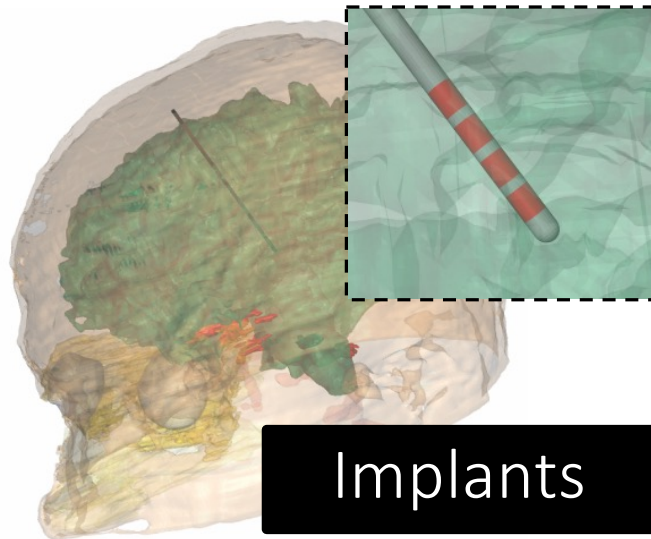


Slides (and these links)



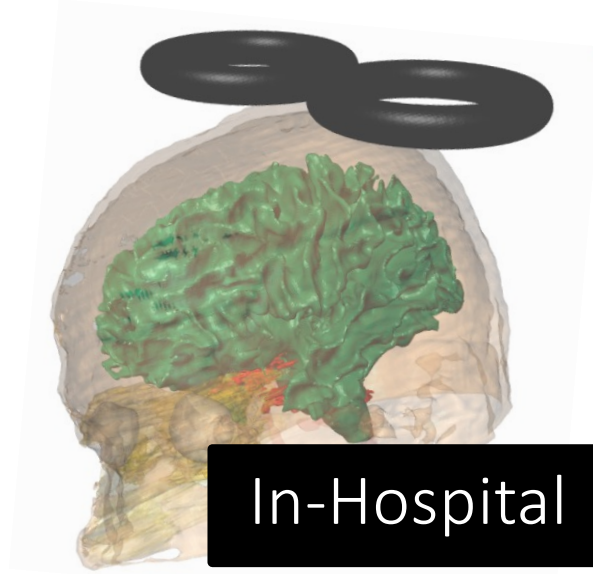
[@marombikson](https://twitter.com/marombikson)

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



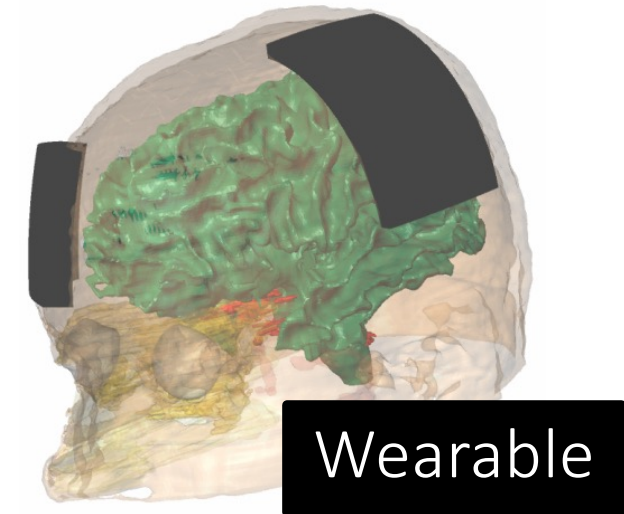
Deep Brain Stimulation (DBS)

Spinal Cord Stimulation (SCS)



Transcranial Magnetic Stimulation (TMS)

Electroconvulsive Therapy



Transcranial Electrical Stimulation (tES)

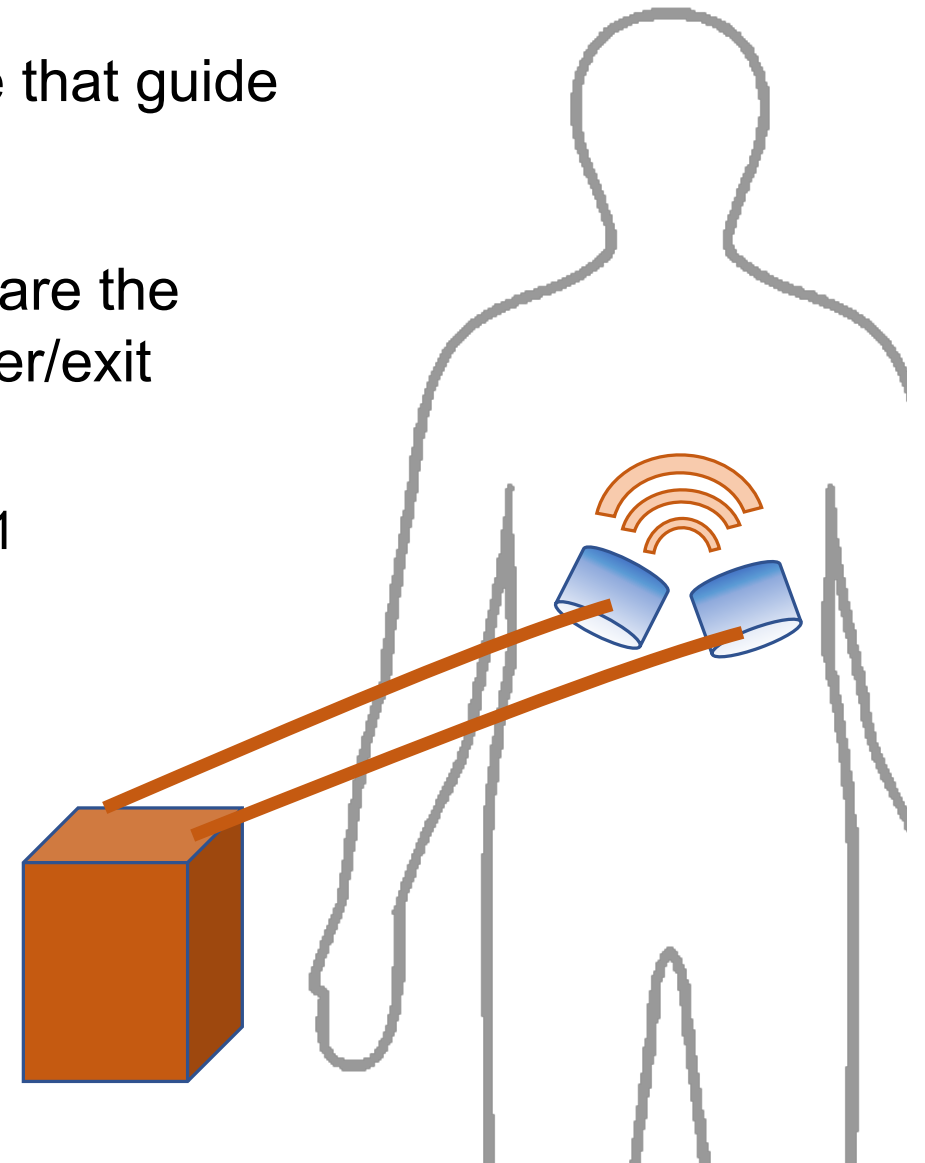
Transcranial Direct Current Stimulation (tDCS)

# 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.
- 2) Example: 1 cm<sup>2</sup> 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

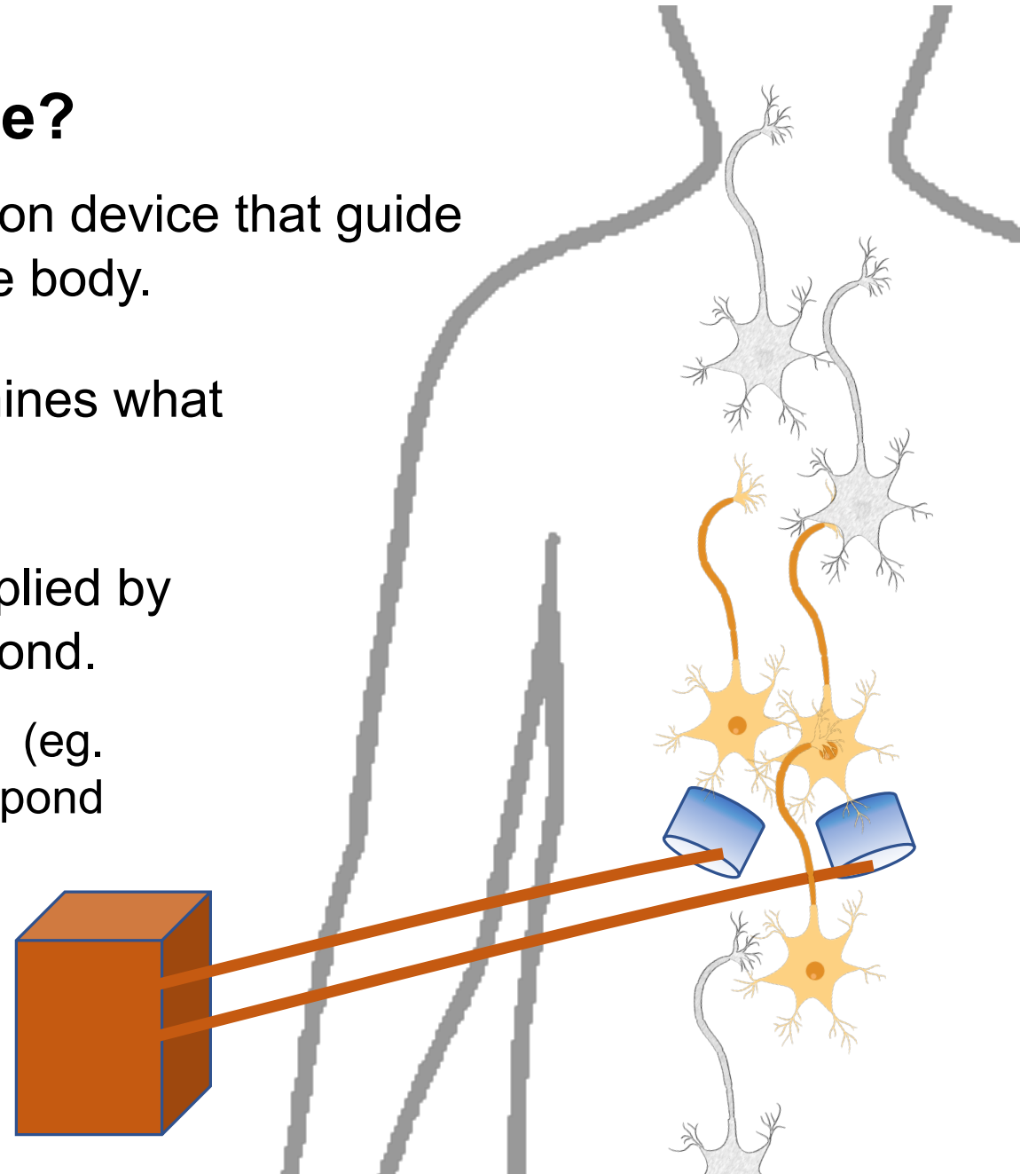


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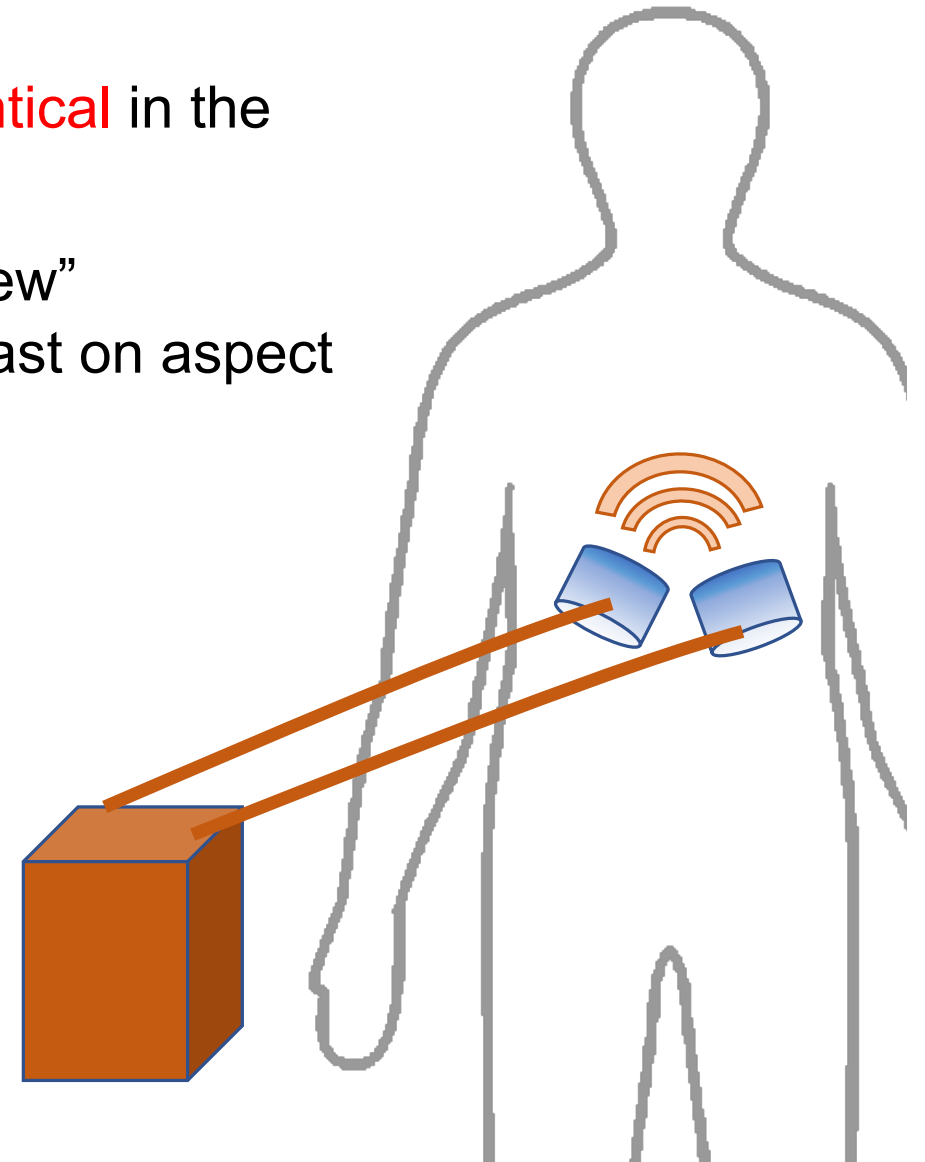
- 1) The position of the electrodes determines what parts /neurons are stimulated.
- 2) The intensity and timing of pulses applied by the device determines how neurons respond.

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

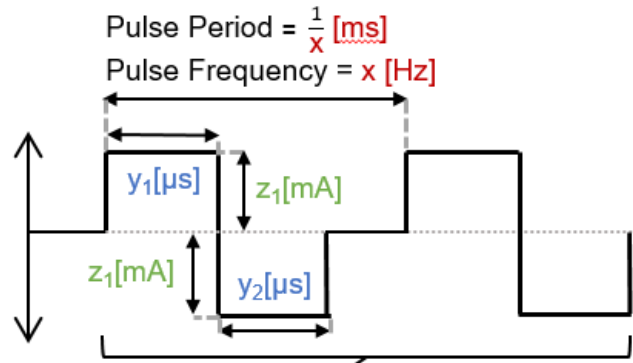


# What is Neuromodulation Dose?

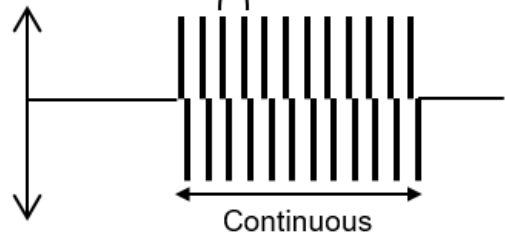
- Two devices that apply the **same dose are identical** in the effects they produce on the body
- Conversely, regarding effects on the body a “new” neuromodulation device should change on at least on aspect of dose.
- Device **features of than those governing dose matter** (e.g., battery life, MRI conditional...) 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.



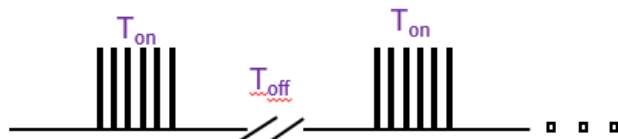
## Pulse Shape and Train



## Burst Patterns



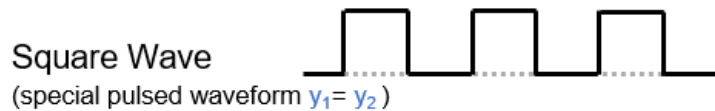
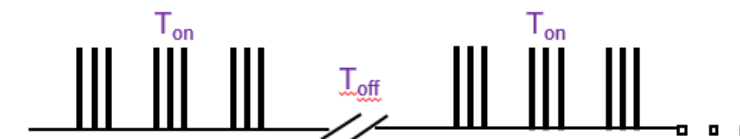
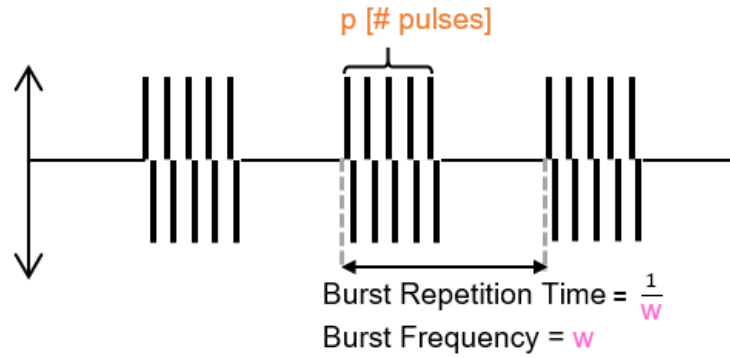
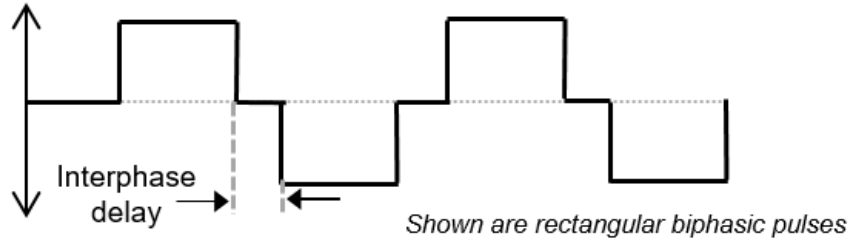
## On/Off (optional)



## Other Waveforms



## Waveform Option\*



Most talk on neuromodulation (how it works) focus on waveform. I will not discuss waveform directly.

\*Each device allows selection of specific waveform sets

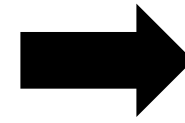
Each device provides dose options (electrode position, waveform)



Operator must try **one** dose option at a time



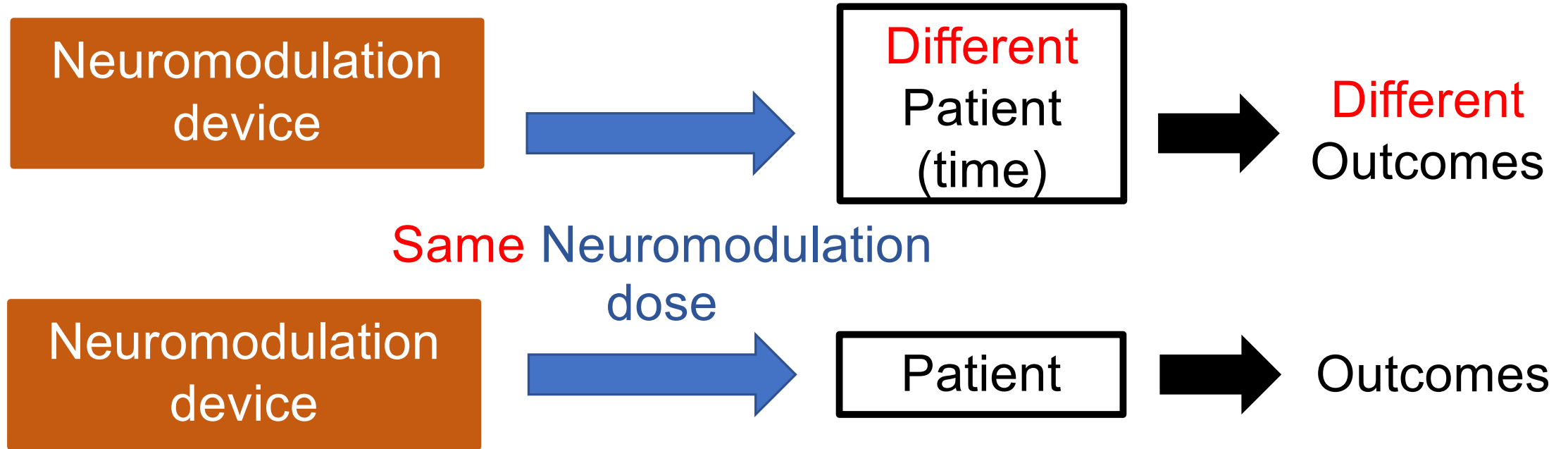
Neuromodulation dose



Outcomes

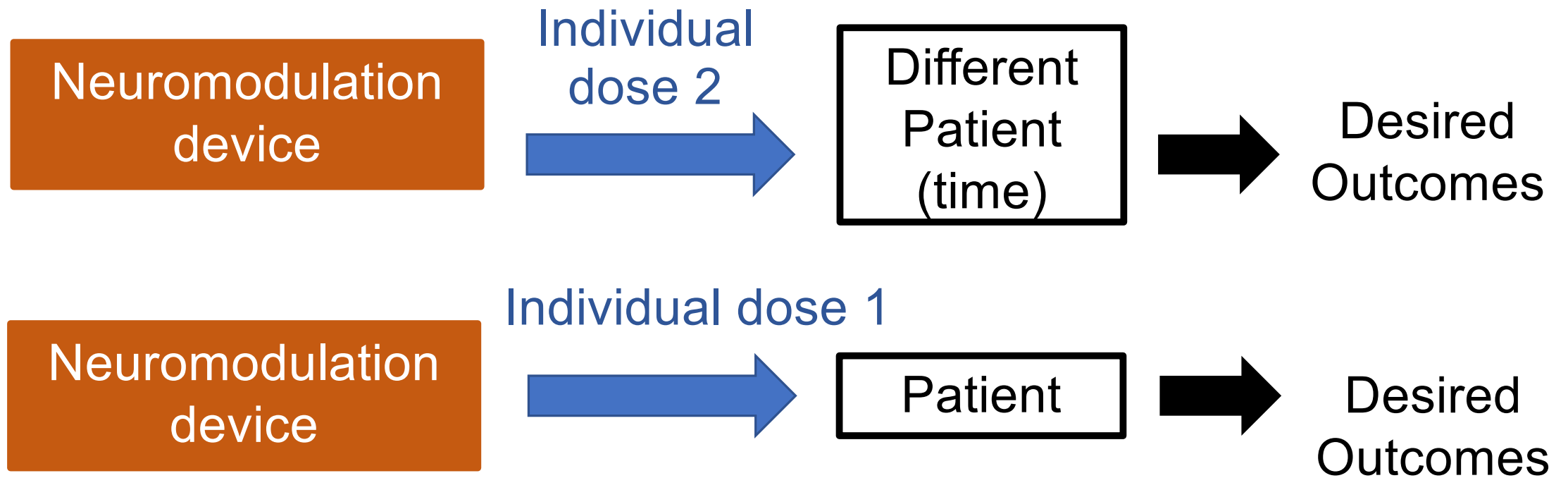
Dose instructions indicate how to adjust dose for each indication / patient





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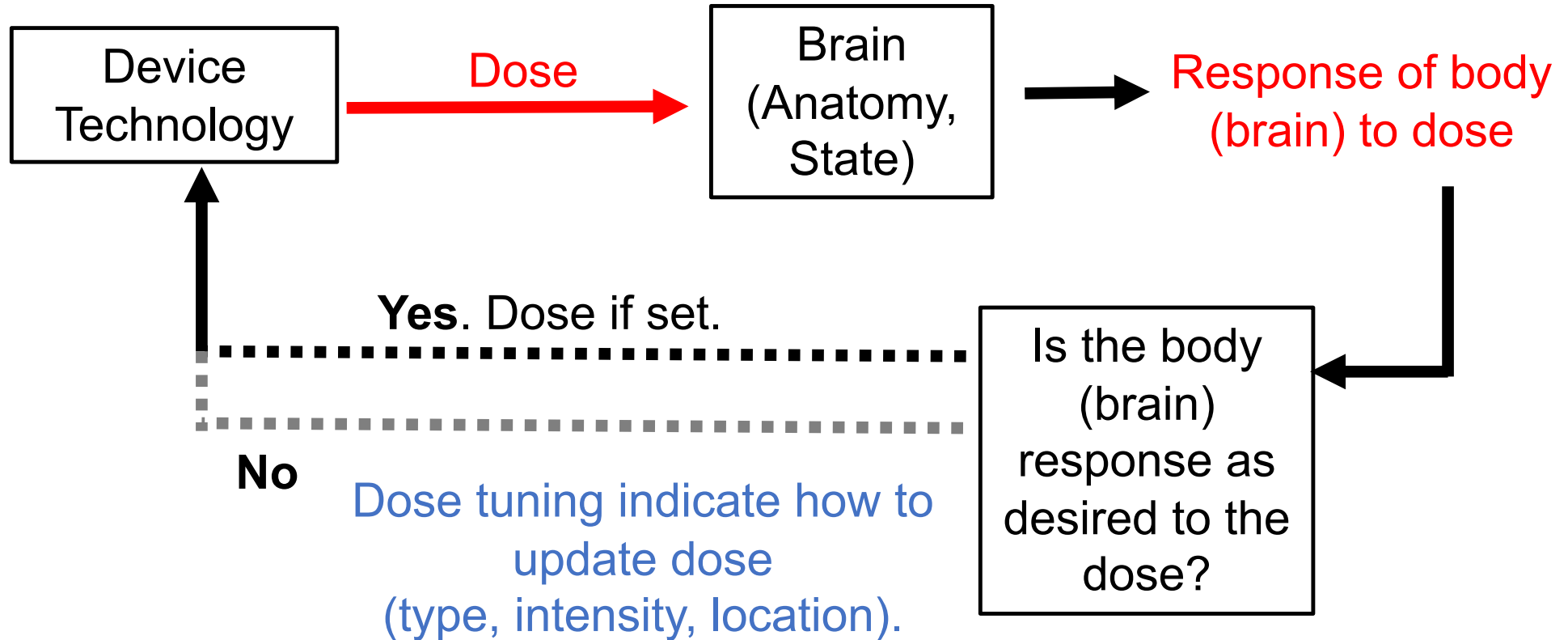
Why? Because different anatomy and different physiology means same dose produces different outcomes.



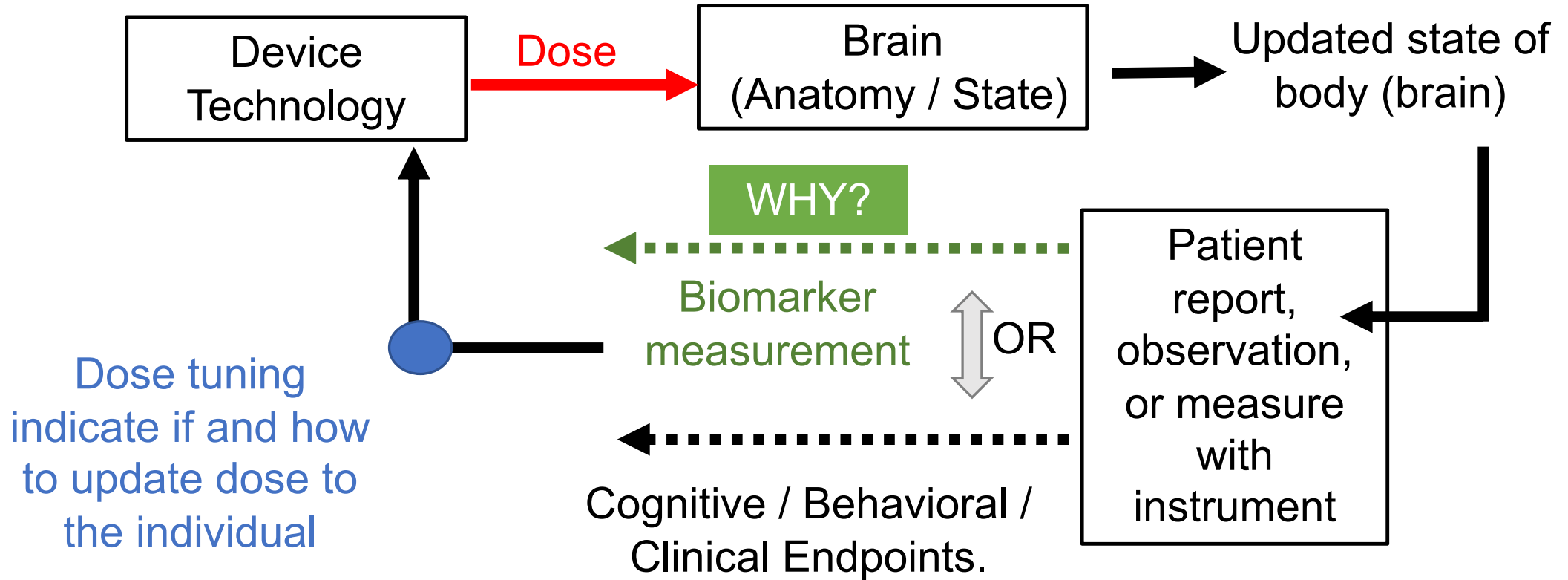
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This is the key problem / opportunity in  
neuromodulation : This is **Neuromodulation Design**

## Reducing variability by individualized neuromodulation dose

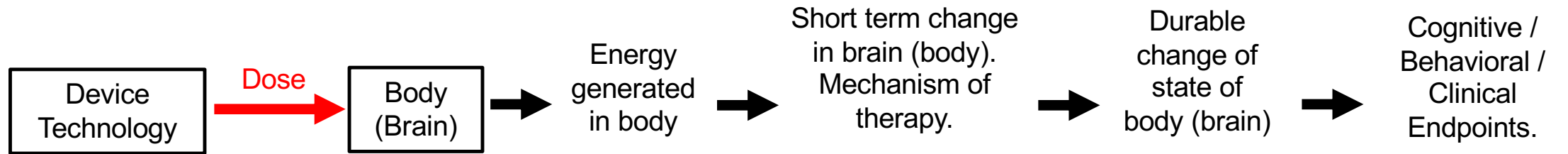


## Reducing variability by individualized neuromodulation dose

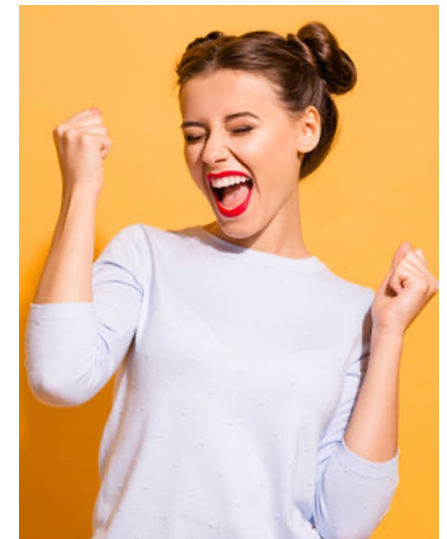
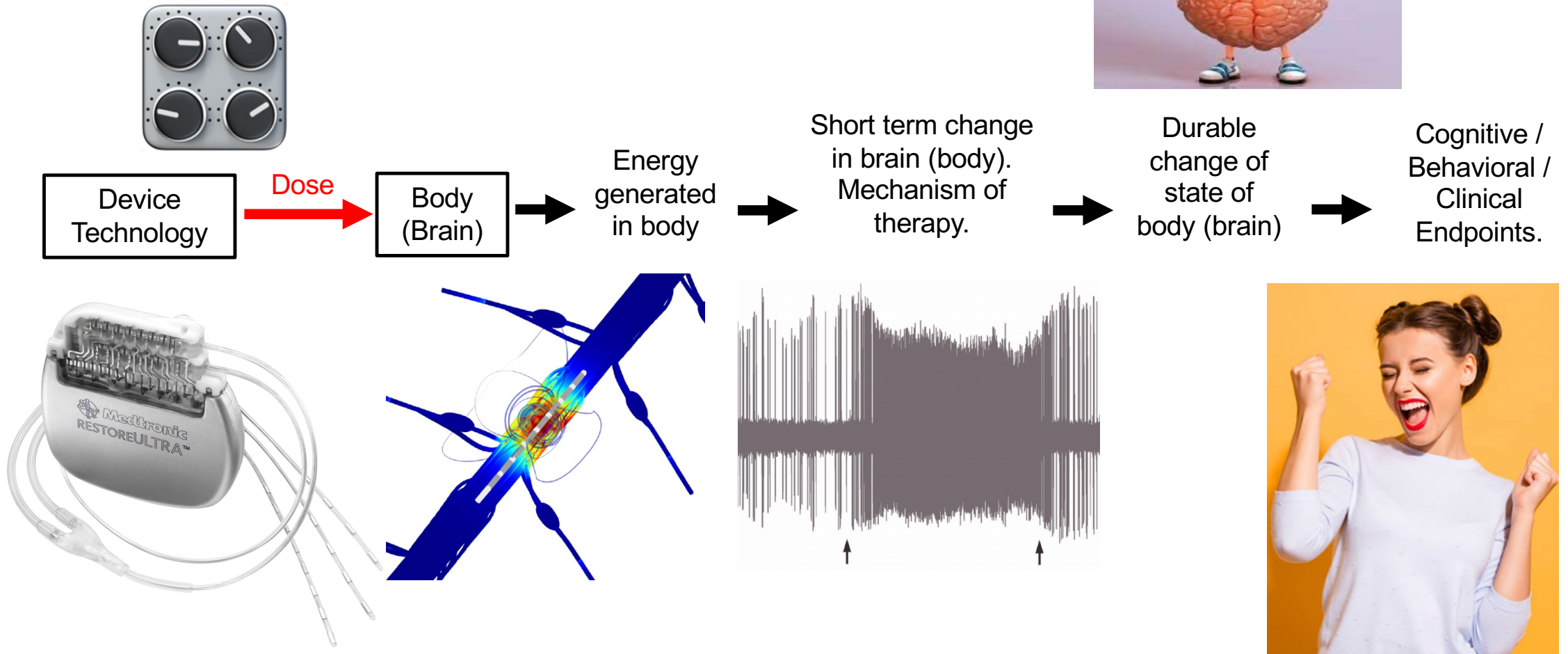


Understanding HOW biomarkers are used (in loops) helps explain WHY biomarkers reduce variability.

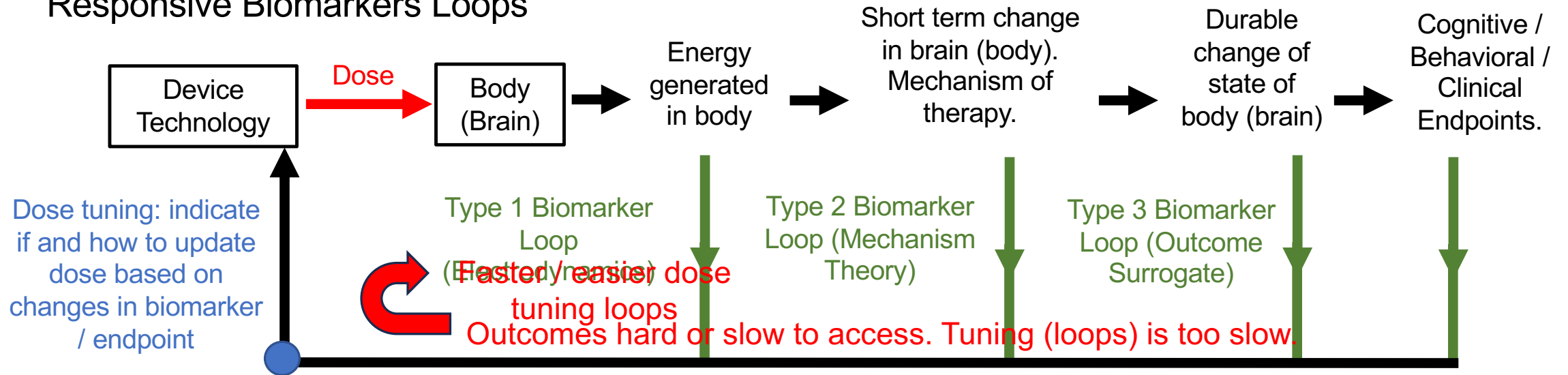
# This is how neuromodulation works.



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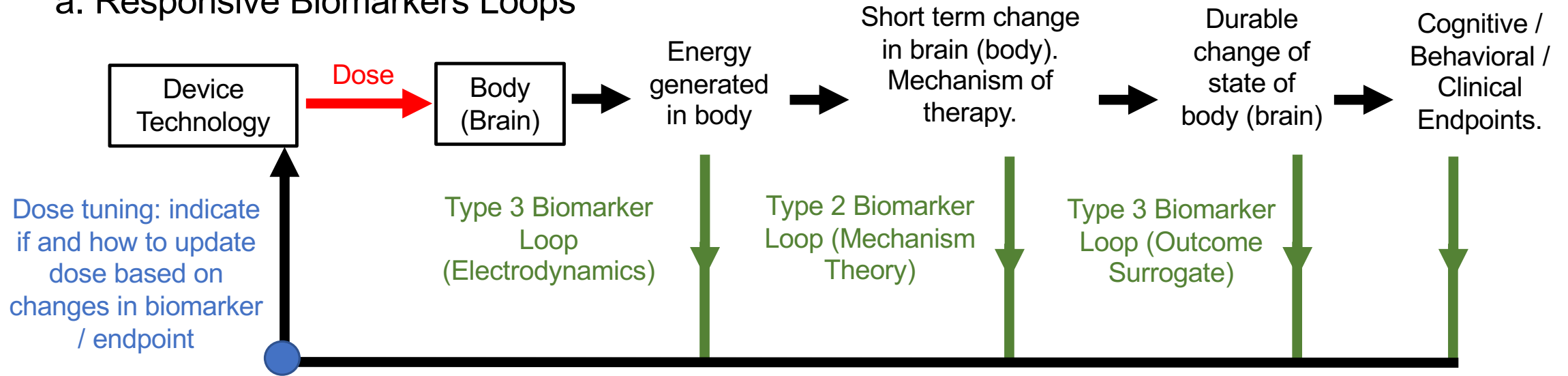


# Responsive Biomarkers Loops

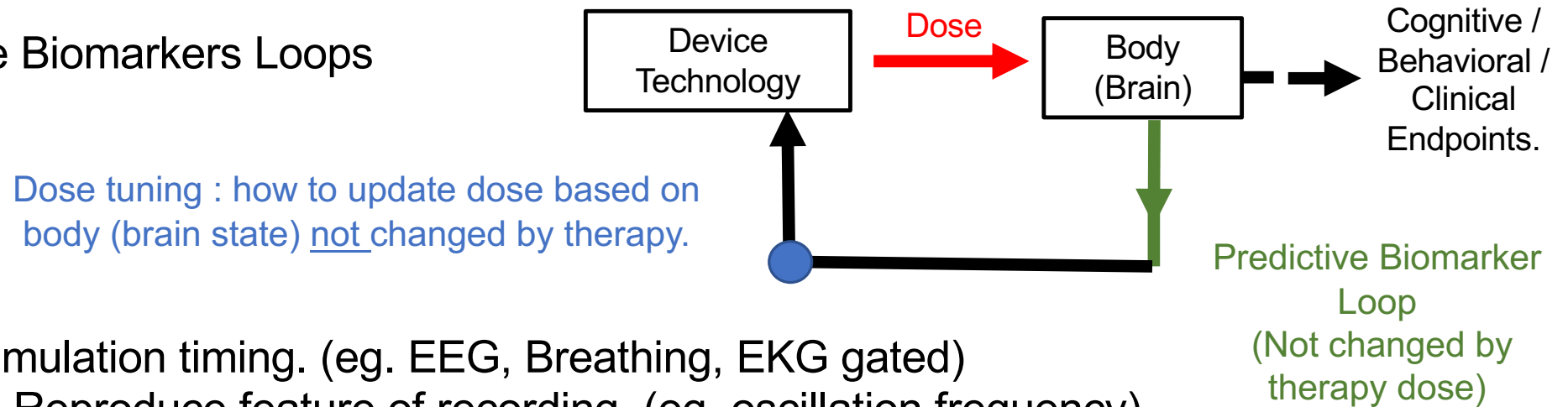


- **Type 2 Responsive Biomarker Loop** (Mechanism of Action). Transient (short term only) response to dose necessarily indicating a dose that also changes primary outcomes.
- **Type 3 Responsive Biomarker Loop** (Outcome Surrogate). Durable response to dose necessarily also tracking changes primary outcomes.
  - Increasing TENS intensity until paresthesia to treat pain (gate control theory of pain)
  - Adjusting position until muscle twitch for neurorehabilitation
  - Tuning frequency until oscillations enhanced to boost cognition
- **Type 1 Responsive Biomarker Loop** (Outcome Surrogate). Instant change in energy necessarily indicating a dose that also changes primary outcomes.
  - Changes short lived (acute). Biomarker can be objective or subjective.
  - Mechanisms is only a theory.

## a. Responsive Biomarkers Loops



## b. Predictive Biomarkers Loops

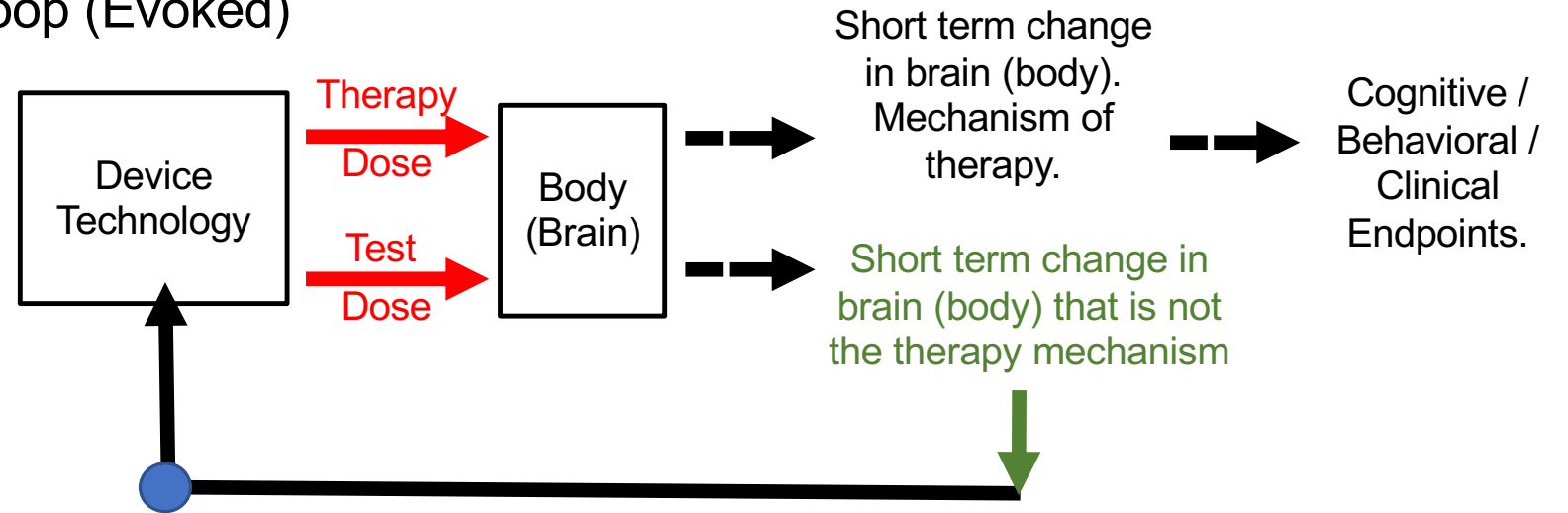


- **Gated:** Stimulation timing. (eg. EEG, Breathing, EKG gated)
- **Playback:** Reproduce feature of recording. (eg. oscillation frequency)



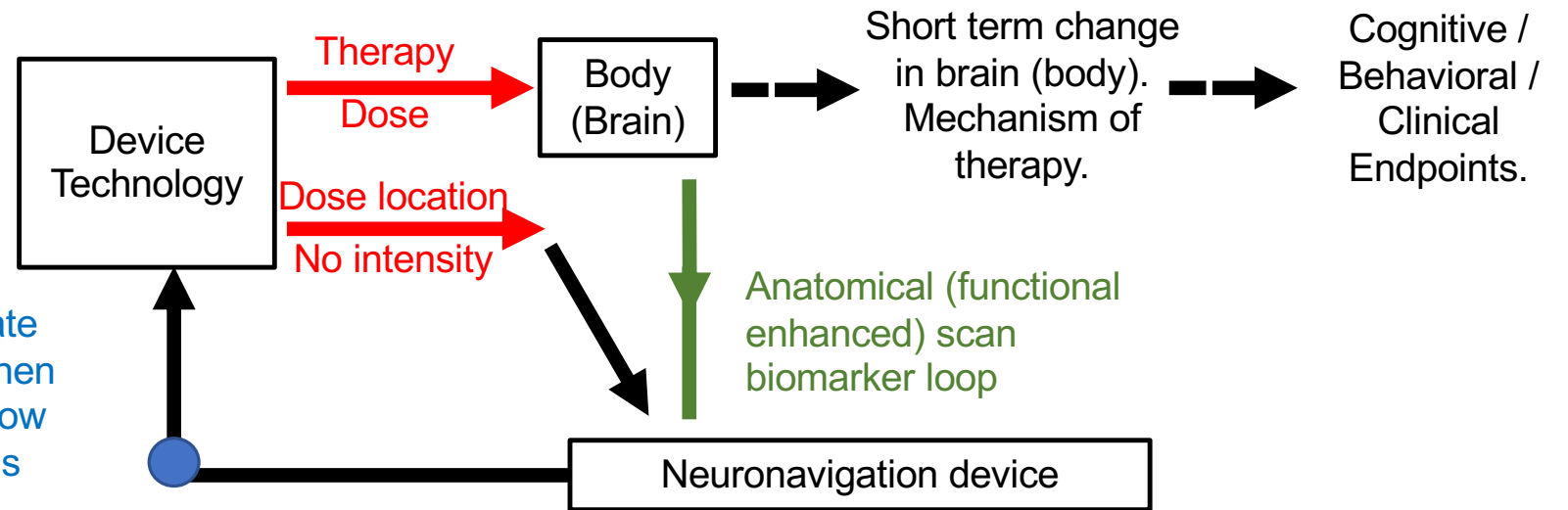
### c Predictive Biomarkers Loop (Evoked)

Dose tuning indicate: update test dose based in the evoked predictive biomarker loop **and** when to exit biomarker-test loop and how to set the therapy dose based on the test dose.



### d Predictive Biomarkers Loop (Neuronavigation)

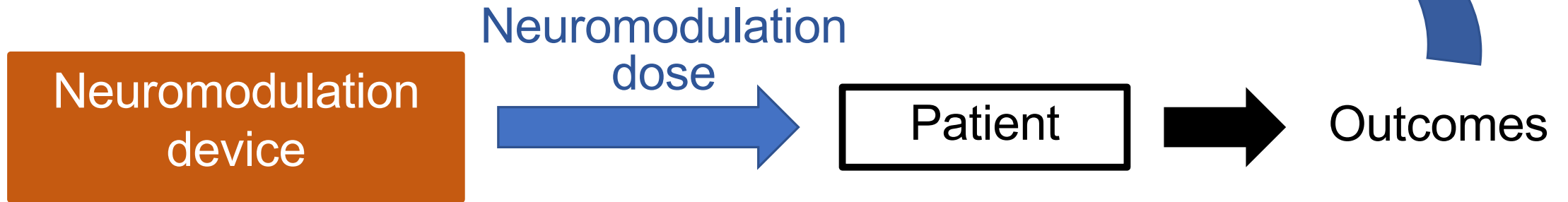
Dose tuning indicate how to update device position relative to body, when to exit device position loop, and how to set therapy dose based on this location.



## OK to be uncertain among Response Biomarkers. Example: Measurement of beta oscillations during DBS for depression

- Beta oscillations mark disease severity (independent of DBS). Any intervention that chronically changes oscillations will improve depression symptoms. **Responsive Biomarker Type 1 (clinical surrogate)**
- Beta oscillations respond acutely to well-tuned DBS, but recover to baseline when stimulation is turned off. Mood does not improve acutely (does not correlate with change in oscillations) but gradually improves— even after stimulation is turned off. **Responsive Biomarker of Type 2 (mechanisms)**
- Beta oscillation respond to specific DBS doses. Dose titration first identifies an optimal electrode to modulate beta oscillations with high intensity ~~and then decreases intensity to a level where beta oscillations are no longer modulated.~~ **Predictive Biomarker : Evoked** **Responsive?**
- Stimulation applied at individual beta frequency irrespective of if oscillations change. **Predictive Biomarker : Playback.** **Measured oscillations do change: Responsive?**
- A computational model based on baseline individual anatomy / physiology. **Depends on biomarker**
- Presence of abnormal beta oscillation predict response to DBS. Improvement in symptoms associated with normalization of beta oscillations. **Responsive Biomarker Type 1**

The treatment is a success. What was tested:  
The ~~Theory~~ or **Device+Dose Instructions**?



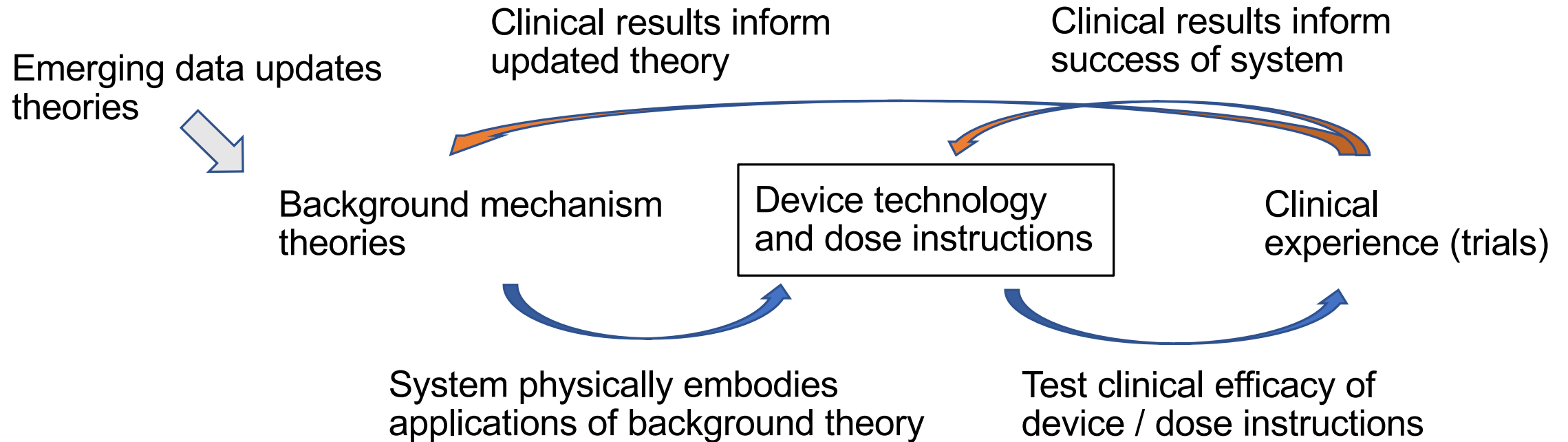
Dose instructions indicate how to adjust dose  
for each indication / patient

Theory (how neuromodulation works) inspires the  
device and dose instructions

## Problems propagate back



Therapeutic success does not prove a mechanism is correct. Limits in therapy success indicate updates in mechanism theory warranted.

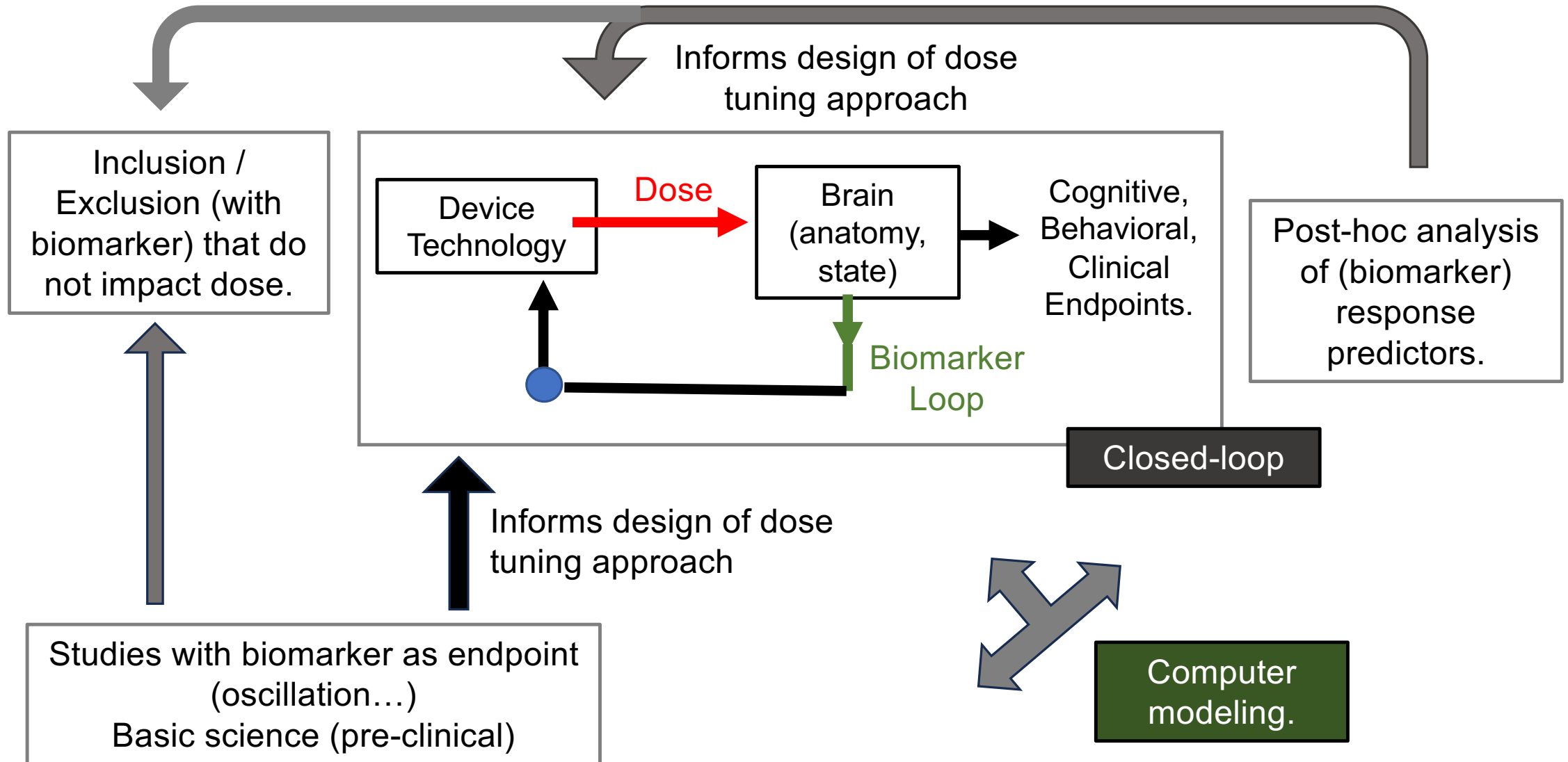


An updated mechanism theory does not impact a given device technology / dose instructions efficacy. But informs invention of new systems.



Solutions propagate forward

Dose is tuned based on biomarker but for cognitive / behavioral / clinical outcome.



## Dose Tuning using Biomarkers: Classification of Dose Titration Loops

1. Dose is device parameters that impact the generation of (electric field) in the body.
2. Outcomes depend on individual anatomy and (time dependent) brain state. **For any given dose, outcomes are variable.**
3. Dose can be tuned to individuals to reduce variability by measuring biomarkers and adjusting dose (in a loop) .

**All dose tuning techniques (to reduce variability) can be classification by loop scheme. [consistent and complete system]**

Responsive Biomarkers: Type 1 (electrodynamic), Type 2 (theory of mechanism), Type 3 (outcome surrogate). Distinguished by time-course.

Predictive Biomarkers: Do not response to therapy dose (as far as dose tuning). Types: Gated, Playback, Evoked, Neuronavigation.

- Closed-loop / Modeling: No change in scheme.
- Inclusion/Exclusion and Biomarkers not used in dose tuning : outside but support scheme.
- Biomarkers in dose tuning are means to and end. Accelerate dose tuning. Studies on controlling biomarkers (TMS-MEPs) are outside but support this scheme.

