Nerve Excitation Control Through AC Regulation

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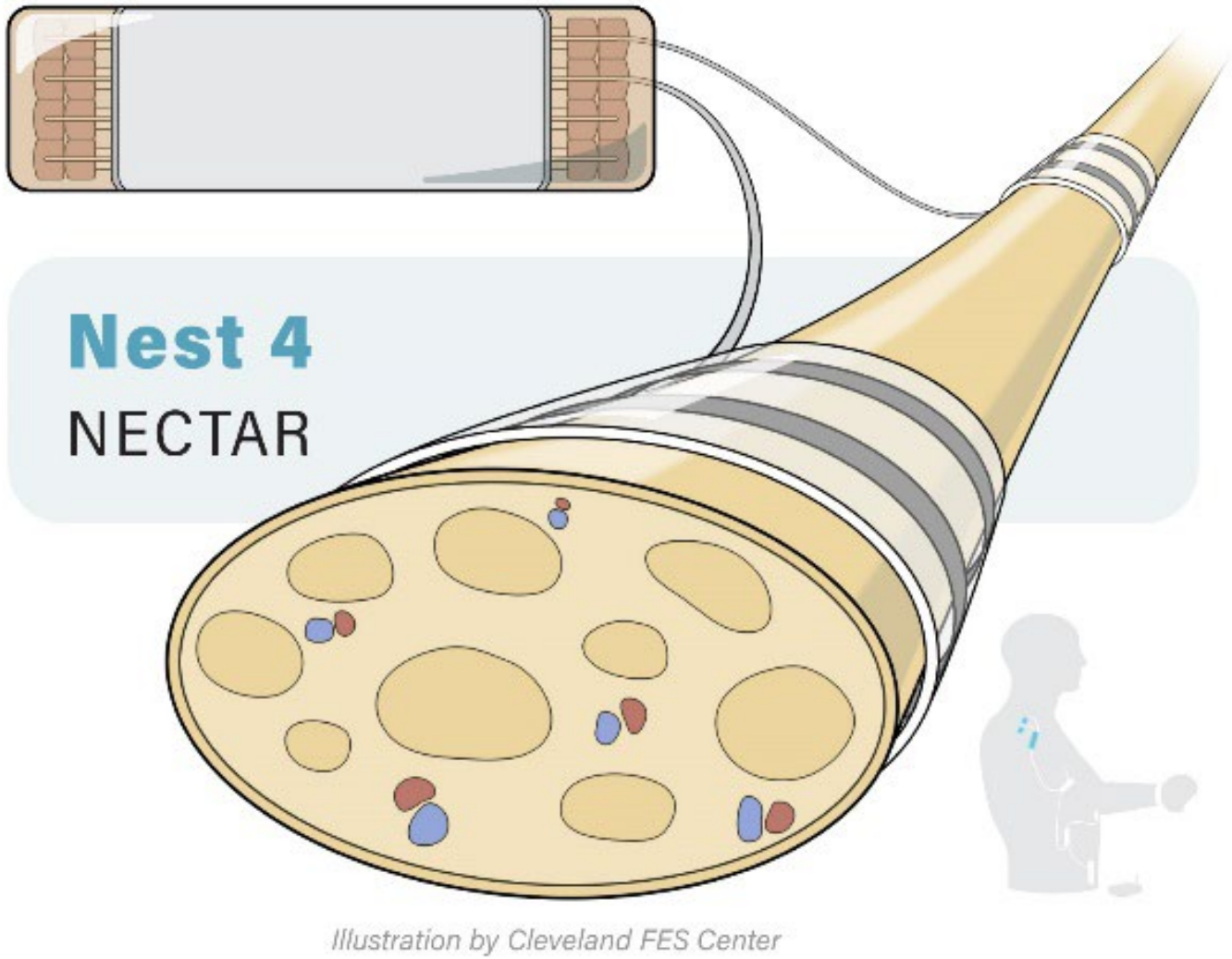
“NECTAR” – Electrical Nerve Block Module



- Aim 1) Develop an open source NECTAR module capable of both upregulation (stimulation) and downregulation (block) for complete closed-loop control
- Aim 2) Fully characterize the therapeutic window of the NECTAR System and provide the complete procedures and data under an open source license.

“NECTAR” – Electrical Nerve Block Module

- **Features:**
  - **Functionality:** Frequencies to apply both stimulation and block to both **upregulate** and **downregulate** the nervous system
  - **Full waveform adjustment:** The waveform can be adjusted in both amplitude and frequency
  - Voltage and current control will both be supported
  - Electrode evaluation capability
- **Performance Considerations:**
  - Ensure amplitude accuracy across all frequencies and realistic load conditions
  - Charge balanced output
  - DC mitigation

NECTAR Module Specifications

	Range	Resolution
Frequency - KHFAC	1KHz - 20KHz	1KHz
Frequency - Stimulation	1-20Hz	1Hz
Amplitude - KHFAC	0-30Vpp	0.1Vpp
Amplitude - Stimulation	0-20mA	0.1mA
KHFAC vs Stimulation	Selectable	
KHFAC Freq Modulation	0-10KHz/sec	
KHFAC Amp Modulation	0-5mA/sec	
KHFAC Charge Balance	<1uA	

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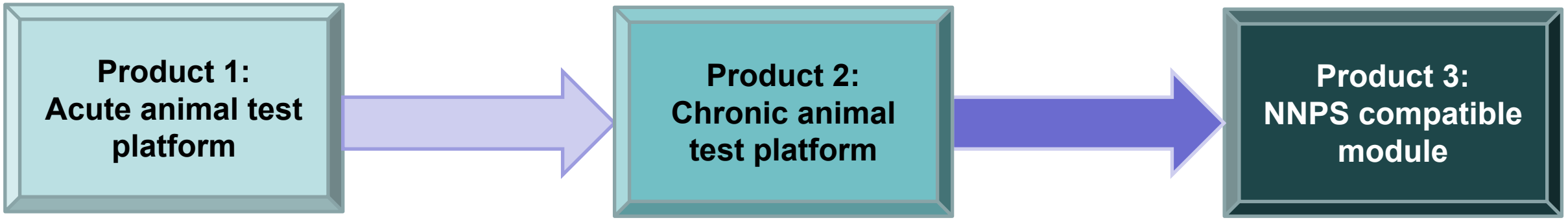
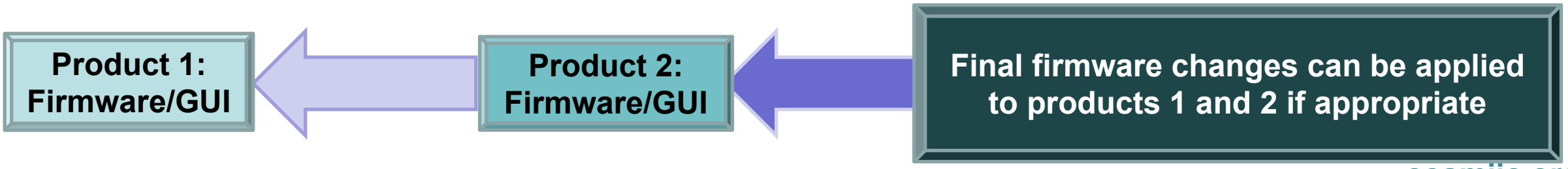
- **Development Strategy**



- **Benchtop form**
- Full frequency and amplitude range
- CIC measurements
- Tethered possibly
- Basic GUI for control
- Preliminary quality testing

- **Chronic small animal form**
- Standalone run mode
- Enhanced firmware for wireless communication
- Preliminary quality testing

- **NNPS form factor**
- CAN interface
- Complete waveform control
- Finalize CIC algorithm
- Formal verification



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- **KHFAC Block Features:**
  - **Frequency/Amplitude range:** As the frequency of KHFAC increases, the block threshold increases but the onset decreases . It is the intent of this device to provide a range of values that allows the use to determine the appropriate compromise for their application.
  - **Square waveform-continuous:** Electrical nerve block using alternating waveforms has been demonstrated in the 10-30 KHz range using several different types of waveforms. Square wave waveforms have the lowest block thresholds. Onset response is larger for lower frequencies, but is unaffected by waveform shape. Therefore, the waveform shape will be constrained to square waveforms.
  - **Current and Voltage Control:** Initial KHFAC experiments used voltage control mode which is easier to implement from a DC mitigation perspective. However, current control limits the amount of charge delivered which is safer for the tissue. Both will be provided to accommodate a range of experimental needs

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- **Module Output Specifications:**
  - The NECTAR device shall provide four independent bipolar channels

- **KHFAC Block Specifications:**
  - The KHFAC device shall provide continuous square waveforms
  - The KHFAC device shall provide current as well as voltage control
  - The KHFAC device shall provide frequencies 10KHz-30KHz in 100 Hz increments
  - The KHFAC device **may** provide frequencies up to 40KHz in 100 Hz increments
  - The KHFAC device shall provide amplitudes up to 20 mApp in 0.1 mA increments
  - The KHFAC device **may** provide amplitudes up to 30 mApp in 0.1 mA increments
  - The KHFAC device shall provide amplitudes up to 20 Vpp in 0.1 V increments
  - The KHFAC device **may** provide amplitudes up to 30 Vpp in 0.1 V increments

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- **Stimulation Features:**
  - **Frequency/Amplitude range:** The ability to use electrical waveforms to both upregulate and downregulate the nervous system creates the possibility of developing closed loop control strategies that can accurately control a measured physiological parameter to mitigate a disease state.
  - **Square waveform-discontinuous:** At lower frequencies that are typically used for stimulation, a continuous waveform would cause the waveform to exceed the safe charge/cycle limit. A discontinuous waveform will be used for these lower frequencies.
  - **Charge limited waveform :** To prevent the device from operating the electrode outside the water window, the user will be able to specify a maximum charge/cycle. This value would typically be determined from the CIC testing but could be adjusted by the user to test electrode limits in vitro or in pre-clinical testing

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- **Stimulation Specifications:**
  - The Stimulation device shall provide discontinuous square waveforms
  - The Stimulation device shall provide frequencies 1Hz-40Hz in 0.1 Hz increments
  - The Stimulation device **may** provide frequencies up to 1 KHz in 0.1Hz increments
  - The Stimulation device shall provide amplitudes up to 20 mApp in 0.1 mA increments
  - The Stimulation device **may** provide amplitudes up to 30 mApp in 0.1 mA increments
  - The Stimulation device shall provide amplitudes up to 20 V in 0.1 V increments
  - The Stimulation device **may** provide amplitudes up to 30 V in 0.1 V increments
  - The Stimulation device shall provide pulse widths 20usec-2 msec in 1 usec increments

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- **Performance Considerations:**
  - **Amplitude accuracy at all frequencies:** Most standard benchtop laboratory stimulators cannot achieve 5kHz or higher, and most commercial stimulators that claim specifications of 5kHz or higher do not achieve their rated frequencies without significant attenuation and distortion. These issues are critical for successful KHFAC block. Therefore, the output of the NECTAR module will be validated across multiple loading conditions and reported as a peak to peak value.
  - **True charge balancing/DC removal:** For KHFAC, the charge imbalance between the cathodic and anodic phases can result in Net DC current, which is defined as the average DC current that occurs over the course of many pulse cycles. Depending on the electrode material, surface area, and target nerve tissue, acceptable levels can be 10-100 nA.

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- **Performance Specifications:**
  - The device shall be tested to ISO 14708-3 standards for DC leakage
  - The device shall provide charge balancing to 0.1 uC
  - The device **may** provide DC removal to 0.01 uC
  - The device shall provide amplitude accuracy to 0.05 mA
  - The device shall provide amplitude accuracy to 0.05 V
  - The device **may** provide amplitude accuracy to 0.01 mA
  - The device **may** provide amplitude accuracy to 0.01 V

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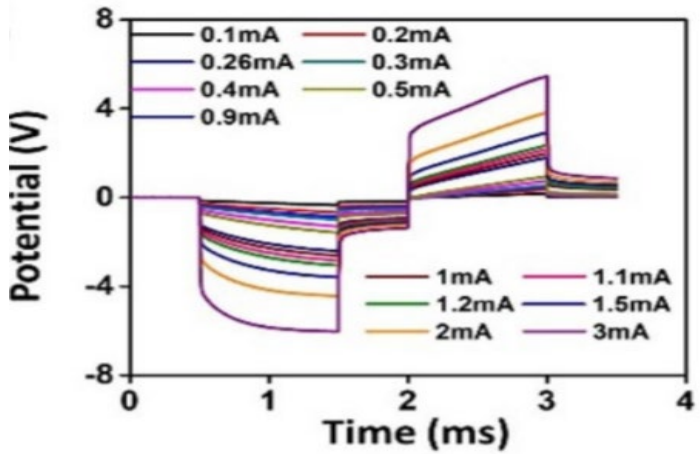
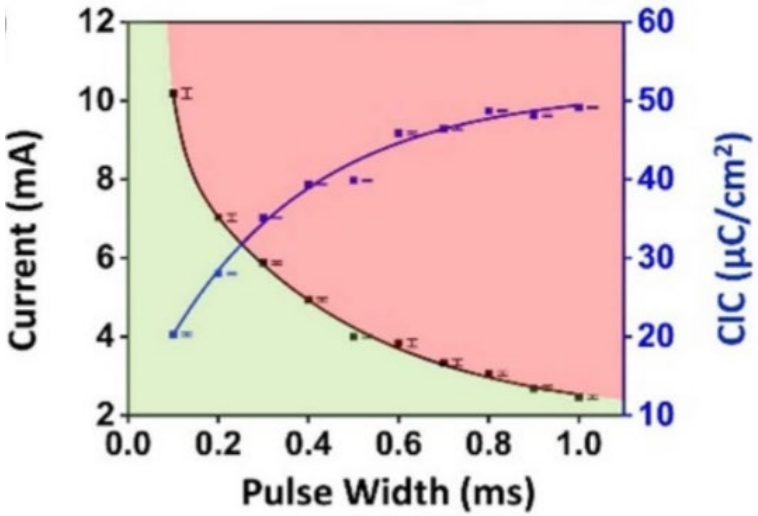
- **Electrode Evaluation Considerations:**
  - Use charge injection capacity (CIC) to determine charge delivery limits
  - Calibration table will be available for operational limit testing
  - Charge limit will be incorporated into the module to limit unsafe pulse widths regardless of frequency
  - Adaptable to different electrode chemistries
  - User would have the ability to develop new algorithms





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- **Electrode Evaluation Specifications:**
  - The device shall be able to measure the voltage of a stimulus pulse at a resolution of 0.05 mV
  - The device **may** be able to measure the voltage of a stimulus pulse at a resolution of 0.01 mV
  - The device shall provide an algorithm to determine the safe range for an electrode in terms of charge: **under development.**
  - The device shall provide the calibration curves to the user for evaluation
  - The device shall provide internal storage for calibration curves.

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- **Programmability Specifications:**
  - The device shall provide amplitude ramping at 1 mA/S
  - The device **may** provide amplitude ramping at 0.1 mA/S
  - The device shall provide amplitude ramping at 1 V/S
  - The device **may** provide amplitude ramping at 0.1 V/S

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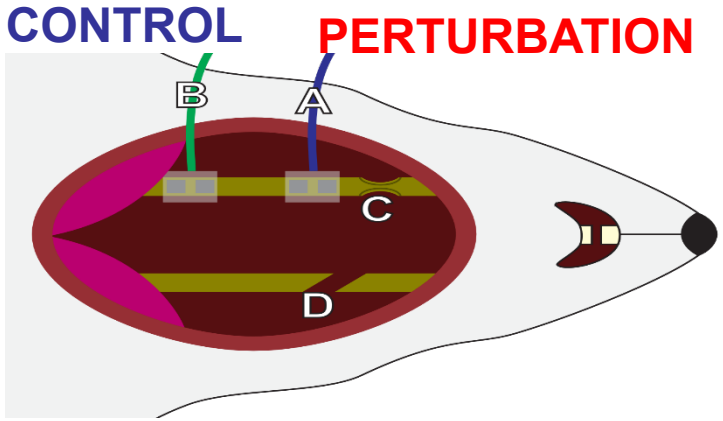
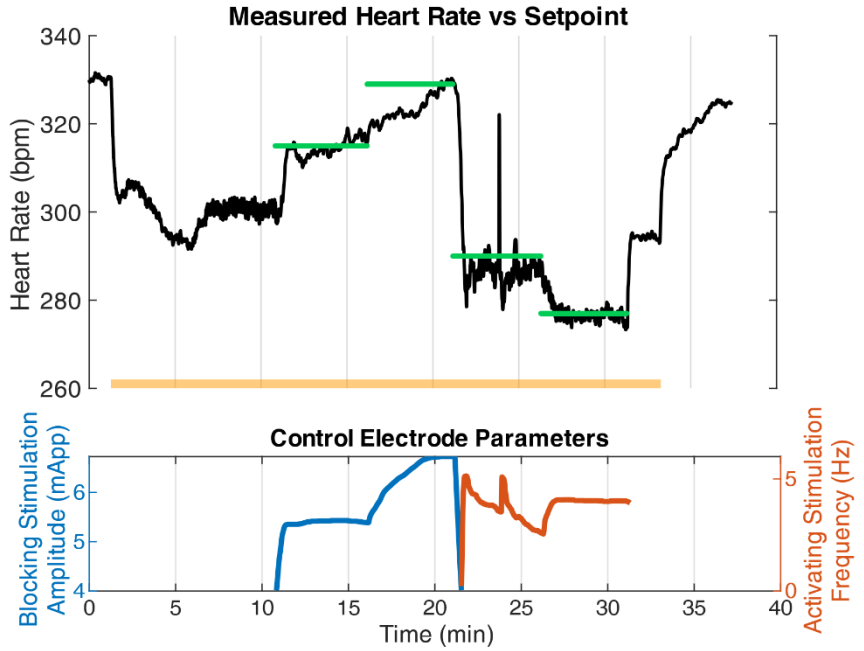
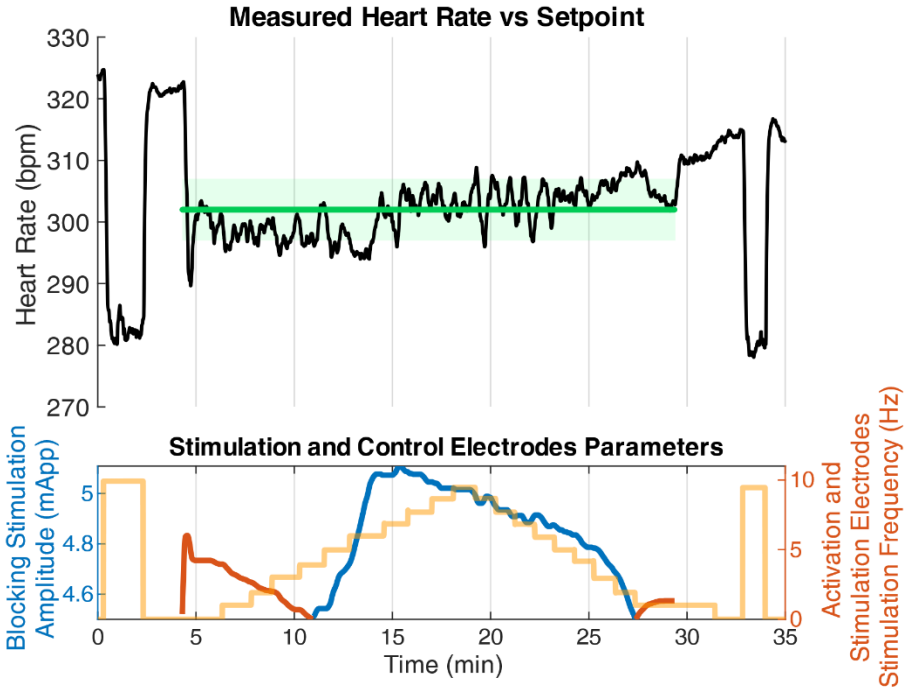
- **Closed Loop Control Example**
  - Bi-modal Neuromodulation
    - **KHFAC amplitude control**
    - **Stimulation frequency control**



Variable Setpoint /Constant Perturbation



Constant Setpoint /Variable Perturbation



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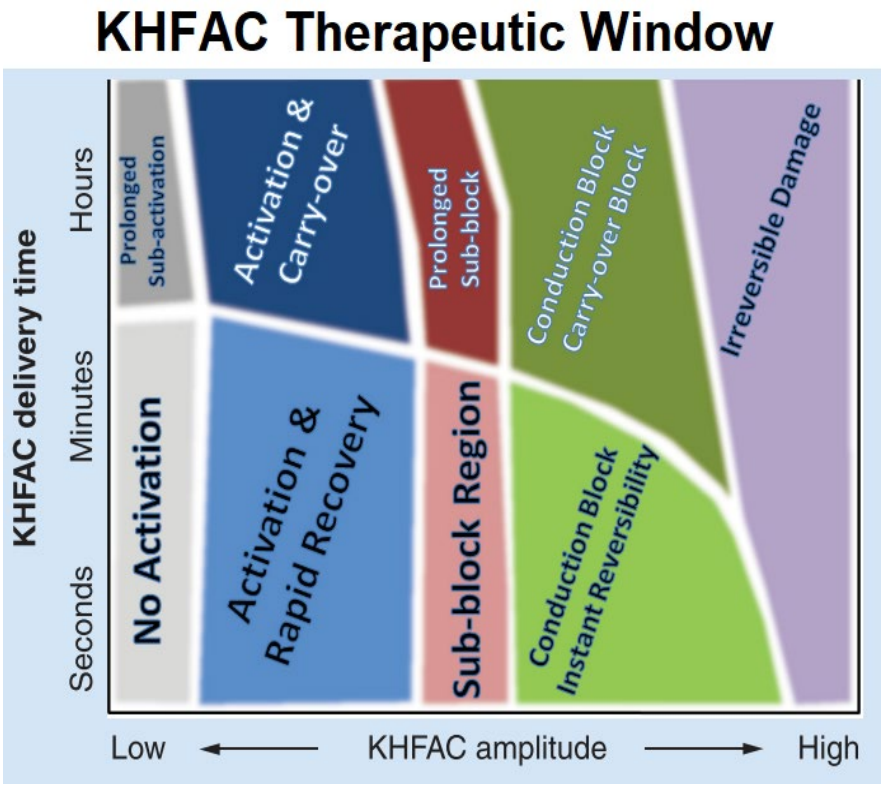
- **KHFAC Therapeutic Window Considerations**
  - **Therapeutic effect of KHFAC is complex and multi-modal**
  - Perform chronic in vivo studies to provide data that establishes the therapeutic window for KHFAC block
  - Evaluate frequency, amplitude, charge delivery, and duty cycle.
  - Include both functional and histological metrics for safety and efficacy
  - FDA engagement to ensure that the results are acceptable as background data for any future IDE submissions using the NECTAR System.



Therapeutic Region	Timeframe	Application
Instant Reversibility	<= 2 seconds	Closed loop control, spasticity
Rapid Reversibility	< 5 minutes	Closed loop control, autonomic
Delayed Reversibility	Within 24 hours	Pain relief
Reversible Damage	More than 24 hours	Similar to neurapraxia, observable histological changes
Irreversible Damage	N/A	Requires nerve regrowth, obvious histological damage

KHFAC Therapeutic Window: Within the Amplitude-Duration space, KHFAC has at least nine possible "effect states", including activation, block, and many longer-term effects.

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- **KHFAC Acute Therapeutic Window Specifications:**
  - KHFAC testing shall be on the rat sciatic nerve
  - Testing of force output will be performed
  - **Static testing**
    - KHFAC shall be tested acutely in durations 5-30 minutes
    - KHFAC **may** be tested acutely in durations >30 minutes
    - KHFAC shall be tested acutely at block threshold amplitudes as well as 150% and 50% of the block threshold
  - **Duty cycle testing**
    - KHFAC shall be tested using repetitive on/off cycles where the "on" cycle duration is 1-30 minutes and the "off" cycle duration is varied between 50% and 250% of the "on" cycle for 5-20 repetitions
    - KHFAC shall be tested acutely at block threshold amplitudes as well as 150% and 50% of the block threshold

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- **KHFAC Chronic Therapeutic Window Specifications:**
  - KHFAC testing shall be on the rat sciatic nerve **or larger animal**
  - Both functional/behavioral and histological testing will be performed
  - **Static testing**
    - KHFAC shall be tested chronically in dosages 5-30 minutes 1-4 times/day
    - KHFAC **may** be tested chronically in durations >30 minutes
    - KHFAC shall be tested chronically at block threshold amplitudes as well as 150% and 50% of the block threshold
  - **Duty cycle testing**
    - KHFAC shall be tested using repetitive on/off cycles where the "on" cycle duration is 1-30 minutes and the "off" cycle duration is varied between 50% and 250% of the "on" cycle for 5-20 repetitions 1-4 times/day
    - KHFAC shall be tested chronically at block threshold amplitudes as well as 150% and 50% of the block threshold