

Biophysical Neuromodulation: *An Integrative Approach*

Joshua Bush¹

¹Department of Bioengineering, George Mason University, Fairfax, VA USA

Abstract:

The brain remains the key to our experiential reality. From sensory perception to an internal expanse the brain remains the hardware and processing unit. The age in which we can precisely alter the hardware with which we process and create experience is dawning. From the advent of optogenetics to the developing use of transcranial magnetic stimulation (TMS), we are rapidly expanding our control over our brains. It is essential that the evolution of our understanding of the brain maintains a reasonable pace with the technological breakthroughs and human urgency. In this pursuit, we explore the emerging methods for biophysical neuromodulation and the materials through which these methods can be enhanced and/or used to develop translational *in vitro* models. The methods involved encompass thermal, electrical, magnetic, optical, and ultrasonic modulation of neurons and neuronal networks. A variety of materials such as conductive polymers, graphene, and optoelectronic semi-conductors have been utilized to harness these physical stimuli in the study of neuromodulation. Materials continue to emerge with greater precision and control over the matrix mechanical properties, conductivity, ligand densities, and nano-architecture. With environmental control, real-time physical neuromodulation, and evolving multiplexed sensing capabilities, the rate at which we can further our comprehensive understanding of neuronal information encoding expands rapidly. This review aims to provide a cohesive overview of the maturing coupling between biomaterials and biophysical neuromodulation.

I. Introduction

Neurons provide an interesting biophysical entity through which our consciousness may flow to perceive this reality. Since the first discovery of their electrical nature we have come a long way to understanding their functioning and yet their complete role in our perception remains elusive. Continuing to develop our understanding, requires accelerated development of the tools and methods we use to study neuronal function. This requires the convergence of multiple disciplines towards precise growth and modulation of the networks that neurons form. Electrical stimulation has long been harnessed to induce neural firing [1]. With the development of microelectrodes and alternative materials, the precision

of neuromodulation continues to increase. Other physical phenomena such as ultrasound [2], light [3], [4], magnetism [5], [6], heat [7], [8], and engineered substrates [9] provide an alternative method of biophysical neuromodulation, though each comes with its own limitations. The advancement and integration of materials has proven a critical factor in alleviating some of these limitations. Proceeding, we will overview different approaches for biophysical neuromodulation, and the materials-based augmentation of these various methods.

II. Electrodynamic Stimulation

Physical neuromodulation began with electrical stimulation and has since been refined in precision from macro-scale approaches, such as transcranial direct current stimulation (tDCS), to localized modulation via deep brain stimulation (DBS). tDCS applies a subtle current across the brain via two external patch electrodes for a few minutes to enhance neural plasticity [10]. Whereas DBS utilizes the implantation of an electrode to a specific brain region of treatment, such as the sub-thalamic nucleus for treating depression [11]. DBS further evolved by implementation of transcranial pulsed magnetic stimulation (TMS). TMS uses pulsed magnetic fields to generate an electrical current within the brain and also was approved for the treatment of depression [6], [10]. While TMS bears the advantage of non-invasiveness it lacks the potential for portability and continued stimulation due to significant power requirements, thus limiting the approach to temporally confined treatment windows. DBS is limited with regards to spatial precision as current leakage to non-target brain regions is suspected to cause mood problems from subthalamic nucleus implantations [12], [13]. Microelectrodes are also being implemented to improve localized spatial resolution, and additionally, to *in vitro* neuronal cultures for study of neural network function and stimuli response [1].

Multi-electrode arrays offer the advantage of interfacing with a neural network in its own ‘language’, defined by the theory of cell assemblies. The theory of cell assemblies describes an individual neuron as a part of the whole and not subject to a specific singular function. Rather, individual neurons serve as a conduit to transfer information from multiple neurons to another multitude of neurons [14]. Multi-electrode

arrays implemented with deep learning technology offer a powerful tool to refine electrical treatments, such as DBS and peripheral nerve interfaces, via locally coordinated network stimulation [15]. DBS is known to elicit a variable response in a frequency dependent manner [16], though currently, the frequency response must be determined experimentally. With advancing deep brain imaging techniques [17], [18], a better understanding of the neural code, and implementation of refined technology and self-learning software [19], the future of programmable neuromodulation draws near.

Recent developments from a materials science perspective aim to overcome limitations such as tissue damage, inflicted by rigid electrodes, and loss of contact with neural networks resulting from glial scar formation and immune response [20]–[23]. Flexible electrodes have been developed to deform with the brain, alleviating shear-induced tissue damage from rigid electrodes [24], [25]. Additional electrode coatings such as poly(3,4-ethylene dioxythiophene) (PEDOT) [26], [27], polypyrrole (PPy) [28], polyaniline (PANI) [29], and carbon nanotubes (CNTs) [30] have been developed to improve long-term contact of the electrode with the tissue, thus alleviating increases in electrode impedance. Furthermore, these flexible fibers have been developed to incorporate optical conduits coupling electrical and optical modulation of neurons. These advancing optoelectronic fibers offer a powerful tool for localized optical neuromodulation in conjunction with real-time electronic feedback.

III. Optical stimulation

Light can be used for neuromodulation, with millisecond temporal resolution, by stimulation of light-sensitive ion channels, opsins. The founding of this method began by delivering the gene for Channelrhodopsin-2 (ChR2), a blue light-sensitive (450–490nm) cation channel, into cultured rat CA3/CA1 neurons. Pulsed illumination produced action potentials within <3ms of stimulation [3]. This approach has been termed optogenetics and continues to develop, encompassing additional opsin channels [31], [32], and improved light/gene delivery methods [33]. While this method boasts direct optical stimulation in comparison with photothermal methods, it functions at a lower wavelength thus enhancing the effects of tissue scattering and limiting the effective penetration depth to a few millimeters. This limitation necessitates the use of optical fibers for precise deep brain stimulation. As well, the need to deliver a genetic package to the target region, inducing opsin expression, presents another challenge. Optical fibers have been developed to overcome these limitations with the

incorporation of microfluidic channels and electrodes to enable electronic feedback [33]. However, the physical limitation of light scattering at visible wavelengths is a difficult barrier to overcome without invasive probes thus, penetrating infrared wavelengths are desirable for neuromodulation.

Infrared neural stimulation (INS) is an indirect method of optical stimulation as the heat generated by absorption of water, or nanoparticles, is suspected to be the cause of neuron depolarization. A model was proposed for thermally altered membrane capacitance inducing action potentials [34], [35]. Additionally, neurons possess an array of heat-sensitive ion channels that may be activated by local photothermal heating. Initial exploration of this phenomenon began with infrared light of wavelengths ~2000nm, near the absorption of water, to heat nerve tissue and induce muscular contractions [4]. Advances in materials science produced plasmonic gold nanoparticles with modular wavelengths of absorption, defined by the geometry of the nanoparticle. As such, gold nanorods with absorption wavelengths ~795nm have been used as a medium to improve the efficiency of photothermal heating, spatial resolution, and penetration depth as the near-infrared light can penetrate tissue with relatively little absorption from water content. Plasmonic gold nanorods can also be coupled with targeting ligands for cell-specific modulation and improve the efficiency of modulation by fixing the nanorods to the cell membrane, thus requiring only localized heating [36]. While physical factors can be tuned for inhibition and excitation of neurons [37], a recent approach couples gold nanorods with an *in vitro* microelectrode surface for independent inhibition and excitation [38]. This approach was used for the functional mapping of neural networks by studying the network response to individual neuron inhibition [7]. Such methods are promising for interpreting the neural code through *in vitro* models. An alternative use of near-infrared light was shown to direct axon growth away from the point of illumination [39]. The mechanism was shown to be the result of local heating and activation of heat-sensitive TRPV1 channels along the extending neurite [8]. These developing methods possess great potential in coordination with holographic light patterning [40], [41] to enable the controlled wiring of neural networks and subsequent inhibition/stimulation to study the network response in pursuit of understanding the neural code.

IV. Ultrasonic stimulation

Similar to optical methods, ultrasound waves can be used to locally heat tissue and elicit neuromodulation [42]. However, ultrasound can directly modulate neural firing through non-thermal

mechanisms, and has been used to stimulate retinal circuits with a spatial resolution $<100\mu\text{m}$ [43]. The primary mechanism is suspected to be the activation of mechano-sensitive ion channels inducing a depolarizing current. An additional perspective to keep in mind is the model of soliton-based action potentials. Which proposes that electromechanical waves propagate along axons as a result of rapid swelling and membrane pressure gradients, while the electrical pulse is rather a byproduct of the resultant ion fluxes [44], [45]. The evidence for this model continues to grow [44]–[46], and is to be considered when pursuing the mechanisms of ultrasound neuromodulation.

The mechanisms by which focused ultrasound modulates neuronal firing continues to be explored, though a few contributing factors have been identified. The applied acoustic wave is expected to propagate through the cell membrane inducing pressure variations throughout the membrane. The altered membrane tension thus activates mechanosensitive ion channels, and potentially attenuates passive diffusion across the membrane through nano-cavitation domains [47], [48]. A few mechanosensitive ion channels were shown to be sensitive to focused ultrasound including, K2P channels and NaV1.5 [49]. However, it is reasonable that additional mechanosensitive ion channels elicit an ultrasound mediated response. The frequency and intensity dependent response of various mechanosensitive ion channels may be a critical factor in enabling the controlled excitation and inhibition of neuronal firing by ultrasound [50].

While the exact mechanisms of action continue to be unraveled, the potential for ultrasonic neuromodulation grows with developing technology. Specifically, acoustic metamaterials [51], micro-piezoelectric transducers [52], and acoustic hyperlenses [53] offer potential for enhanced resolution of focused ultrasonic profiles. Acoustic holography enables the dynamic spatial patterning of ultrasonic waves and thus precise neuromodulation. This holographic ultrasound approach has been successfully implemented to enable prosthetic stimulation of retinal circuits for precise delivery of visual information [54], [55]. Progressing to super-resolution deep brain ultrasound stimulation (dbUS) will however require the circumvention of heterogenous mechanical properties in the brain tissue.

V. Tissue Engineering

The mechanical properties of native tissue are known to play a critical role in gene expression, cytoskeletal dynamics, and viability. Synchronously, the spatial conformation and species of ligands to which a cell adheres, plays a critical role in the cell's response to the mechanical environment [56]–[58]. While the

field of tissue engineering presents its own wealth of information, the extent of tissue engineering discussed in this review will be only to draw attention to the available degrees of freedom to control neurogenesis, neurite growth, and active materials to attenuate biophysical neuromodulation. Specifically, integrin-ECM binding domains YIGSR and IKVAV, derived from laminin, have been shown to inhibit and induce neurogenesis when individually coated to a surface for neural stem cell culture, respectively [59], [60]. Additionally, a gradient of IKVAV peptide surface coating can direct the alignment of neurite growth cones [61]. Substrate stiffness matching can be tuned to affect the density of neurite branching [62]. As well, substrate stiffness plays a critical role in neural stem cell differentiation through a variety of mechano-transduction pathways which can also depend upon the specific integrin-ECM domains [56]. Substrates may be patterned with different nano-topographical motifs to control focal adhesion formation, and affect neural stem cell differentiation and neurite growth [63].

Conductive species have been integrated within artificial tissue constructs to improve the biocompatibility and electrical connection for recording and stimulation of neural network cultures [28], [29]. An interesting advantage to some of these conductive polymers is their potential for electrochemical deposition, providing the opportunity for controlled polymerization within tissue and thus encapsulation of neurons [26], [27]. More intriguingly, optically responsive semi-conductors have been integrated in tissue constructs to provide optically transduced control of neurons. Poly(3-hexylthiophene) (P3HT) is sensitive to light between $\sim 450\text{-}600\text{nm}$ and was used to direct LED-induced differentiation and axon growth of PC12 cells. The P3HT based scaffolds were constructed by self-assembly, electrospinning, and photolithography to produce nanofiber, microfiber, and patterned motifs, respectively. LED irradiation was able to increase neurite extension length and direct neurite growth along photolithographically patterned P3HT substrates [64]. As well, photo-sensitive reduced graphene oxide substrates were shown to stimulate electrical activity in response to light irradiation [65].

VI. Discussion

Neurons present a fascinating biophysical medium with multiple modes for stimulation. Each method of dynamic modulation hinges at a similar point, that which the neuron is depolarized above a threshold potential and then propagates the stimulation on its own accord. Electrical stimulation induces this depolarization directly while optical, thermal, and mechanical methods alter the conductivity and/or capacitance of the membrane to elicit a response. The

model for soliton-based action potentials would argue the mechanical method of neuromodulation is the most direct approach, though, electrically driven action potentials are the most supported convention. The succeeding discussion aims to merge the linking and contrasting concepts of these different approaches for the curious mind to ponder integrative solutions.

Electrodynamic therapies boast the most documented evidence for effectiveness and treatments of specific brain regions for therapeutic intervention. While the current electrical methods are faced with crippling physical limitations for micron scale non-invasive stimulation, the advent of materials science and optimized electrodes provides a suitable means for the soonest treatment potential. However, a recently demonstrated method applies two high-frequency AC currents, from two pairs of external electrodes, with a slight difference in frequency. The point of interference between these currents produces a lower beat frequency, corresponding to the difference in applied frequencies, for electrical stimulation affecting only the target brain region [66], [67]. TMS is also a promising non-invasive approach though the lack of portability, and thus temporally limited treatment window, makes it less suitable for continual treatment, where DBS can maintain modulation of the target region throughout the patient's daily life. Alternate magnetic approaches to neuromodulation include magnetothermal [68] and magneto-mechanical [5], [69], [70] stimulation through magnetic nanoparticles. As well, direct magnetic modulation remains a possibility through the development of magnetically sensitive ion channels, termed magnetogenetics [71]. Magnetically operated modulation of neurons suffers little from tissue interference and thus is limited primarily by the magnetic nanoparticles' delivery method and composition. Both avenues offer many degrees of freedom, and thus, great potential in the long-term for neuromodulation. Magnetothermal and photothermal approaches are in the same 'carrier wave', as nanoparticles are non-invasively heated by a stimulus that easily penetrates tissue. The differences in these methods lie in their potential for delivery and biocompatibility of the pertinent nanoparticles, along with potential for high-resolution patterning of the stimuli, light or magnetism. Light offers great potential for spatial resolution with developing holography, while patterned magnetic fields of similar resolution are a much greater challenge, due to magneto-electrodynamic feedback and heterogeneous tissue properties [72].

Optogenetics is a powerful solution nearing application thanks to the development of opto-

electronic fibers with microfluidic channels for genetic treatment. However, optogenetics is currently confined to visible wavelengths and thus, invasive optical fibers. A developing alternative to optical fibers for enabling optogenetics, is the use of upconversion nanoparticles which convert near-infrared light into visible light which can be used for non-invasive optogenetic neuromodulation [73]–[75]. However, this approach still relies on delivery of genetic packages and upconversion nanoparticles, rendering ultrasonic neuromodulation as a leading candidate for purely non-invasive modulation. The potential for ultrasound to be projected in holographic patterns rivals the potential for high spatial and temporal resolution of optical approaches. However, ultrasonic neuromodulation is still in its early developing stages and will require time and coordinated effort to fulfill its potential. Since many of these methods either depend on, or are strongly attenuated by the development of materials science technology, it is necessary to address tissue engineering strategies for effective *in vitro* modulation and culture of neural networks to further bridge our micro-to-macro understanding of their function. Substrate stiffness matching offers a direct route for differentiating neural stem cells and influencing the density of neurite growth, and thus synaptic connections. As well, cell adhesion ligands can be patterned and selected to attenuate neurogenesis and direct neurite growth. Nanotopographical patterning and coating of the substrate offers direct control of neural network formation which can be supported by the coating of photo-responsive materials to direct network formation. Additionally, spatially controlled stimuli and substrate attenuation enables the controlled mapping of neural network function and programming.

VII. Conclusion

Biophysical neuromodulation is a rapidly developing field that has been strongly enabled by developments in materials. The potential for precise non-invasive control of the brain and our developing comprehension of neural information encoding is supported by these numerous methods and approaches. The similarities between each approach are abundant, and thus this review presented these connections, in coordination with the strengths and limitations of each, for an integrative approach to biophysical neuromodulation. While no individual method provides a certain final solution for precise non-invasive neuromodulation, the integration of multiple biophysical modes and materials expands this realm of possibilities

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