Perspective: Do Macromolecules Play a Role in the Mechanisms of Nerve Stimulation and Nervous Transmission?

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ABSTRACT: Fibrillar macromolecular networks are ubiquitous in biological systems, from cellular cytoskeletons to tissues such as muscle and tendon. The presence of such networks in neuronal tissue is known, for example, in the cytoskeleton and extracellular matrix in and around neuronal and glial cells, but their function is believed to be principally mechanical/structural in nature. However, there has long been speculation regarding a broader role for neuronal fibrillar macromolecules, which are anionic polyelectrolytes, specifically regarding their participation in nervous stimulation and transmission. This Perspective reviews literature that spans more than a century, including very recent work, and attempts to build a case for considering a multifunctional role for such macromolecules that includes participation in not only nervous activity but also in diverse phenomena including electric communication within and between cells and mechanisms of anesthetic action. Perhaps the creation and utilization of “artificial axons” is within reach with design rules coming at least in part from fundamental considerations of macromolecular science. © 2015 Wiley Periodicals, Inc. J. Polym. Sci., Part B: Polym. Phys. 2016, 54, 7–14

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INTRODUCTION Biological cells are laden with fibers, from chromatin in the nucleus to the complex and dynamic cytoskeleton. Indeed, Chambers¹ noted long ago that “the physical properties which so fundamentally characterize protoplasm, such as elasticity, rigidity, and imbibition, exist only in virtue of its fibrous structure.” Cells are, in fact, soft materials.² The cell with its cytoskeleton is perhaps rather well described as a viscoelastic, nanofibrous cation exchanger, the latter property being the result of fixed anions from ionized aspartic and glutamic acid units. The presence of polyelectrolytes in a crowded cellular environment can be considered, from a polymer physicist’s perspective, as a “Coulomb soup,”³ and complex intracellular phenomena that can result are only beginning to be studied in detail.

As pointed out by McNiven,⁴ the structure–function relationships between the components of the nanofibrous cytoskeleton continue to be defined and understood. Furthermore, these key nanofibrous components of cytoskeleton, namely, actin, intermediate filaments, and microtubules, are connected through the cell membrane to the materials of the extracellular matrix such as collagen. Cellular assemblies in tissues and organs can thus be considered as a continuous fibrous network connecting nucleus to cytoskeleton to extracellular matrix to many (most?) other cells, with important physiological consequences that likely have yet to be revealed from this complex and quite literal web of interactions. It is therefore most interesting that Needham⁵ presciently remarked in 1936 that “biology is largely the study of fibers.”

Let us now briefly turn attention to irritability, a term used many decades ago to offer a contrast between living and nonliving systems. For example, according to Heilbrunn,⁶ “Exposed to a sudden change in its environment, a living system typically shows a reaction or a response … This characteristic of living material is called “irritability” and, perhaps more than any other vital characteristic, serves to distinguish living systems from non-living.” Muscle and nerve combine to form the prototypical irritable system where a macroscopic effect, specifically motion in the form of muscle contraction, is observed. Muscle has been studied in much detail from a macromolecular perspective beginning decades ago,⁷ and the sliding filament model of muscle contraction is well established. Nerves, on the other hand, have received much less attention in this regard, which is interesting given an admittedly tenuous premise by the author that muscle
and nerve might have evolved in concert. However, a significant body of literature, for example that of Tasaki, contained in two monographs and many papers (cf. refs. 10–13), suggests that fibrous, cation-exchanger macromolecules may play a key role in nervous stimulation and transmission. Others have also supported this view, suggesting that the entire cell surface of an axon, namely, the cell membrane, sometimes called the axolemma, plus the immediately underlying cytoplasmic structure, referred to as the ectoplasm—a polyelectrolyte network and biological ion exchanger—is responsible for the nervous excitation process. Altogether, the neuronal membrane plus underlying macromolecular fiber system has been referred to as the axolemma–ectoplasm complex.

Thus, the main aim of this Perspective is to review these ideas and to extend them with a small refinement, albeit untested, of a mechanism for nervous excitation or stimulation and transmission which involves direct participation of macromolecules. Credit for promoting an awareness of Tasaki’s and related work goes to Pollack, who has also offered much original thinking about cellular phenomena from a macromolecular perspective and who stresses the importance of phase transitions in many biological systems.

NERVE STIMULATION AND NERVOUS TRANSMISSION

The seat of excitability of nerve has generally been believed to be the lipid membrane in which ion channels are activated transiently on stimulation, with signal propagation resulting from successive opening of voltage-gated channels as summarized in Figure 1.

The details of this process represent the foundation of the Hodgkin–Huxley (HH) model and remains the principal basis for rationalizing nervous stimulation and transmission. Recently, however, the HH model has been criticized by Heimburg and Jackson as being confined to an electrical analysis without physicochemical considerations including heat release and absorption (during initiation and termination of a nerve signal pulse, respectively) as well as mechanical changes (swelling and contraction, again during initiation and termination), as previously emphasized by Tasaki. In an attempt to reconcile all of these points, Heimburg proposed that quantized conduction events coupled with reversible thermal and thickness changes can be explained by considering nervous transmission as a “pulse along the membrane” with the propagation of a soliton wave through the lipid bilayer being responsible for nervous transmission (Fig. 2).

Neither the classical HH nor the recent Heimburg models include macromolecules in the mechanism of nerve excitation and signal propagation. Is there a missing link?

MACROMOLECULES AND NERVE PHYSIOLOGY

As noted earlier, it has long been recognized that a macro-molecular network exists just under the lipid bilayer outer membrane of nerve, and this macromolecular network or layer is sometimes referred to as the ectoplasm. This layer has the properties of a cation exchanger and suggests that the protein components are rich in anionic amino acids (e.g., glutamic and aspartic acids, substantially ionized at physiological pH). As summarized by Tasaki, the colloidal state of the surface layer of the nerve and muscle fiber is regulated by a change in the ratio of the concentration of Ca ions to that of univalent cations. They proposed that the process of nerve excitation involves a rapid change from a compact, Ca-rich state to a swollen, Ca-deficient state. It is notable that “They” in the sentence above refers to Loeb and Höber, who made such a proposal over a century ago. Tasaki also pointed out the significance of rapid switching due to a cooperative transition between the compact and swollen states, and this bistability is believed to be crucial to nervous excitation and transmission. Interestingly, modern books on the subject, compare ref. 24, note the presence of this fibrillar protein network but emphasize its role in material (e.g., membrane and secretory protein) transport and the mechanical role of dictating neuron shape. Components of the network include microtubules (outside diameter of about 25 nm), neurofilaments (about 10 nm in diameter), which are related to intermediate filaments in the cytoskeleton of other cell types, and actin-based microfilaments (3–5 nm in diameter). However, no consideration is apparently given to the possibility of a cortical layer of such materials actively participating in nerve stimulation and nervous transmission.

The structure of this fibrillar macromolecular layer has been studied in some detail [ref. 25(a,b); see also ref. 9, Chapter 9], and Figure 9.2 from Tasaki’s book (ref. 9, p. 162) is reproduced below (Fig. 3). Interestingly, the nanofibers are aligned (within about 5° to 10°) along the long axis of the axon.

The finding that these macromolecular fibers are important for nerve stimulation and signal transmission is suggested by experiments wherein the axoplasm (gel inside the axon) is removed and the inside is perfused with appropriate salt solutions with a Ca-containing solution available on the outside. Among the key observations are that (1) the
axoplasm gel is apparently not necessary for nerve excitability; (2) \( \text{Ca}^{2+} \) is essential, but only if present on the outside of the axon, consistent with the old ion-exchange idea mentioned previously; and (3) excitability is lost if the inside of the axon is treated with a proteolytic enzyme, suggesting that degradation of the macromolecular fiber network is linked to loss of excitability.

SYNTHETIC MACROMOLECULAR MIMICS

Tasaki coupled these collective observations with studies on synthetic, polyanionic gels to outline important ideas about the role of macromolecules in nervous transmission. Key observations with spheres or thick fibers of crosslinked poly(sodium acrylate) include volume shrinkage of the \( \text{Na}^+ \)-form on titration with \( \text{CaCl}_2 \), with the transition sharpening in the presence of a bathing salt solution of appropriate concentration. Figure 4 shows a discontinuous volume change for a polyacrylate gel fiber immersed in 40 mM \( \text{NaCl} \) and titrated with \( \text{CaCl}_2 \). The abrupt diameter reduction suggests a cooperative transition at a critical \( \text{Ca}^{2+} \) concentration.

The \( \text{Ca}^{2+} \)-contracted form of the synthetic poly(acrylate) gels was proposed to represent the resting ectoplasm of nerve, with the swollen, \( \text{Na}^+ \)-form being the excited (stimulated) form. The potential importance of this phase transition in nervous transmission has been additionally emphasized by Pollack.

Interestingly, Shashoua demonstrated that bilayer complexes of synthetic, oppositely charged polyelectrolytes such as poly(acrylic acid-co-acrylamide) and poly(dimethylamino ethylacrylate) are capable of spontaneously generating transient electrical signals with d.c. fields that have time constants and amplitudes which are analogous to spike potentials of neuronal membranes. It is of particular interest that polyacrylate membranes exposed at one surface to calcium hydroxide also exhibited spike generation. Subsequently, Huang and Spangler demonstrated oscillatory activity in poly(glutamic acid)/\( \text{Ca}^{2+} \) asymmetric membranes, and it was proposed that ion accumulation in the interfacial region alters poly(glutamic acid) conformation and hence ion permeability.

FIGURE 1 From Ref. 16b: “The basic elements of the Hodgkin-Huxley model. The nerve pulse from the original publication of Hodgkin and Huxley (top left) [17] is generated by the transient opening of sodium and potassium channels (bottom). Sodium and potassium ions flow through the channel proteins that are embedded in the membrane (top right). The corresponding electrical currents can be represented by an equivalent electrical circuit diagram (bottom right). Here, \( V_m \) is the observed membrane voltage. The quantities \( I \) are the ion currents, the \( E_{\text{Na}} \) and \( E_{\text{K}} \) are the Nernst potentials of sodium and potassium. \( C_m \) is the membrane capacitance. Adapted from [16e].”

FIGURE 2 Solitons propagate with a velocity close to the lateral speed of sound of lipid membranes, that is, with about 100 m/s. This corresponds to the pulse velocity of myelinated nerves. See Ref. 16(b).
occur in nerve. In the model, two options for ion exchange account for the exotherm on stimulation, which is known to and excited states of nerve are represented by the Ca\(^{2+}\) and/or Cl\(^{-}\) extracted and the swollen monovalent (Na\(^{+}\)) component may be important. A key premise is that the resting and excited states of nerve are represented by the Ca\(^{2+}\)-contracted and the swollen monovalent (Na\(^{+}\)/K\(^{+}\))-forms, respectively, and that the ionic environment is such that facile switching is allowed between the two states. An excitation (electrical, mechanical, and thermal) destabilizes the resting form, leading to rapid exchange with monovalent ions, principally Na\(^{+}\) and K\(^{+}\). The finding that this exchange is exothermic in inanimate macromolecular ion exchangers can account for the exotherm on stimulation, which is known to occur in nerve. In the model, two options for ion exchange include Ca\(^{2+}\), leaving the polyanionic macromolecular layer and/or Cl\(^{-}\) entering to preserve electrical neutrality if the mobility of Ca\(^{2+}\) for escape from the layer is sufficiently slow. The “interphase” within the fiber between adjacent stimulated and resting zones is bistable, and the excited zone can move (toward the right in Figure 5, although that can occur in both directions) with creation of a new excited zone, whereas the previous zone relaxes back to the resting state. This would be an adiabatic process, consistent with expectations. As noted by Tasaki (Ref. 7, pp. 128–129), termination of an action potential is a spontaneous process. Therefore, for the free energy change \(\Delta G\) to be negative at termination, the endothermic transition to the Ca\(^{2+}\)-resting state must be accompanied by an increase in entropy, and it has been proposed that liberation of water molecules surrounding the expanded Na\(^{+}\)-form on Ca\(^{2+}\) binding is the source of the entropy gain in addition to the polyanion releasing two moles of Na\(^{+}\) per mole of Ca\(^{2+}\) bound.

A key point in Figure 5 is that the lower impedance excitation zone advances axially via a series of closely coupled ion exchange events that occur radially. Thus, the excitation is propagated by a series of successive and very local macromolecular phase transitions. It is suggested here that such an excitation along a microfilament network can occur as propagating solitons. Channels and pumps in the plasma membrane could ensure that the [monovalent]/[divalent] balance is set correctly for a hair-trigger phase transition between resting and excited states. Moreover, as the ectoplasm is bonded to the underside of the membrane, there may be a synergistic coupling between radial ion exchange and the proposed signal propagation in the ectoplasm (e.g., a pulse along the nanofiber matrix) and Heimburg’s “pulse along the membrane” model. It is interesting to speculate about the collapse of the ectoplasm to the resting state as the excitation propagates. Conversion back to the Ca\(^{2+}\)-compacted resting state may not be immediately reversible, with instead ion exchange leading to a more compact (more so than the original resting state) transient state that over a short time relaxes to the equilibrium resting state as a result of the kinetics of multistep ion-exchange processes and water redistribution around mobile ions and macromolecular fixed charges. Such a relaxation process may contribute to the well-known refractory period where some time must pass before an impulse can be triggered once again.

It would be of great interest to elucidate whether macromolecular phase transitions coupled with ion transport make significant contributions to the nerve signal propagation process versus ion transport directly along polyelectrolyte fiber surfaces. Perhaps both mechanisms can be operative depending on specific cell environment conditions. Toward that end, it must be noted that proposals for soliton transport in cytoskeletal proteins, with actin being a major component, are not new. For example, it has been observed that actin filaments, considered as highly charged, one-dimensional polyelectrolytes, can have significant ionic movements along the fiber axis connected to “counter-anionic clouds,” affording propagation of soliton-like, traveling ionic waves. It has been suggested these intracellular transmission lines may be the basis of a wide variety of physiological effects.

We conclude this section with a connection to anesthetic action. Heimburg noted that the mechanism of action of
anesthetics has remained somewhat of a mystery for at least 150 years and that much can be explained by the influence of anesthetics on the melting transitions of lipid bilayers which in turn can influence soliton wave propagation along the bilayer. However, a possible mechanism of anesthetic action could also be associated with the “two-state” ion-exchanging, polyanionic ectoplasm model discussed above. Specifically, any substance that could increase the stability of the resting (Ca\(^{2+}\)-bound) form would render stimulation and transition to the swollen, monovalent-exchanged form more difficult. Many anesthetics are rather nonpolar but also contain dipoles and sites for hydrogen bonding, and many of these molecules may work in complex ways to stabilize multivalent ion-containing polyelectrolytes. Studies of the stabilities of synthetic polyelectrolyte systems in the presence of anesthetics may be a fruitful area of investigation.

As a final thought, it is interesting that plants, which lack formal neurons, are nevertheless affected by anesthetics. Although plant roots (the “brains” of plants) contain membranes and ion channels which may be the locus on anesthetic action, they are also composed of a cytoskeletal network of macromolecular fibers (e.g., actin and microtubules). Perhaps the diminution of excitability in plant roots in the presence of anesthetics is at least partially due to the enhanced stabilization of the resting macromolecular ion complex in Figure 5, thereby raising the threshold for excitability.

**FIGURE 5** Proposed soliton-like mechanism of nervous transmission along ectoplasm fibers: (a) resting (Ca\(^{2+}\)-bound) state; (b) stimulated zone resulting in Ca\(^{2+}\)/monovalent ion exchange and local swelling; and (c) propagation of stimulation through an adjacent interphase region. The process can continue via successive steps in both directions. The degree of swelling is arbitrary.
TOWARD "ARTIFICIAL NERVES"

Although there is a robust research interest in artificial muscles, much less attention has been directed toward artificial nerves perhaps because of a lack of broad material design rules. A few are now offered based on the premise that a key seat of electrical activity in nerve, as outlined by Tasaki, is a nanofibrous network (ectoplasm) that can reversibly exchange monovalent and divalent metal ions, the latter most appropriately being Ca\(^{2+}\). The nanofibers should principally be oriented longitudinally as part of a tubular construct and should contain fixed anions at a desired pH to allow for cation exchange. Importantly, the transition between a compact, Ca\(^{2+}\)-contracted form and a more swollen, monovalent cation-exchanged form should be very sharp such that small disturbances (electrical, thermal, and mechanical) of the stability of the Ca\(^{2+}\)-form can initiate ion exchange.

Much fundamental work on synthetic polyanionic gel beads and threads by Tasaki\(^9\)–\(^12\) and Horkay et al.\(^34,35\) have laid the foundations for simple mimics of the properties noted above. One important conclusion from this work is that the volume shrinkage due to Ca\(^{2+}\) binding by sodium polyacrylate gels is not the result of tight ionic bridge formation but rather the result of an increase in the Flory–Huggins \(\chi\) parameter indicating that Ca\(^{2+}\) binding modulates the solvent quality of water thereby increasing chain–chain aggregation. Polyanionic gels also exhibit interesting electrical properties, including static potentials of negative several tens of millivolts which is curiously in the range of biological cell resting potentials.\(^36\) The broad connection between ion exchanger properties and cell cytoplasm was suggested nearly a century ago by Loeb\(^37\) and developed in more detail by Damadian\(^38\) and Ling.\(^39\)

As a first step toward extending ideas from bulk gels to fibrous constructs of synthetic polyanions, we recently reported\(^40\) on the electrospinning and crosslinking of poly(acrylic acid) (PAA) tubular fiber constructs, with fibers rather randomly arranged, that show reversible length changes when the Na\(^+\)-form it titrated with CaCl\(_2\) and then titrated with the chelator sodium citrate. The reversible length change transition is especially sharp if carried out with the tubes immersed in 150 mM NaCl. Work is in progress to fabricate highly aligned, crosslinked PAA fibers and to study electrical stimulation under conditions of bistability of monovalent–divalent cation exchange in an effort to test the general model outlined previously. It is hoped that at a minimum, efforts to design and fabricate artificial nerves will contribute to fundamental understanding of the behavior of polyelectrolytes and ion-exchanging nanofiber assemblies, aid in the design of improved interfaces that connect neurons with electrodes,\(^41\) make important contributions to the development of smart materials systems and functional artificial neuron construction, and perhaps serve as crude models of the early versions of biological cell assemblages which were capable of exhibiting excitability and motion as well as bioelectric phenomena. It is likely that the potentially complex state of water around networks of polyelectrolyte fibers and attendant counterions will need to be considered for a more full understanding and exploitation of these ideas.\(^42\) Toward that end, it is suggested that important clues lie in literature over many decades which must be acknowledged and critically reviewed.

CONCLUSIONS AND OUTLOOK

A key point of this Perspective has been advocacy of a consideration of nervous excitation and transmission in terms of roles that fibrillar macromolecular systems may play in this important area of physiology. Significant past work points to the intermediacy of macromolecules, and possible directions for the pursuit of "neuromimicking" materials is especially intriguing. Important information about diverse phenomena including electric communication within and between cells, mechanisms of anesthetic action, and cognition and memory,\(^43\) as well as improved therapies for nerve repair and regeneration and mitigation of neurodegenerative and other diseases, may result from considerations of polyelectrolyte fibers as a possible component of the seat of electrical activity in nerves.

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