Activation of Sub-epidermal C-Fiber Afferent Nerve Endings and Nocioceptors by Avazzia Bio-Electric Stimulation Technology

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ABSTRACT:

***Bio-Electric-Stimulation Technology (BEST™)* is briefly reviewed and an explanation of sinusoidal waveform effect on evocation of action potentials based upon charge loading, voltage, cell membrane capacitance, neuronal cell membrane and cytoplasmic resistances, and other mathematically expressed electrical properties of non-myelinated C fiber neurons. Stimulation of sub-epidermal afferent C fibers is therapeutically desirable to inhibit pain transmission and release neuropeptides such as endorphins and enkephalins, regulatory neuropeptides, neurotransmitters such as serotonin and nitric oxide released from stimulated tissues and neurons.**

Key Words: Avazzia, BEST, Micro-current, Neuropeptides, C-fiber activation

Introduction: Nerve Fiber Classifications and Function

Nocioceptors are Receptors at terminal afferent C-nerve fiber endings that receive noxious stimulation from biochemical transmitters released from injured cells. Nociceptors are found in skin, muscles, joints, and the viscera. They are particularly adept at responding to noxious (painful) levels of mechanical stimulation and temperatures below 10°. Polymodal nociceptors respond to noxious (painful) levels of mechanical, heat, and chemical stimulation and are also terminal endings of C fibers.

BEST devices generate electrical impulses that are physiologically similar to neurological impulses generated by C nerve fibers which consist of 85% of all nerves found in the body and are embedded in most tissues as well as the CNS.[1]

BEST signaling also effects "fast" pain "A" fibers by the pain gate mechanism. A-fiber axons are surrounded by a myelin sheath created by Schwann cells. Schwann cells are glial, circumferential support cells of the peripheral nervous system (PNS): These cells generate extensive sheets that wrap the axons repeatedly to form lipid rich myelin. The myelin sheath acts as insulation on a wire and is essential for rapid conduction of impulses along the large nerve axons. Myelin acts as a dielectric and increases membrane resistance and membrane capacitance for charge accumulating inside a neuron. Myelination and increased diameter of A fibers accelerate nerve conduction velocity. In comparing Type C to Type A fibers, their diameter increases tenfold in A fibers but the propagation speed increases by 140 times! Myelin insulation, increases membrane resistance (insulator effect) and boosts propagating signals by providing voltage gated ion channels at intermittent nodes which acting like signal boosting stations along the axons and dendrites of the neuron. This type of conduction is termed "saltatory" conduction. Myelinated A fibers are responsible for sharp fast pain and exhibit rapid nerve conduction velocity.

C-type fibers are small and non-myelinated, with a diameter of 1-2 μm. C-fibers conduct charge by Electrotonic Conduction. After the initial point of depolarization on the nerve ending membrane each adjacent region depolarizes as the action potential propagates down the axon. Electrotonic Conduction allows for propagation of an action potential without decrement the entire length of the fiber. It is not as efficient or fast as saltatory conduction.

C fibers are responsible for slow diffuse pain, but more importantly nerve endings, axon bodies and the presynaptic membrane secrete neuropeptides into synaptic clefts, Cerebral Spinal Fluid, and bloodstream capable of blocking pain perception via

afferent signaling to the cortical centers in the brain.[2] Stimulation of acupuncture points and/or embedded afferent C fibers transmits impulses via the cord to the dorsal medulla and thalamic areas of the brain, which produce nitric oxide and a host of other neuro-active mediators.[3] Nitric oxide then acts as a neurotransmitter for induction of opioid neuro-peptide production, i.e. beta- endorphins, dynorphins met-enkephalins, serotonin, nitric oxide and other neuro-peptide and neuro-modulators. [4,5]

A class of neuropeptides secreted locally is termed *Regulatory Neuropeptides (RNP)*. RNP within C fibers directly increases further peptide synthesis, neurotransmitters, serotonin, histamine, and other peptide hormones production by modifying genomic activity, up-regulating gene expression, and enzyme synthesis.[6]

C-Fiber Activation is Therapeutically Desirable

Although BEST signals have some effect on all types of fibers and excitable tissues, the most effective and desirable therapeutic response involves stimulating peptide secreting C nerve fibers.[7] But C-fibers are much more difficult to effectively evoke propagatable, neuronal action potentials by an outside stimulus than are myelinated A and B fibers. If a transcutaneous stimulus is applied it must be of adequate intensity, current flow and duration to evoke a response. If a stimulus is too short, even a strong pulse will not be effective. A long pulse below certain intensity will evoke only a local non-propagated response. The size of the spike recorded from a nerve bundle depends on how many fibers are activated. A weak stimulus pulse may excite only a few fibers, producing only a small signal.

Various combinations of intensities and duration will adequately generate enough action potentials to stimulate a post synaptic transmission to higher order neurons or secretion of NPs. BEST signaling is configured in such a way as to provide maximum C-

fiber stimulation without habituation, accommodation and never induce neuronal cell damage from thermal damage due to resistance from high current loading.

Basic Laws of Charge Conduction

Ohm's law states that "**current = voltage/resistance**" or **I = V/R.** and applies to axons and dendrites of living cells nerve as well as Direct Current (DC) non-living electronic circuits. Impedance **(Z)** is used to describe the measure of the opposition to an alternating current (AC). The concept of Impedance is the same as resistance except applied to AC circuits. In AC circuits, amplitudes of both voltage and current, the phases, are shifting and relative to each other. Impedance, in its simplest form, exists with Direct Current (DC) as no different than resistance. Resistance is something that "oppose or resist" the flow of current. It prevents the electrons from passing through and usually takes the form of leak energy which is usually heat.

Resistance only has to deal with non-shifting phases of voltage and current which makes it simple. Impedance is determined by an additional component, based on phase shifts, aside from just resistance. That component is termed "reactance".

Reactance, which is either inductive or capacitive, is a circuit element's opposition to an alternating current. Knowing the reactance in addition to the resistance, one will be able to determine the impedance. This is to say that when one has to determine impedance, they will require an overall or a more extensive figure of the circuit.

Both resistance and impedance are expressed in unit ohms. Mathematically, however, they are denoted differently. Impedance is often denoted with symbol (Z) while resistance is often in (R). Many people, including engineers and electronic enthusiasts use the terms loosely. They often use the terms interchangeably especially in forms It is always assumed that impedance is just another word for resistance.

Therefore, it should be understood that the effect of resistance is constant regardless of the frequency. On the other hand, mixing the effects of capacitance and inductance will always result in impedance. It basically means that impedance varies with frequency values.

The charged flux of sodium, potassium and calcium ions across a living nerve cell membrane generates alternating voltage and phase changes that are described by sinusoidal wave forms and exhibit impedance.

Clinically Biological Impedance tissue measurements are useful for measuring electrolyte flux across cell membranes and determining hydration at the cellular level and lean muscle mass.

Summary:

1. Impedance **(Z)** is the measure of opposition to an alternating current (AC) while resistance usually refers to direct current (DC).

2. Resistance is simple while Impedance will consider reactance in addition to resistance to determine it.

3. Resistance is pure ohmic impedance (absence phase shift).

4. Impedance is denoted by (Z) while Resistance is denoted by (R).

5. Impedance may often take into consideration the overall cir

Read more: Difference Between Resistance and Impedance | Difference Between | Resistance vs Impedance http://www.differencebetween.net/science/difference-between-resistance-and-impedance/#ixzz48UNy5YHg

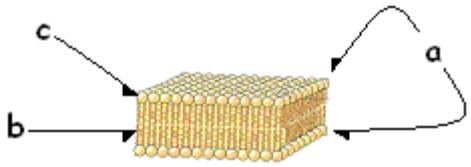
The measure of potential energy in the form of charged ions across a neuronal cell membrane is **voltage**. Voltage is always measured between two points and is called the potential difference or potential between the two points, in this case the difference between points inside of a neuronal cell, separated by a semipermeable membrane and points outside – the extracellular space.

The flow of electrical charge in the form of charged ions, usually anions Na^{+}, K^{+}. Ca^{++} across the neuronal cell membrane is called current. (micro or milliamps)

Current is proportional to voltage (the greater the voltage, the greater the current) and is inversely proportional to resistance (the greater the resistance, the less the current).

Resistance, measured in **Ohms (Ω)** is the amount of charge moving between two points depends on voltage and resistance (hindering of flow of charge) or **impedance** also measured in ohms, when dealing with alternating current.

The Dielectric Nature of Cell Membranes

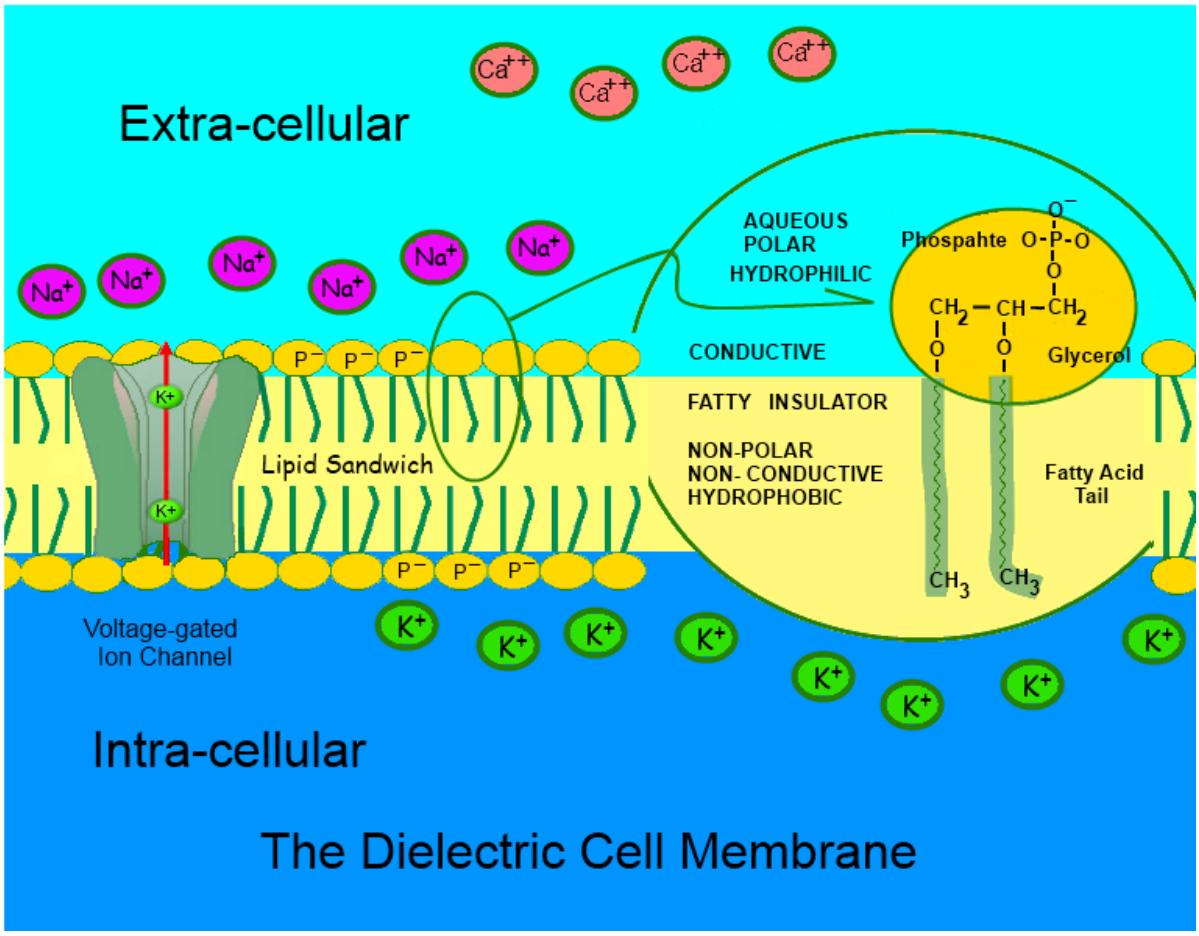


A cell membrane consists of lipid molecules with hydrophilic (electron conducting) carboxylic acid groups (c) and hydrophobic (electron insulating) hydrocarbon tail chains (b). The membrane thickness is the gap (c). The membrane acts as a dielectric to store electrons and transfers them to the cytoplasm upon demand.

The accumulation of charge in the form of anions on either side of the cell membrane is similar to a capacitor. Connecting a capacitor to a cell causes a buildup of charge on the polar plates (Phosphate bound to di-glyceride interior) although the rate of addition keeps decreasing due to increase in voltage between the plates. Glycerol, an alcohol bridges the charged phosphate with the aliphatic fatty acid tail to form the phosphor-lipid cell membrane. The Phosphate (hydrophilic) –faces out toward the aqueous extracellular fluid and the opposite bilayer phosphate in toward the aqueous cytoplasm. A fatty-acid, (hydrophobic) non-polar, glycerol-bound fatty acids composes the bi-layered interior. The fatty acid tails form the insulation layer of the dielectric. A typical cell membrane is 8nm thick and has a dielectric constant of 5.00. [8] The inner and outer surfaces of a cell membrane carry a negative and positive charge, respectively. Because of these charges, a potential difference of about 70 mV exists across the membrane.

The cell membrane exhibits a selective permeable nature because of this bi-layer hydrophilic/phobic property. Small hydrophobic substances (fat-soluble) get through relatively easily while charged (water-soluble) ions can only enter through passive or voltage-gated channels.

Positively charged ions (anions -- primarily Na^{+}, K^{+}, Ca^{++}) pass through ion specific channels that causes charge to buildup on either side of the membrane gradually increasing the voltage until equilibrium occurs.



Capacitance is the property of a circuit element, in this case the cell membrane, to absorb and store electric charges. Capacitance of a neuronal membrane composing a nerve fiber is the ratio of charge to potential on an electrically charged, isolated cell membrane. The cell membrane acts as a dielectric with lipid molecules acting as the insulator. Capacitance is expressed in Farads or micro-farads.

In the body, electrical currents correspond to the flow of ions across cellular membranes and any resistance is provided by the membrane themselves. Ions move

along chemical gradients (due to diffusion) and along electrical gradients (move toward an opposite charge); therefore ions flow along electrochemical gradients.

The resting membrane potential is combined function of electrical (differential of net ionic charges) and osmotic (differential of concentration) properties.

Passive diffusion of electrolytes, based upon concentration gradients (osmolality and charge flow through channels on the semi-permeable cell membrane until both osmotic and electrical equilibrium is achieved. Metabolic (chemical) energy in the form of ATP is necessary to maintain and restore respective ion concentration on either side of the cell membrane after depolarization for the resting potential to be restored. Non-charged crystalloid molecules such as sugars and starches balance according to (by osmotic force) concentration.

Voltage Gated Ion Channels

Channels embedded in the neuronal cell membrane allow for the passage of charged ions between the inside and outside of cells. Passive (leakage) channels are always open. Active (gated) channels that are made up of one or more proteins are capable of undergoing changes to open or close. Chemically gated channels - respond to neurotransmitters like nitric oxide. C fibers and nerve endings embedded in the sub-epidermis contain Voltage-gated ion channels which respond to membrane potential changes especially when charged with transcutaneous high voltage micro-current signaling. Voltage-gated Calcium channels are the facilitator of depolarization in C-fiber endings and Ca^{++} ions, ionic charge mediators are required in adequate amounts for effective functioning.

Factors that Determine the Excitability and Propagation of C-fiber Action Potentials.

Factors that determine the rate of propagation of the action potential in C fibers are based upon the passive properties of neuronal membranes expressed as the **Length Constant (LC)** that reflect longitudinal cytoplasmic core resistance and the **Time Constant (TC)** that reflects neuronal membrane resistance. LC and TC are not directly dependent on metabolism or any voltage-dependent permeability changes. They are reflections of the physical properties of the neuronal membrane, the diameter of neurons, the resistive properties of cellular structural and cytoplasmic substances.

The Time Constant

The Time Constant of a neuronal membrane is expressed as:

$$\mathbf{T_m = R_m C_m}$$

Time Constant = Resistance · Capacitance

Time Constant is amount of time it takes following the injection of current for the potential to change to 63% of its final value. In other words, indicates how quickly a cell membrane depolarizes in response to an inward current or how quickly it hyperpolarizes in response to an outward current. The smaller this property, the greater will be the propagation velocity.

Membrane Resistance is inversely related to the permeability. When this property is high, it means low permeability decreasing the ability of the membrane to allow Na^+ influx to occur as rapidly, effectively increasing the time constant.

Membrane Capacitance describes the ability of the membrane to store charge to make the membrane potential change necessary. The larger this property, the greater the amount of charge that must flow to depolarize the membrane, the longer the time constant will be. The larger the diameter of the cytoplasmic core the lower the resistance will be in a given length due to the greater number of charges carriers at any given point. If $\Delta V = Q/C$ where Q = charge and C = capacitance, then the larger membrane capacitance the more charge must be deposited on the membrane to change the potential across the membrane, so the more time required to generate a depolarization.

The Length Constant

The Length Constant of a neuron is expressed as:

$$LC = \sqrt{Rm / Ri}$$

Length Constant = Square Root of (R*esistance* membrane / Resistance interior)

The length or space constant is defined as the distance it takes for the depolarization to decay by 63% or decays to 37% its initial value. The greater the length/space constant, the greater and further will be the propagation velocity and distance reflecting reduced longitudinal resistance. The LC indicates how far a depolarizing current will spread along a nerve. In other words, the larger the length constant, the farther the current spreads down the nerve fiber.

The cytoplasmic core of a C-fiber neuronal dendrite/axon offers significant longitudinal resistance to the flow of current because it has a relatively small cross sectional area and ions flowing down the axon collide with other molecules. This resistance can also be expressed as the axial resistance: Ω/cm (ohms/cm) and depends on both the specific resistivity of the cytoplasm termed "p" and measured in Ω/cm and the cross-

sectional area ($\pi \cdot \text{radius}^2$) of the axon with a radius – "a": $\mathbf{r_a = p/(\pi a^2)}$ where resistance = (resistivity, in ohm-cm, multiplied by the length of axon, measured in cm,)/ cross-sectional area of the axon, measured in cm squared) $\mathbf{r=p/\pi a^2}$

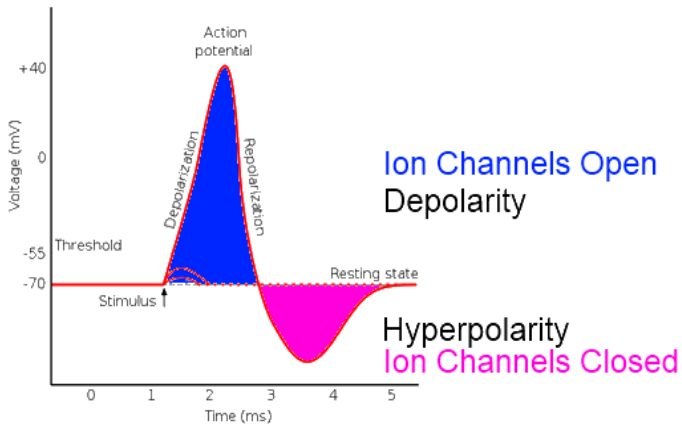
According to Ohms law **I = V/R,** the larger the cytoplasmic resistance the smaller the current flow around the loop and the longer it takes for the charge on the adjacent membrane segment to change. In addition the greater the length of the cytoplasmic core the greater resistance since ions experience more collisions the further they travel.

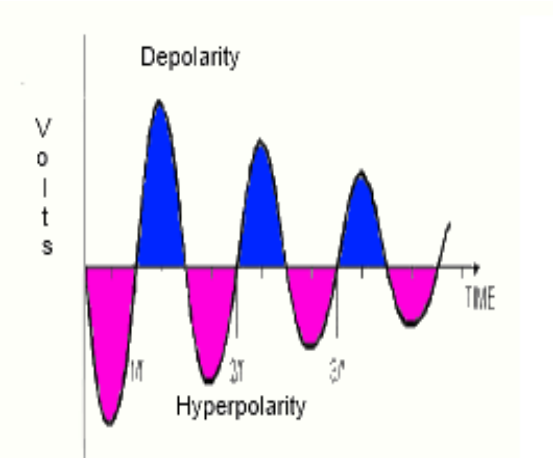
The value of the threshold of electrical excitement is in direct inverse proportion to the diameter of the fiber. Therefore, based upon diameter alone, the electromotive force (Voltage) necessary to excite C-fiber should be 15-40 times higher than A α fibers

The Effect of Sinusoidal Waveform Signaling

Depolarization occurs when the neuronal membrane potential is less negative than the resting potential the cell is depolarization, a decrease in potential difference (e.g., a change from -70 mV to -40 mV). Voltage gated ion channels open and initiate a depolarization as seen on the right below.

Hyperpolarization occurs when the neuronal membrane potential is more negative, the cell is Hyperpolarization and this occurs when polarization across the membrane is increased (e.g., a change from -70 mV to -100 mV). Voltage gated ion channels are closed and the neuron is refractory to stimulation.





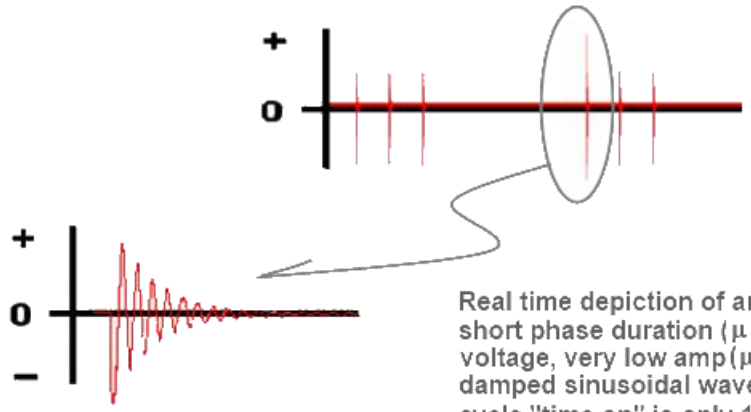
C-Fiber Action Potential **Avazzia Best Signal**

Avazzia BEST signals delivers voltage to the neuronal cell membrane to open ion channels and effect depolarization and reduces voltage to close ion channels by hyperpolarization of neuronal membranes. Impedance determines the phase signals time and damped amplitude characteristics based upon cybernetic feedback information delivered back to the device by the target tissue and based upon up to a million operations per second measurements by the microprocessor and software in the Avazzia device

High Voltage, Low Current, Extremely Short Pulses

C-fibers are difficult to stimulate to depolarization by conventional electro-stimulation devices including TENS. Avazzia BEST signaling in high voltage 200-300 volts, extremely short duration (micro seconds 10^{-6} seconds pulse width), extremely low current (micro amps - 10^{-6} amps) damped, biphasic sinusoidal waveform that is impedance modulated by a cybernetic feedback loop between the target tissue and the analog characteristics of the device. With each applied stimulation pulse, the electrical propertied of the tissue changes thus influencing the next output signal.

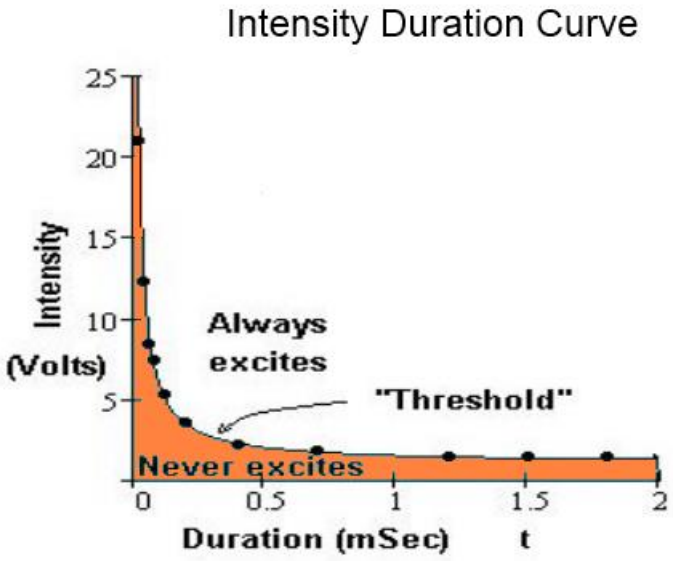
High voltage for prolonged time or high current for prolonged exposure can damage C-fiber cells by thermal damage due to high resistance.



Real time depiction of an extremely short phase duration (μ sec.), high voltage, very low amp (μ amps) damped sinusoidal waveform. Duty cycle "time on" is only 1-2% of total.

The duty cycle on Avazzia BEST devices consists of 1-2% of time "on" emitting signaling and 98-99% "off". Therefore there is no opportunity for cell damage due to thermal build up from resistance/impedance. Signals consisting of short clusters of sinusoidal (depolarization hyperpolarization cycle) micro-current lock the neurons and their C-fibers in the target field of electrode application into a **synchronization** pattern for effective AP deliveries in mass to presynaptic membranes in the spinal cord and potentiated activation of second order neurons for transmission to higher brain centers.

Avazzia BEST generates rapid depolarization in C-fibers with very short time constants and large length constant. In the equation: Tm= Rm Cm -- Capacitance is low due to a lack of myelin sheath to seal in ion flux, (increased porosity). Resistance component is high due to small cross sectional area. High voltage and a very short duration and duty cycle are used to overcome the high resistance and low capacitance of C-fibers.



BEST transcutaneous stimulation signals are a "clusters of energy" delivered to the C – nerve fiber ending embedded in the skin (Nocioceptors). They displace electric charges. A "weak" pulse (low voltage) of long duration can evoke the same response as a "strong: (high voltage) pulse of short duration. Avazzia signaling utilizes the extreme right side of the above graph by being very high voltage and very short duration to achieve hyper threshold triggering of depolarization.

In respect to the Length Constant: Avazzia BEST also utilizes high voltage to "push" the generated action potential, complete propagation the entire length of the dendrite/axon membrane and cytoplasmic core by Electrotonic conduction.

References:

Kandel Eric R.: Passive Properties of the Neuron
Essential of neural Science and Behavior pgs. 149-159

Fundamental Neuroscience
Chapters 1-5: Essential Concepts
Duane E. Haines PhD, Churchill Livingstone, New York

Notes on Neuro-Physiology: The Stanfield Lectures 1-7
http://www.flashcardmachine.com/stanfield-lecture-1.html

[1] Willis, W. D., Jr., and Coggeshall, R. E., *Sensory Mechanisms of the Spinal Cord*., New York: Plenum, 1991.

[2] JD Levine, HL Fields and AI Basbaum,. *Peptides and the primary afferent nociceptor* Journal of Neuroscience, Vol. 13, 2273-2286, 1993

13 Sing Shu Ma, Review: *Neurobiology of Acupuncture Toward*: CAM, eCAM 2004; 1(1) 41-47

[3] Sing Shu Ma, Shuang Chen, *Nitric Oxide In Gracile Nucleus Mediates Depressor Response to Acupuncture (ST36)*, J Neurophys. 90 780-785, April 2003

[4] Han JS, Zhang M, and Ren MF. *The effect of spinal transection on acupuncture analgesia and morphine analgesia*. Kexue Tongbao 31: 710–715, 1986.

[5] Ma Sx, Review: A Novel Signal Pathway, Nitric Oxide mediates acupuncture induced neuronal activity and analgesia in the dorsal medulla-thalamic tract. First World Congress on Chinese Medicine 2003; 95:A7

[6] Ashmarin I.P., Obuchova M.F. Content of regulative peptides in the brain cortex and their central activity, "Highest nervous activity", v.35, No.2, p. 211-221.

[7] Ansel JC, Armstrong CA, Song I, Quinlan KL, Olerud JE, Caughman SW, Bunnett NW. *Interactions of the skin and nervous system.* J Investig Dermatol Symp Proc. 1997 Aug;2(1):23-6.

[8] W Huang and D G Levitt, *Theoretical calculation of the dielectric constant of a bilayer membrane* Biophys J. 1977 February; 17(2): 111–128. PMCID: PMC1473453

Appendix

Comparison of Conventional Electro-therapy to Avazzia BEST

BEST	CONVENTIONAL ELECTRO-THERAPY
Signals in the frequency range of less than 1Hz to 1500 Hz, high intensity pulses, direct effect on secretory C fibers, also significant CNS effects via C afferents to spinal ascending and opiod mediated descending inhibitory pathways.	Signals in the frequency range of 1Hz to 100 Hz, low intensity pulses, activation of Type I and A-β afferent fibers based upon Gate control theory mechanism and signal blocking or diversion
Damped asymmetrical biphasic sinusoidal waveform	Mono-phasic or asymmetrical biphasic waveform
High intensity, short duration pulses, induces neuropeptide release, initiates long term cascading effects and up-regulation of NP, endorphin, serotonin, and enkephalin synthesis.	Low intensity activates large muscle (type I) and large skin A-β nerves for Gate effect
Non-segmental and segmental effects: neuropeptide cascade initiated by small C fibers act generally as well as locally: in spine, brainstem and CNS.	Segmental effects based on Gate Theory: large diameter fibers inhibit pain from small fibers.
Analgesia starts within moments and lasts up to twelve hours with both local and systemic pain relief	Analgesia starts within a few moments of stimulation and disappears within seconds of switching the machine off. TENS must be used for long periods of time for sustained relief.
BEST will typically not burn or damage the skin	High intensity of most TENS and other electro-therapy devices can cause burning of skin
No Pads are necessary as the electrode on the unit both transmits and receives. The unit can be placed on acupuncture points or over subcutaneous large diameter nerves as well as directly on areas of interest or pain. Probes for point source delivery are available. For Convenience, pads and conductive garments are attachable.	Pads are placed near the site of pain as large diameter fibers are widely distributed.
Because of dynamic waveform and	Tolerance (accommodation and

cybernetic feedback no habituation or accommodation develops	habituation phenomenon) develops over time
Short duty cycle with BEST. Typical unit is off over 99% of the time and emits burst signals less than 1%	Prolonged duty cycle, long durations of "on" operation compared to off
BEST delivers signals with voltages and currents varying as the impedance of the skin is changed as result to prior stimulation pulses.	TENS is constant voltage signal with variable changes in current and resistance/ impedance over the pulse interval
Cybernetic loop whereby BEST and the patient's neurological system form a mutually interacting communication and control system via automatic bio-feedback and impedance signaling of affected tissues.	External control with no bio-feedback modulation of the output signal. TENS and many other electro-therapy signaling is constant although some models have a fixed external program that varies of signaling to resist accommodation or habituation.

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