Exploring Brain Information Storage/Reading for Neuronal Connectivity Using Macromolecular Electrochemical Sensing Motors

Toribio Fernández Otero

This article is dedicated to the memory of my wife.

Dense electroactive gels of conducting polymers, carbon nanotubes, or graphene, constituted by multisensing macromolecular electrochemical motors, are presented herein as model materials to get a physicochemical characterization of the opening/closing cycles of ion protein channels in neurons. The conformational contracted energetic states of these macromolecular motors store both long-term and short-term information packages. Under a potential cycle, the energy of each ionic pulse generated during the channel opening reads the stored information, which is restored during the channel conformational closing. Simultaneously the motor actuation senses the working physical and chemical energetic conditions, transferring to the ionic pulse energy those sensing information packages. A quantitative description of the stored and read information packages is attained from basic electrochemical, mechanical, and polymeric concepts. Translated to ion channel proteins in brain dendrites, it can describe brain information storage mechanisms and the energetic information packages read and carried through each ionic pulse to the action potential.

1.1. Protein Channel Motors and Electro-Chemo-Mechanical Ionic Pulses

Brain functions (memory, proprioception, consciousness, vision, and so on) emerge from synaptic communications between neurons driven by the action potential (AP) generated by chemical reactions involving ATP, molecular machines (ion protein channels), and electric flow (ionic pulses) during the channel opening/closing cycle. Neither synaptic communication’s codes to produce brain functions nor the generated brain changes to store and read information have been identified and decoded yet. The local neuronal changes storing brain information remain unknown.

Neurotransmitters (chemical synapse) and ionic pulses through intracellular ionic channels (electrical synapse) are the main components of the interneuronal information traffic driven by the action potential. The shape of the action potential has been replicated from basic physical and electrical principles by different treatments. Nevertheless, the generation of the action potential, which is generally accepted to be initiated by the ionic flow through the ionic channels (mainly Ca$^{2+}$ and Na$^{+}$), has received little quantitative attention. Each electric ionic pulse arises from the ionic flow generated during the opening/closing cycle of an ion protein channel across the neuron membrane. The different theoretical treatments of the ionic pulses do not pay great attention either to the chemical origin of the biological process or to the macromolecular nature (polymer science) of the protein channels. Nevertheless, it is well known that the channel structure (ion channel mutants) is involved in a variety of diseases, including epilepsy, cardiac arrhythmias, neuropathic pain, and Parkinson’s disease.

1. Introduction

How information is stored, read, and carried between neurons in the brain remains an unsolved scientific question.

T. F. Otero
Laboratory of Electrochemistry
Intelligent Materials and Devices
Technical University of Cartagena
Campus Alfonso XIII, 30203 Cartagena, Spain
E-mail: toribio.fotero@upct.es

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each specific protein channel relaxes, opening the channel and generating the concomitant transmembrane ionic flow. The channel protein acts as an electrochemical-driven macromolecular machine or macromolecular motor. With the ionic flow, both the transmembrane concentration gradient and the concomitant potential gradient drop, recovering, beyond the closing potential threshold ($E_c$), the initial conformational closed–contracted energetic state of the channel protein. The generated transmembrane current pulse (ionic carriers) presents a characteristic maximum. Each pulse includes chemical (ions) and electrical (charges) energetic flow emerging from the conformational (mechanical energetic transition through the opening–closing cycle) movements of the channel proteins. The neuron channels are electro-chemo-mechanical macromolecular motors or electro-chemo-mechanical transducers. Thus, each neuronal AP originated by actuation of many electrochemical protein channels may carry the concomitant chemical, electrical, and mechanical quantitative energetic information packages, which should be transferred between neurons by the associated chemical and electrical synapse. The synaptic action should include the quantitative information stored by and coming from all and every one of the original ionic channels.

1.2. Basic Hypothesis for the Brain Information Storage and Information Reading

In this context, as initial hypothesis we can accept that 1) most of the brain permanent information should be stored as conformational (electro-chemo-mechanical) energetic states by each of the ion channel proteins in the neuron membranes: the channel protein should be the basic unit for information storage in neurons (BIUSN). 2) The energy of each ionic pulse flowing through an ion protein channel during its opening/closing cycle, stimulated by a potential cycle, reads and carries the stored information constituting a carrier unit of neuronal information (CUNI). 3) Every CUNI carries, at least, three basic quantitative energetic codes (chemical, electrical, and mechanical), which can be translated (communicated) to the next neuron through the action potential by the chemical and electrical synaptic components. A good fraction of the quantitative information transferred between neurons to originate brain functions should be collected and carried there.

1.3. Scientific Challenges: Determination of the Conformational Energy of Compacted and Relaxed Folded Proteins

In this context the initial step to explore, understand, quantify, and reproduce brain functions should be identifying the nature of the different elements of quantitative information involved by the actuation of any individual ion protein channel. To attain this aim, a good control of individual protein channels is required, allowing the subsequent electrochemical characterization and quantification of the generated ionic pulse under the influence of different physical and chemical variables of both the channel ambient and the structure-composition states (or conformation-composition energetic states) of the channel protein itself. Our present control of the individual ion protein channels, although increasing very fast, does not allow a full physical-chemical characterization of the channel actuation following the generated current/time peak under different and well-controlled physical and chemical conditions. Several problems emerge: the chemical concentration and temperature ranges required for a good characterization can promote the protein denaturation and, the most important, despite the incredible CASP progress attained during the last decade to predict 3D protein-folded structures, the definition of the open and closed energetic states of channel proteins remains unattainable. Under similar scientific challenges, scientists often try to find model systems or model materials suitable for the experimental quantification and theoretical description of those energetic states and energetic transitions. As an initial step, we can approach those artificial materials used to get computer/brain communication.

1.4. Current Artificial Approaches to Computer/Brain Communication and Challenges

At the moment any attempts to mimic brain functions are based on solid-state physical electronic devices from computers driven by electronic codes. Any direct and reversible communication between computers and the brain must transfer carriers with specific quantitative information by direct current flow: electrons, computer carriers, must be transformed to ions, neuronal carriers, and vice versa, keeping the information. It is generally accepted that any electrochemical reaction happening at any electrode/electrolyte interface is the most efficient quantitative (Faradaic) electron/ion transducer. Scientists use metals or semiconductors as electrodes through the named invasive direct methodologies. The connection fails because neurons do not understand electron’s codes from the connecting electrodes and the present sensors do not understand brain mecano-chemo-electrical codes carried by ions and chemicals through the synapse. The electronic transfer also originates water splitting and strong local pH variations, not compatible for a long time with the neuron life.

New electron/ion transducers are required to build direct communication between electrodes and neurons improving, in parallel, any electrochemical technology. Researchers have substituted the metal electrode by solid-state ionic transistors (transferring ions instead of electrons) to get the computer/neuron communication goal. The lifetime is improved but the question now is how the ionic flow can be modulated to replicate ionic protein channels and their electro-chemo-mechanical signals: the transducer electrode must be constituted by electrochemical macromolecular machines reacting, with the concomitant exchange of ions, inside the water potential window (between hydrogen and oxygen evolution potentials to avoid strong bioincompatible local pH variations).

This scientific field involving chemical- or electrochemical-driven artificial molecular machines or molecular motors is quite recent. Professors Sauvage, Stoddart, and Feringa received the Nobel Prize in Chemistry 2016 by the synthesis of artificial monostep chemical and electrochemical molecular machines. They have opened the way toward the use of materials constituted by electrochemical molecular or macromolecular motors as electrodes for the development of new neuronal interfaces. In parallel, they can allow the replication of either natural macromolecular motors (as ion channel proteins), organs driven by actuation of their constituent macromolecular motors (muscles, brain), or the concomitant biological functions...
originated by their actuation (muscular action, respiration, brain functions, enzymatic reactions). Those model materials could be used for a full physical–chemical characterization of the different conformational (folded) energetic states that can be attained by macromolecular electrochemical motors able to mimic both the opening/closing cycle of protein channels and the generated ionic pulse. Then we can investigate how many packages of quantitative information the generated ionic pulse reads and carries. Here we will describe the state of the art and the future scientific and technological perspectives.

2. Model Materials Constituted by Macromolecular Electrochemical Motors

In this context, any brain model material must be, in an initial approach, a soft and wet dense gel constituted by electrochemical macromolecular motors, ions, and solvent replicating both the nature and the ambience of the protein motor. Under electrochemical stimulation, the material actuation must replicate the opening/closing cycle of ionic channels across the material controlling the flow of specific ionic (anions or cations) pulses. Intrinsically conducting polymers, redox polymers, fullerences, carbon nanotubes or graphene derivatives, among other material families developed in the last decades, can fulfill these conditions. They form electronic conducting and electroactive (by reversible oxidation/reduction reactions) films. They can be used as self-supported electrodes (films, wires, pressed powders) or as films coating metal or semiconductor electrodes in electrolytes. Some of the material families based on conducting polymers exchange anions during reactions: basic conducting polymers, substituted polymers, or composites with nonelectroactive materials. Other families follow a prevalent exchange of cations: self-doped conducting polymers and blends of conducting polymers with macroanions. Subsequently we will focus on those families of conducting polymers exchanging anions (better studied than those exchanging cations) and solvents with the electrolyte during electro-chemical stimuli. To avoid any parallel water electrolysis, some characteristics require the use of organic solvents having a larger potential window than that of the aqueous solutions. The attained conclusions on general application to any model material exchanging cations or anions with the ambient under electrochemical stimulation.

2.1. Replicating Biological Functional Materials

Stimulated by potential cycles or current cycles in liquid electrolytes (Section 2.2) every chain, tube, or nanosheet from films of conducting polymers, carbon nanotubes, or graphenes behaves as a macromolecular electrochemical motor (Section 2.3 and 2.4). The cooperative reversible actuation of those film motors generates/destroys free interchain volume (Section 2.5) by cyclic opening/closing, respectively, of ionic channels (Section 2.5.1) with the parallel flow of a pulse of ions and solvent required for charge and osmotic balance. The material becomes a dense gel constituted by macromolecular electrochemical motors, ions, and solvent. Its reversible actuation replicates the opening/closing cycle of ion channel proteins (macromolecular electrochemical motors) in neuron membranes stimulated by a potential cycle generating the concomitant ionic pulse as an electric peak.

The electrochemically stimulated conformational relaxation (ESCR) model states that during conformational contraction beyond the closing potential (Ec) the macromolecular motors attain rising conformational contracted energetic states. Submitted to potential cycles in liquid electrolytes, the energy of the generated ionic pulse reads and carries quantitative information of the initial conformational compacted energetic state (Section 3). In addition, those macromolecular motors have an unparalleled property: during actuation they respond to, adapt to, and sense the working mechanical, chemical, and thermal conditions and the energy of the generated ionic pulse also drives this quantitative information (Section 3.1 and 4).

Here we will focus on the identification and quantification of the packages of quantitative information stored by the closed–compacted conformational structures, read by actuation of the sensing motor and carried by the energy of the generated ionic pulse.

2.2. Electrochemical Reactions Driving Macromolecular Motors

The energy required to state the transmembrane potential gradient in neuron membranes driving the electrochemical actuation of protein channels comes, as stated earlier, from the ATP reaction. In films of conducting polymers the exchange of anions with the electrolyte is driven by the oxidation/reduction (p-doping/p-dedoping) reaction of the polymer chains, which can be written in its simplest expression (not including the ion-trapping effects) as

\[
\text{Pol}^+ + nA_{\text{solv}} + pS_{\text{solv}} \rightleftharpoons [(\text{Pol})^n]^-(A^-)_{n}\text{gel} + n(e^-)_{\text{metal wire}}
\]

(1)

where Pol represents each active center involving three to five monomeric units of any polymer chain in the film where a π-conjugated polaronic structure (a radical cation; hence, it is called p [positive] doping) is generated by extraction of one electron (one-step oxidation); A− is the solvated monovalent anions from the salt (solved and dissociated) present in the electrolyte that must be exchanged with the polymer film for charge balance; \(S_{\text{solv}}\) is the solvent molecules present in the electrolyte exchanged with the polymer for osmotic balance (broken by the entrance of anions); \(ne^-\) indicates that \(n\) electrons are extracted through \(n\) consecutive steps (each involving one electron transfer and the exchange of one anion) during the chain oxidation; the subscript gel indicates a dense gel structure, and the subscript metal wire means that the electronic exchange from the polymer chains imposed by the potentiostat–galvanostat occurs through the metal wire connecting the generator and the polymer gel. The reversible oxidation/reduction of the material by application of a potential cycle gives a reverse ionic flow (entrance/expulsion) across the polymer/solution interface.

2.3. One-Step Polaronic Motor

In fact, the chain reaction 1 occurs through \(n\) consecutive steps following the first, second, third, ..., \(nth\) ionization potentials of the chain, each involving one electron.
(Pol$^+$) + A$_{solv}^-$ + aS$_{solv}$ ⇌ [(Pol$^+$)(A$^-$)(S)$_n$]$_{gel}$ + (e$^-$)$_{metal}$ \hspace{1cm} (2)

[(Pol$^+$)(A$^-$)(S)$_n$$_{gel}$] + A$_{solv}^-$ + bS$_{solv}$ ⇌ [(Pol$^{2+}$)(A$^-$)$^2$](S)$_{a+}$$_{gel}$ + (e$^-$)$_{metal}$ \hspace{1cm} (3)

[(Pol$^{n-1+}$)(A$^-$)$_{n-1}$](S)$_0$$_{gel}$] + A$_{solv}^-$ + qS$_{solv}$ ⇌ [(Pol$^{n+}$)(A$^-$)$_n$](S)$_p$$_{gel}$ + (e$^-$)$_{metal}$ \hspace{1cm} (4)

Each electronic extraction transforms (Figure 1a) σ bonds between three-five consecutive monomeric units (allowing their free rotation, getting, above the glass transition temperature of the polymer, $T_g$, different possible conformations) into a π-conjugated flat polaronic structure (only a flat conformation is permitted). The reaction drives a small conformational movement of the chain; this is the basic monostep (monoelectronic) polaronic molecular motor. By electrochemical reduction with the injection of one electron to the oxidized chain (backward reaction in Figure 1a), the original conformation is recovered.

2.4. Multistep Macromolecular Motor: Function Amplifier

The consecutive extraction (one by one) of $n$ electrons from the chain (reactions (2)–(4)) at rising potentials related to its consecutive ionization potentials drives large conformational

![Figure 1](https://www.advancedsciencenews.com)

**Figure 1.** a) Five monomeric units from a polypyrrole chain in a film present in the reduced state a σ bond between neighboring monomeric units (first reaction par), guaranteeing its free rotation to attain many conformations. By extraction of one or two electrons, they move to a polaronic, or bipolaronic, respectively, planar π-conjugated structure (second reaction term). Counterions and solvent penetrate from the solution for charge balance in the film and osmotic balance between the film and the solution. The reduction reaction drives reverse conformational movements originating monostep or bistep polymeric motors. b) Any reduced polymer chain attached by one end to a metal electrode should present in an aqueous electrolyte a final coil-like structure as a result of free conformational movements and strong polymer–polymer interactions. During oxidation, the emerging planar n polaronic structures and the concomitant Coulombic repulsions originate conformational movements, giving a stick-like structure. By electrochemical reduction, the chain comes back to the coil-like structure: a reversible multistep (n steps) molecular machine. c–f) 2D view (from the polymer/solution to the polymer/metal interfaces) of the structural variations (swelling/shrinking) induced by the reversible film oxidation/reduction driven by the cooperative actuation (relaxation/contraction, respectively) of the constitutive electrochemical macromolecular machines (chains). The film swelling opens ionic channels through the reactive dense gel. During the film reduction, both the reaction and processes are reversed: the film shrinks by cooperative actuation of the macromolecular machines, expelling anions and solvent toward the solution and closing the intramolecular channels, trapping some counterions in the film (from f back to c). g) 3D structural changes (relaxation–swelling/shrinking–closing–compaction) generated in a cubic material unit by the cooperative actuation of the constitutive macromolecular motors during reversible oxidation/reduction. Adapted with permission. Copyright 1999, Springer.
movements by consecutive formation and actuation of \( n \) polaronic (elemental molecular motor) structures along the oxidation time.\(^{[85]}\) As a consequence, any physical, chemical, or biomimetic property of any monostep macromolecular motor should be amplified (\( n \) times) by our polymeric motor where up to \( n \) monostep molecular motors work during the oxidation completion: the model material should act as an amplifier of any property or function of any chemical or electrochemical monostep macromolecular motor, whether artificial or natural.

In this context, we can imagine an isolated polymeric (e.g., polypyrrole) chain in its reduced state inside an aqueous electrolyte and attached by one end to a mental electrode. If the polymer–polymer interactions are greater than the polymer–solvent interactions, the available free rotations between monomeric units originate at ambient temperature (above the glass transition temperature, \( T_g \), of the polymer) a coil-like structure (Figure 1b).\(^{[68]}\) During the chain oxidation, following reactions (2)–(4) consecutive positive-charged flat polaronic structures emerge along the chain (Figure 1a), originating the chain conformational relaxation pushed by strong Coulombic repulsions between emerging neighboring positive charges and strong polaron–counterion and polaron–solvent attractions. Consequently the initial reduced coil-like structure relaxes, evolving during the chain oxidation by actuation of consecutive monostep molecular motors toward a stick-like structure, surrounded by solvent and counterions (Figure 1b).\(^{[52,68,75]}\) The concomitant events are reversed by electrochemical reduction, recovering one of the possible initial coil-like structures. The chain acts as a reversible multistep (\( n \) steps by exchange of \( n \) electrons) electrochemical macromolecular motor.

### 2.5. Cooperative Actuation of the Film Electrochemical Macromolecular Motors

During any film oxidation (reaction (1) forward) in a liquid electrolyte, the cooperative actuation (conformational relaxation)\(^{[76,77]}\) of the constitutive macromolecular machines (chains) promotes the film swelling. The originated free volume opens interchain channels.\(^{[52]}\) The generated volume guarantees the simultaneous entrance of anions (ionic flow required for charge balance) and solvent (required for osmotic balance) from the electrolyte, getting a soft, wet, and reactive dense gel (Figure 1c,d,f). The final gel content (macromolecular electrochemical machines, ions, and water) replicates, in its simplest expression, the basic functional elements of the intracellular matrix (ICM) from functional cells (e.g., muscle’s cells).\(^{[66,78]}\) The film material swelling propelled by the electrochemically driven actuation of macromolecular motors takes seconds. Similar swelling using films of commodity polymers in solvents (without actuation of chemical or electrochemical molecular motors) takes hours or days.\(^{[79–81]}\)

#### 2.5.1. Replicating Opening/Closing Cycles from Ion Protein Channels

The consecutive events described in the previous section replicate the opening of transmembrane protein channels with the concomitant ionic flow. Here the flow is driven by the opening of a plethora of ionic channels at the film/electrolyte interface.

During reduction (an electron’s injection to chains during reaction (1) backward), the reverse reaction and processes occur: the polymer film shrinks by cooperative contraction of the electrochemical macromolecular machines, expelling anions and solvent toward the solution to keep balance. The intermolecular channels close, trapping a high fraction of the exchanged counterions (up to 40%) when the average distance between chains becomes smaller than the diameter of the moving counterion unity (Figure 1g).\(^{[62,82–85]}\)

Thus, the potential cycle drives the opening/closing cycle of ionic channels through the conducting polymer film.

#### 2.5.2. Conformational Contracted Energetic States in Macromolecular Motors. Energetic Memory

But this is a soft material: after structural closing the reduction–shrinking of the dense gel goes on expelling trapped counterions to get rising conformational compacted energetic states of the chains\(^{[86]}\) (Figure 1g) at higher overpotentials (thus, by consumption of higher energies) and lower reaction rates. The expelled counterions push apart the chains of the rising packed conformational structure to open a way toward the electrolyte. Then, by conformational movements, the chains occupy the volume behind the ions, getting a most compacted conformational energetic structure.

Starting every time from the same oxidized and swollen state, rising reduced and conformational compacted (chemomechanical) energetic states of the film chains are attained, in a very reproducible way, by reduction at rising constant cathodic potentials for a constant reduction time each\(^{[52,87–93]}\) or by applying a constant reduction potential for a rising time each.\(^{[91,94–96]}\) Any of those conformational contracted energetic states of the macromolecular motors remain stable for a long time after interruption of the applied potential: each of them keeps the conformational energetic memory.

#### 2.5.3. Model Materials of Functional Ion Protein Channels

Thus, the film oxidation/reduction cycle drives the actuation of the macromolecular machines and the concomitant opening/closing cycles of intra-macromolecular channels from the polymer/solution interface across the film (Figure 2), supporting the concomitant flow of an ionic pulse. Every attained average conformational compacted energetic state should mimic similar contracted energetic states of different channel proteins each stated by the local physical–chemical conditions at the channel formation time.

The electrochemical reaction (Figure 1a) guarantees that the electronic charge flowing by the external circuit of the electrochemical cell equals the charge driven by the ionic flow through the polymer/electrolyte interface, which is parallel to the conformational relaxation (mechanical) rate of the involved macromolecular machines.

Under these conditions, conducting polymers can be used as model materials to attempt the Physical–chemical characterization of the different energetic states that can be stored by the closed conformations of different macromolecular motors.
nuclei growth giving rising currents and the opening of new ionic channels at the polymer/solution interface end at the chronoamperometric maximum by coalescence of the growing nuclei. From there, the uniform entrance of counterions and solvent through the channel at the polymer/solution interface goes on and the anodic current drops until the film oxidation completion.

The shape of the generated ionic pulse (Figure 3b) replicates at an amplified scale the ionic pulse generated by actuation of any ion protein channel (Figure 4a).

2.5.5. Influence of the Initial Conformational Energetic State (stored information) on the Ionic Pulse

Starting every time from a more compacted conformational energetic state of the film (equivalent to individual protein channels each storing a higher conformational energy of the initial contracted state, or a higher stored energetic memory stated (Section 5.1), by the local physical-chemical conditions at each protein channel formation time), the peak shifts to higher times and lower currents, consuming rising oxidation charges (Figure 4b). Each of the attained responses using model materials is fully reproducible by repeating the experimental conditions. This figure indicates that the shape of the ionic current (current and time at the maximum) includes quantitative information about the energy stored by the initial conformational contracted state of the macromolecular motors (stored conformational energy or stored energetic information).

When submitted to potential steps from the same initial potential (same conformational contracted energetic state every time) under constant electrolyte concentration and constant temperature to a different final potential, Figure 5b[108] and Figure 4a show, respectively, the anionic current flowing through the model material (conducting polymer film) replicates the shape of the potassium current, through a potassium protein channel. Anodic (positive in the conducting polymer) or cathodic (negative in channels) currents indicate the flow of anions or cations, respectively. Time and current scales are orders of magnitude higher (amplifier effect) in conducting polymers: they correspond to the simultaneous actuation of a plethora of ion channels through the polymer/solution interface with conformational relaxation of the chains. During the anodic response, we can visualize (using electrochromic films deposited on a mirror-polished metal electrode) three different regions (Figure 3b). Each current/time response shows an initial sharp peak related to the charge of the electrical double layer. The subsequent minimum indicates the beginning of the movement, by conformational relaxation, of the polymeric motors. This is a nucleation process: the movement of the macromolecular motors starts at those points (nuclei) of the polymer/solution interface having higher chain mobilities [97–101]. The conformational relaxation of the macromolecular motors opens intramolecular channels supporting the entrance of balancing anions from the solution. The

2.5.4. Replication of Ionic Pulses through Ion Protein Channels

Each initial compacted energetic state of the artificial polymeric molecular motors taken part of the film responds to a square potential cycle (the amplitude of which ranges from a few millivolts to 2 V) by flow of an anodic current peak during the film oxidation followed by the concomitant cathodic current peak during the film reduction (Figure 3a; chronoamperometric responses). The current at any time of the peak evolution quantifies (Faraday laws) the number of electrons flowing by the electronic circuit, which equals (Kirchhoff law and reaction (I)) the number of monovalent anions moving across the channels open at the polymer/solution interface by conformational relaxation of the chains. During the anodic response, we can visualize (using electrochromic films deposited on a mirror-polished metal electrode) three different regions (Figure 3b). Each current/time response shows an initial sharp peak related to the charge of the electrical double layer. The subsequent minimum indicates the beginning of the movement, by conformational relaxation, of the polymeric motors. This is a nucleation process: the movement of the macromolecular motors starts at those points (nuclei) of the polymer/solution interface having higher chain mobilities [97–101]. The conformational relaxation of the macromolecular motors opens intramolecular channels supporting the entrance of balancing anions from the solution. The

Figure 2. Reversible-reaction-driven a) conformational movements at the polymer/solution interface showing the opening/closing of the anionic channel and b) concomitant 2D structural changes at the polymer/solution interface driving the entrance/expulsion, respectively, of the anions from the solution during the film oxidation/reduction, respectively. Adapted with permission[68] Copyright 1999, Springer.
the ambient and the conformational structure of macromolecular motors, on the different packages of energetic information that can be read and carried by each generated ionic pulse. Here we will try to identify and quantify these information packages, getting a theoretical description for some of the possible mechanisms used by ion protein channels in the brain to store and read information. As an initial step, we will focus on the empirical description of the information storage and influence of the working conditions on the generated ionic pulses.

3. Quantitative Energetic Information Stored by Contracted Conformations and Read by the Ionic Pulse

Conducting polymer films were submitted to square potential pulses in liquid electrolytes to quantify how the generated ionic pulse is influenced by the working physical and chemical conditions and by the macromolecular motor chemical and physical structure. Thus, we can follow empirically the influence on

Figure 3. a) Chronoamperometric response using a 22 μm thick polypyrrole film submitted to a potential step from −600 mV (maintained 1 min) to 900 mV (30 s) and back to −600 mV (30 s) in 0.2 LiClO₄ acetonitrile solution at room temperature. Reproduced with permission.[68] Copyright 1999, Springer. b) Anodic branches showing the polypyrrole film compacted by cathodic polarization at −1200 mV, maintained for 60 s, and oxidized by a potential step to 100 mV, showing the formation and growth of oxidized nuclei (dark blue) on the compacted and reduced film (yellow) for 0, 3, 5, 8, 12, and 15 s up to the end (consecutive pictures) of the nucleation/coalescence and oxidation processes. Potentials are referred to the Ag/AgClₑₒ₆ electrode. Adapted with permission.[172] Copyright 2003, Wiley.

Figure 4. a) Voltage clamp behavior of variants of potassium protein channel 89 for different activation potential steps: −100 mV to potentials ranging between −50 and −10 mV. Reproduced with permission.[173] Copyright 2006, Wiley. b) Stationary chronoamperometric responses of a polythiophene-coated platinum electrode in 0.1 m LiClO₄ acetonitrile solution, submitted to potential steps from different cathodic potentials, kept for 30 s, indicated on the figure to the same anodic potential of 950 mV every time. Reproduced with permission.[121] Copyright 2008, Elsevier.
the generated ionic pulses of different conducting polymers, the same conducting polymer with different crosslinking degrees, different initial conformational compacted energetic states, different electrolyte concentrations, different temperatures, or arriving to different final conformational relaxed energetic states.

Figure 5a (full lines) shows the attained chronoamperometric responses (ionic pulses) starting from a different conformational compacted energetic state every time attained, as indicated previously, by reduction of the swollen film at increasing cathodic potentials, indicated on the figure, applied for a constant time each. The rest of the experimental variables, the oxidation potential, electrolyte concentration, temperature, and the mechanical conditions remain constant. Greater was the initial average conformational energy stored by the macromolecular motors (the initial conformational compacted state of the polymer chains; Figure 1g), slower was the conformational relaxation/opening rate of the ionic channels, shifting the maximum of the ionic pulse to rising times and lower currents. Those results indicate that the maximum of the ionic pulse (current and time) can carry quantitative information about the average conformational compacted energy stored by the initial contracted state of the macromolecular motors.

Each current/time response is fully reproducible: the initial average energy stored by the conformational compacted structure is recovered at the end of the applied square potential cycle by the film reduction at the initial potential for the same reduction time. Thus, at the end of the potential cycle the initial energetic state of the conformational contracted structure is recovered.

If we do not consider that we start from different initial conformational compacted states of the macromolecular motor results shown in Figure 5a should result counterintuitive from an electrochemical point of view: a higher initial concentration of reduced states attained after reducing the material at rising cathodic potentials should give, following the basic reaction (1) rate equation, faster subsequent oxidation reaction rates instead of the observed decreasing experimental oxidation rates (decreasing currents).
3.1. The Stored Conformational Energy Is Influenced by the Local Electrical, Thermal, and Chemical Conditions: Sensing Information Packages

When the experimental procedure was repeated beginning every experiment from the same average conformational energetic state changing one of the reaction electrical (oxidation–relaxation potential), chemical (salt concentration, solved anion, or solvent), or thermal variable, every time the chronomperometric responses (ionic pulses) showed (Figure 5b–d, respectively) how the local energetic conditions induce some maximum shift. The higher is the local energy (electrical, chemical, or thermal), the faster does the oxidation–relaxation process shift the maximum toward shorter times and higher current densities. These facts mean that the reaction-driven actuation of the electrochemical macromolecular motors senses the local working physical and chemical energetic conditions: they are sensing motors behaving as thermo-electro-chemo-mechanical transducers. This sensing information is read and carried simultaneously to the conformational energy stored by the initial contracted state by the generated ionic pulse.

As conclusion, the maximum of the ionic pulse can carry quantitative information about: the conformational energy stored by the initial compacted state and the rate of conformational movements (current per unit of time) during the opening/closing cycle (mechanical information); the chemical nature of the ionic flow and the ionic and chemical concentrations (chemical information); the driving potential gradient, the flowing electric (ionic) charge, and, probably, the involved electrical energy (electrical information).

3.2. Quantitative Description of the Molar Conformational Energetic Components: Stored Conformational Energy or Stored Memory

The empirical study of the reaction (1) kinetics using model materials provides a quantitative determination of the stored and released molar conformational energies of macromolecular motors under different experimental conditions. The ESCR model and its relative the conformational or structural chemical kinetic (SCK) model give the keys for a quantitative decoding of the different information packages read during the actuation of the macromolecular motors and carried by the generated ionic pulse.

The ESCR model states that any reaction (chemical or electrochemical) driving macromolecular conformational or allosteric movements of the involved macromolecular motors opening ionic channels includes three molar energetic components: the energetic transition of the macromolecular system (conducting polymer electrolyte here or protein-neuron membrane extracellular and intracellular matrix for nervous pulses) between the initial (conformational compacted) and conformational relaxed state in the absence of reactions or electric fields (ΔUr), as defined by polymer science; the increase of the molar conformational energy stored by the polymer reduction–compaction (ΔUc) (or the equivalent initial conformational energetic state of a closed–contracted channel protein); and the drop of the molar conformational energy by oxidation-conformational relaxation (–ΔUr) or molar energy consumed (required) to relax the contracted conformational states opening the intramolecular ionic channels and allowing the concomitant ionic flow, which corresponds to the energy provided by the transmembrane potential gradient to relax and open the ion protein channel.

Thus, the molar energy (U) involved by the actuation of any electro-chemical-driven conformational movement of artificial or biological macromolecular machines results from the sum of these three molar energetic components

$$\Delta U = \Delta U^* + \Delta U_c - \Delta U_r$$  \hspace{1cm} (5)

3.3. Relaxation Time and Relaxation Current

The actuation of any conformational compacted macromolecular motor begins under conformational relaxation kinetic control, followed by the ion diffusion kinetic control. By similitude with the concomitant responses attained in any other relaxation model (magnetic, mechanical, or electrical), current and time at the chronomperometric (or protein channel ionic pulse) maximum (relaxation time or relaxation current) are exponential functions of both, the involved energy defined here by Equation (3) and the working temperature (T).

$$t_{max} = \frac{\phi_{max}}{z_e - 2}$$  \hspace{1cm} (6)

where $\phi_{max}$ is related to the cylindrical geometry of the conformational relaxation process. Equation (6) describes that the peak of the ionic current generated during the conformational relaxation of the macromolecular motors reads the conformational energy stored by their initial compacted structure, $\Delta U_c$, carrying this quantitative information. Moreover, it carries quantitative information related to each of the energetic components of the conformational energetic transition, $\Delta U^*$ and $\Delta U_r$, which will respond to (and sense) the working physical and chemical conditions.

For conducting polymers, the molar conformational energy of packed conformations ($\Delta U_c$) is the applied overpotential of reduction–compaction, $\eta_c$ (mV), times the charge consumed to reduce–compact 1 mole of polymeric segments, $z_e$ (mC)

$$\Delta U_c = \eta_c \cdot z_e$$  \hspace{1cm} (7)

where the compaction overpotential, $\eta_c$, is the applied reduction potential ($E$) related to the closing potential ($E_c$): $\eta_c = |E - E_c|$ [111] By similitude for protein channels $E_c$ is the transmembrane potential threshold for the channel closing/contraction.

The relaxation molar conformational energy ($\Delta U_r$) in conducting polymers is the oxidation–relaxation overpotential, $\eta$ (mV), multiplied by the charge consumed to relax 1 mole of polymeric segments, $z_i$ (mC) (Equation (8))

$$\Delta U_r = \eta z_i$$  \hspace{1cm} (8)

where the oxidation–relaxation overpotential is $\eta = |E - E_0|$, $E$ being the applied oxidation potential and $E_0$ the standard oxidation potential of a noncompacted polymer. By similitude for protein channels $E_0$ is the minimum transmembrane potential threshold required for the channel relaxation, $E$ being the...
transmembrane potential driving the channel opening and the flow of the ionic pulse.

The constants $z_c$ and $z_r$ are attained empirically\cite{111,113}. $\Delta U_c$ and $\Delta U_r$ become empirical magnitudes.

### 3.4. The Activation Energy of the Driving Reaction Also Includes the Stored Conformational Energy, or Stored Memory

In addition, the current at the maximum gives the initial rate (flowing charge per unit of time carried by both electrons in the electric circuit or ions through the polymeric channels at the polymer/electrolyte interface) of the reaction-driven conformational energetic movements.\cite{116,119}

Following chemical-kinetic methodologies, the empirical activation energy of the driving reaction ($E_a$) is attained using those reaction rates measured at different experimental temperatures.\cite{112}

By repeating now the procedure starting from a different conformational relaxed or conformational compacted state every time, a different activation energy was attained for every experimental series. The final result is that the empirical activation energy of the reaction driving the macromolecular motors includes the three molar conformational energetic components from Equation (5)\cite{112}

$$E_a = RT + \Delta U^* + \Delta U_c - \Delta U_r \tag{9}$$

Through Equation (9), the chemical kinetics becomes conformational, allosteric, mechanical, or structural chemical kinetics (SCK).\cite{112,120}

The activation energy includes quantitative information about the initial (stored–compacted) conformational energetic state of the molecular motor under well-defined empirical conditions. The activation energy ($E_a$) of any reaction-driven conformational movements of the reacting macromolecular motors rises (Figure 6a; presented in Figure 6b as energetic conformational states vs the reaction coordinate) as a linear function of $E_a$ or, taking into account Equation (7), a linear function of the molar compacted conformational energy, $\Delta U_c$ of the initial state. Thus, Equation (9) and Figure 6 mean that the conformational energy stored by the initial state of the macromolecular electrochemical motor described by Equation (7) can be experimentally attained from the activation energy of the reaction driving the actuation of any electrochemical macromolecular motor.

When we start the material oxidation using a shrunk film (or an equivalent relaxed ionic channel) attained by reduction at any potential lower than the closing potential ($\Delta U_r = 0$), the activation energy under the aforementioned experimental conditions, $(E_a)_0 = RT + \Delta U^* - \Delta U_r$, becomes a constant (Figure 6a), as described by present chemical and biochemical textbooks.

As conclusion, the activation energy of any reaction driving the actuation of macromolecular machines is no longer a constant magnitude including (Equation (9)) two components: the electro-chemo-mechanical energy stored by the initial conformational compacted (or contracted) state ($\Delta U_c$) and the constant chemical activation energy ($E_a$) attained when the initial state for the reaction-driven transition (actuation of the macromolecular motor) is a partially relaxed–open conformational state. The ESCR model describes, through Equation (9), the different conformational compacted energetic states (Figure 6b) attained using different conducting polymers in different electrolytes (salts and solvents).\cite{75,118,121,123}

If translated to ion protein channels, these compacted energies should quantify the energetic levels stored by different protein channels: the stored memory.

---

**Figure 6.** a) Evolution of the experimental and theoretical (Equation 7) activation energy ($E_a$) for the polypyrrole oxidation by a potential step to the same oxidation potential as a function of the cathodic potential of reduction–compaction ($E_c$) for a constant reduction time (rising initial energetic states of packed conformations attained at more cathodic potentials). Reproduced with permission.\cite{174} Copyright 2008, Elsevier. b) Initial energetic states (relaxed or conformational contracted), activated state, and final oxidized state as a function of the reaction coordinate: the activation energy for the oxidation is constituted by two components, the constant electrochemical activation energy and the energy required to relax the initial packed conformations of the polymer chains. Adapted with permission.\cite{120} Copyright 2017, RSC.
4. Self-Multisensing Motors: The Macromolecular Motor Actuation Responds to (Senses) the Working Conditions

As stated in the two previous sections, each ionic pulse generated by macromolecular electrochemical machines responds to the local chemical, thermal, etc., working conditions by shifting the maximum of the ionic pulse (Figure 5), acting as a thermo-electro-chemo-mechanical transducer. Thus, the actuation of macromolecular motors provides an unparalleled property: it senses the working physical and chemical conditions behaving as a self-multisensing motor. As electrochemically driven devices, they must follow the Butler–Volmer basic equation of electrochemical kinetics. From there, taking into account that the evolution of the charge consumed at any reaction time defines the concentration evolution of the active macromolecular centers (see below) in the film, we can describe the evolution of both the motor potential and the consumed energy during the macromolecular motor actuation. The evolution of the energy consumed during the motor actuation time (the energy of the ionic flow) results [126,127]

\[
U_n(t) = Q_n E = i_n \int E(t) dt
\]

\[
= E_0 + Zf_i t + \Delta E(n - 1)i_n t + \frac{\Delta (PV)}{1 - \alpha} F
+ \frac{RTt}{1 - \alpha} F \{a \ln[A^+] - b \ln([PP]_{\text{initial}} - \frac{\omega}{k'FV}) - 1 \}
- \ln \left( \frac{\beta}{k'FV} \right) - \ln k_{a_0}
\]

(10)

describing a new multisensing principle: the evolution of the energy consumed by actuation of the macromolecular motors (natural or artificial) should respond to, adapt to, or sense, instantaneously, the mechanical, \(\Delta(PV)\), thermal \((T)\), chemical \([A^+]\), or electrical \((i)\) working conditions, or any instantaneous perturbation of those magnitudes, where \(\omega\) is the rate of motor displacement \((\omega = k_i a_i)\), \(\beta\) is the amplitude of the displacement \((\beta = k'q_\alpha)\), where \(k\) and \(k'\) are constants, \(k_{a_0} = A_0 \exp(-\Delta G_{a_0}/RT)\) is the standard rate coefficient, \(\alpha\) is the electrochemical symmetry factor, \(E\) (V) is the potential passed applied to the material, \(E_0\) is the standard potential, \(P\) (N m\(^{-3}\)) is the working pressure, and \([PP] = q_\alpha(t)/FV\) describes the evolution of the concentration of active macromolecular centers during the reaction time, \(q_\alpha(t)\) being the anodic charge consumed by flow of the constant current during a time \(t\) (s). [128] During actuation in a constrained electro-chemo-mechanical macromolecular motor, the energy of the generated ionic pulse (electrochemical response) instantaneously adapts to (Equation (10)), responds to, and reads any change of the local physical and chemical working energetic conditions, becoming a self-multisensor. [129–132]

Both the charge and current at the chronocoulometric peak respond to and sense (carrying quantitative information about) the working energetic conditions (Figure 5b–d). Thus, the permanent conformational energetic memory (permanent memory) stored by a closed–contracted macromolecular ionic channel will experience during the opening/closing cycle minor shifts, in a reversible way, induced by the local physical and chemical conditions (short-term memory of the local conditions) at the actuation time. Those temporal changes of the permanent conformational energetic memory will be read and erased by the next ionic pulse storing now, during the channel closing, quantitative information about the new local chemical, thermal, mechanical, or electrical working conditions. Thus, any information stored as a minor change of the permanent conformational energetic memory disappears after being read by a new opening/closing cycle: it constitutes the short-term storage of the local sensing energetic information packages or short-term memory.

The theoretical sensing Equation (10) was empirically corroborated using different model materials in different electrolytes following the variation of one of the energetic variables every time. [78,128,130,133,134] At the moment, we have not developed the experimental methodologies to change simultaneously two or more ambient variables to investigate the splitting of the two energy components from the generated ionic pulse. This could help understand how different ion protein channels from neurons respond specifically to the mechanical, thermal, or chemical components of the energy with the concomitant differentiation of the sensing effects by brain.

The theoretical sensing equations describing the responses to potential or current driving cycles were also attained from the basic equation of the driving reaction rate. [78,135]

The sensing responses to each of the involved physical and chemical conditions have been empirically studied and theoretically described for different electrochemical methodologies using films of carbon nanotubes [105–130] or graphenes [140–142], this is a general property of macromolecular electrochemical motors.

Translated to channel proteins, the energy of every generated ionic pulse can drive simultaneously quantitative information of both the long-term stored conformational energy and the short-term sensing information related to the different physical and chemical conditions. Nowadays technologies do not offer any equivalent motor infroming by itself during actuation of both the actuation magnitudes (position and movement rate) and the sensing ambient physical and chemical conditions being all the concomitant information packages included simultaneously in only an electrical (ionic) pulse.

Summarizing, the electrochemical actuation of any macromolecular motor reads both the permanent energetic conformational memory stored by its conformational compacted structure (long-term memory) and the local physical and chemical energetic conditions (short-term memory). These packages of quantitative information—the stored permanent conformational energy and the local mechanical, [128] chemical, [113,135] thermal, [78,136,143,144] and electrical [145,146] energetic conditions—are carried simultaneously by the energy of the generated ionic pulse (Equation (9) and (10)).
4.1. Temporal Physical or Chemical Interruption of the Nerve Pulses

Otherwise Equation (10) describes the interaction between the actuation of the macromolecular motors, the energetic elements carried by the generated ionic pulses, and the local mechanical, chemical, electrical, and thermal conditions. If any nervous pulse transferring information between neurons in the brain or between the brain and organs is a result of the cooperative actuation of protein channels in neurons, Equation (10) can constitute the physical chemical foundation for a quantitative description of the local mechanical, chemical, electrical, or thermal specific limiting conditions required for a temporal suspension (anesthesia) of the neuronal communication.\textsuperscript{[147–149]} The theoretical description of this empirical medical and biological anesthetic field could be improved now.

5. Long-Term Stored Energetic Information and Related Structural Changes

Summarizing the previous sections by submitting a film of the model material to consecutive square potential cycles, or square current cycles, in a liquid electrolyte the average electro-chemo-conformational energetic memory stored in the macromolecular motors by their initial conformational compacted structure (Figure 6b) is read and erased and rewritten during a full oxidation–relaxation/reduction–compaction cycle. The energy of the ionic pulse generated during the channel opening/closing cycle reads and carries (Equation (5)–(10)) the different packs of stored and sensed energetic information.

If those conclusions can be translated to the electrochemical macromolecular motors constituting the ion protein channels in the neuron dendrites, the energy of the ionic pulse generated during the channel opening/closing cycle (driven by a potential cycle) reads and carries quantitative information about the long-term conformational energy stored (permanent stored information or energetic memory) by the initial compacted state (Figure 6b). The initial basic compacted state of each channel is recovered at the end of the potential cycle during the channel closing.

5.1. The Energetic Context at the Macromolecule Formation Time Imposes the Permanent Stored Memory

The molar conformational energy stored in conducting polymers (electro-chemo-mechanical energetic memory) under well-defined control conditions was stated by the physical and chemical conditions at the polymerization time.\textsuperscript{[157,121,150,151]} Translated to protein channels, the basic long-term conformational (electro-chemo-mechanical) energetic memory stored in the compact folded conformational state should be different for every protein channel, being defined by the local physical and chemical conditions at the channel formation time. Those local chemical conditions must be originated by the visual, olfactory, taste, or emotional conditions, among others, around the neuron membrane at the protein time of the channel’s birth. Thus, each protein channel is expected to store a different basic permanent energetic (electro-chemo-conformational) memory stated at its formation time. Along the channel life, each ionic pulse generated by a potential cycle will read this stored energetic memory when the channel opens, being restored when the channel closes at the end of the potential cycle.

6. Brain-Stored Conformational and Structural Memory

Under these conditions at a defined brain lifetime, the ensemble of long-term basic conformational energetic states of all the ion protein channels in the brain should define the brain conformational energetic and structural state of the living being. The full conformational energy stored by the ion protein channels in the brain after a lifetime and the specific treatment of this information by the different brain regions should quantify and define both brain functions and the individual rational and irrational personality (life and dreams) of any animal or human being at that time.

The formation of new channel proteins under everyday specific experiences, each storing a characteristic energy defined by its conformational compacted state (or after an irreversible chemical transformation in any old channel protein; see later), should constitute the basic structural brain transformations by everyday experiences, modifying continuously the long-term information storage in any animal brain. Each channel protein should constitute a single basic piece of long-term (permanent) electro-chemo-conformational energetic memory, permanent stored energetic information, or permanent chemo-conformational brain energetic and structural state.

6.1. Irreversible Conformational Transformations and Functional Diseases

This basic stored energetic memory, or reference memory, in a channel of the model material can be perturbed in an irreversible way (long-term memory perturbation) by deep local physical–chemical changes giving transformations originating irreversible changes on the inter or intramolecular forces, formation of new ionic bonds by ion-trapping effects, or by permanent intra- or intermolecular cross-linking (degradation) reactions.\textsuperscript{[152–154]} Then, any chronosomperometric response to a potential stimulus reads this new permanent macromolecular energetic state, which is restored at the end of the cyclic potential pulse. In each channel protein, those irreversible structural changes produced by strong permanent and local physical or chemical changes can be linked to permanent disorders in the brain or neuronal functions, as mentioned in the Introduction.

7. Information Packages Carried by the Ionic Pulse Originated by the Self-Sensing Motor: Summary

Summarizing any electro-chemo-conformational macromolecular machine is a multifunctional self-multisensing-motor that, during any cyclic actuation (opening/closing) driven by a potential or current cycle, originates an ionic pulse. The pulse electrical energy reads and carries quantitative information about both the
motor actuation (position and movement rate) and the sensing working mechanical, chemical, electrical, and chemical energetic conditions. One cyclic electric pulse drives one motor that, simultaneously, acts as several sensors.

If the information attained from the model materials can be translated to each ionic pulse generated through a protein channel, the information carried by the shape (charge and energy at any pulse time) of each generated ionic pulse (the basic unit for information storage in neurons, BU1SN) drives five packages of energetic information quantified by Equation (5)–(9)—electrical information pack: 1) the initial transmembrane potential gradient opening the channel and driving the ionic pulse (\( q \), Equation (8)); 2) the experimental current and charge (number of ions times the charge of each ion) flowing by the channel after any pulse time (Figure 5 and 6), and 3) the electrical energy at any pulse time (Equation (10)); chemical information pack: 4) the rate of the driving electro-chemo-conformational reaction (current and time, Equation 6, at the maximum), 5) the ion concentration (Equation (10)), and 6) the chemical nature of the flowing ion; thermal information pack: 7) the working temperature (Equation (6) and (10)); chemomechanical information pack: 8) the initial conformational energetic state of the closed-channel protein (long-term stored energetic information or energetic memory, Equation (5), (6), (7), and (9)), 9) the conformational energetic state of the open (relaxed)-channel protein (Equation (5), (6), (7), and (9)), 10) the conformational (or allosteric) activation energy of the driving conformational reaction (Equation (9)); and sensing information pack of the 11) electrical, chemical, thermal, and mechanical conditions of the channel and channel surroundings (Equation (10)), including any instantaneous variation of those conditions.

This huge amount of quantitative information per ionic pulse being carried by a very low amount of flowing charge and being pushed by a few-millivolt potential gradient across the channel could explain why the nervous system and brain (electro-chemo-conformational wet organ) can store, drive, and treat massive amounts of information consuming a very small amount of chemical and electrical energy. Comparatively many orders of magnitude higher amounts of electrical energy are required to treat similar information packages by current solid-state computers (electronic dry devices).

8. Biological Perspectives

The corroboration of both information storage and a neuron’s connectivity (conveying the information provided by the protein channel to both the action potential and the synapses) transferring the different packages of quantitative information between neurons should initiate the long scientific way toward a quantitative description of brain connectivity, information treatment by the different brain parts, and the final quantitative description of the different brain functions (and malfunctions).

Here we have presented how motor proteins from the ionic channel could store both long-term and short-term quantitative information (memory), which is read by each ionic pulse generated by any opening/closing channel cycle, replicating that of the voltage-type-ion channel.

The use of substituted monomers (pyrroles, thiophenes, anilines, and so on),[51] the substituents of which can act as chemical receptors, gives substituted conducting polymers. When the interaction between the substituent and the receptor changes the conformational energy of the polymeric chain, allowing the opening of the channels, the new model materials can replicate receptor-type ion channels. If we accept that the previously presented long-term and short-term information storage describes the ways to store and read conformational information, Section 7 still should describe the stored information packages, now gated by the receptor interaction.

The next step should be corroborating that different ion channels (i.e., sodium channels) in neuron membranes checked under the same physical and chemical conditions (potential cycle, electrolyte concentration, temperature, pressure) give different chronoamperometric responses because they store different conformational energetic states. The expected results should be similar to those shown in Figure 4b, taking into account the amplifier effect of the model material: the initial and final potential must be constant here because the different initial conformational energetic states that we expect were generated here by the specific local physical chemical conditions at the channel formation time. Those results should open the way to investigate how the action potential is generated by actuation of different ionic channels and how it collects the quantitative information from the ionic pulses generated by each of the actuating ion channels.

The brain and brain functions could be reconsidered now from a new quantitative perspective, opening new experimental and theoretical possibilities for neuroscientists, behavioral scientists, chemists, biochemists, physicists, engineers, robot designers, and computer designers, among others. The experimental methodologies here used can be translated to ion channels to corroborate the conformational energetic states of each of the different protein channels.

8.1. Toward the Description of Biological Functions by Physical–Chemical Equations

Despite the fascinating developments of physical and chemical models during the last century, one of the basic questions at the borders of scientific knowledge is why biological functions have not been described yet by predictive physical–chemical equations. If we accept that life and biological functions are based on biochemical reactions, the second question should be, which aspects of the functional biochemical reactions have not been considered yet by chemical and biochemical models? The answer, related to the subject of this article, is that most of those reactions involve macromolecular motors as reactants and the chemical models described by current textbooks do not take into account that the reaction drives their conformational movements. Chemical and biochemical models from the textbooks do not include those conformational and structural changes. Only quite recently the ESCR model and the SCK model initiated the theoretical description involving basic chemical, electrical, and mechanical principles (Equation (5)–(10)). Now the way is open to go on corroborating these theoretical descriptions when applied to biological macromolecular motors and describing in a
most precise and predictive way any biological function and malfunction based on their actuation.

8.2. Proprioception: Quantitative Approach after Description of Self-Multisensing Macromolecular Motors

Cells from different organs took advantage of the great effort developed by nature to attain by evolution chemical-driven multifunctional macromolecular sensing motors, developing, using those tools, other biological functions as muscular actuation based on haptic muscles. Haptic muscles involve macromolecular motors (e.g., actin–myosin–ATP reaction), a motor neuron driving brain orders through nervous pulses, a sensory neuron translating mechanical, thermal, and chemical information from the muscle to the brain, which treats the information, taking decisions and sending back new orders to control the muscle movement. The brain is aware at any time of the muscles’ position, movement rate, and relative position related to any other body part. The ensemble involving several muscles originates mechanical proprioception. Now, using electrochemical sensing motors from conducting polymers (and other electroactive materials) we can construct artificial devices replicating muscular actions. Thus, multisensing artificial muscles1353 and tactile artificial muscles1356 replicating haptic muscles have been constructed. Mimicking the two connecting neurons in muscles, actuating and sensing information packages (charge, current, muscle potential, and involved energy) are simultaneously available, at any actuation time, in the only two connecting wires. The same physical–chemical equation here presented (Equation (10)), attained from the conformational chemical models describes the empirical self-awareness results.130 Now these artificial devices with a primitive proprioception can be designed and checked providing feedback information to understand proprioception and to improve treatments of proprioceptive troubles in human beings.

In addition, the physical–chemical characterization and theoretical description of these devices based on the actuation of electrochemical macromolecular motors have provided and will continue providing some of the quantitative theoretical descriptions of the macromolecular sensing motors, such as those presented in this article, paving the way for and supporting the long and complex journey to deciphering brain functions.126,128,130,145,157

8.3. Ectotherm Animals

When our artificial macromolecular motors are used as model materials of the muscle sarcomere, we can characterize the influence of the experimental temperature between 5 and 50 °C on the energy consumed to perform the same reaction extension, which is equivalent to say the same muscular displacement every time.78,148 A similar thermal characterization of artificial muscles corroborates that electrochemical macromolecular motors behave, simultaneously, as thermomechanical transducers. As a result, muscles harvest thermal energy from the thermal ambient, saving up to 60% of the consumed electrical energy to perform the same displacement when the muscle temperature increases from 5 to 45 °C. Equation (10) describes the results providing, if translated to ectotherm muscles, an initial step to describe some of the physical–chemical reasons behind the selection by nature of ectotherm animals.

8.4. Hypothesis for the Origin of the Nervous Pulse Informing the Brain about Any Organ’s Working Conditions

Otherwise, if the energy of the muscular reaction involving actin and myosin macromolecular motors instantaneously adapts to (and senses) the working mechanical, chemical, electrical, or thermal conditions (Equation (10)) a fraction of this energy could generate (solving a pending point) in the concomitant sensing protein channels at the sensory neuron/muscle cell interface the nervous pulse transferring to the brain this full package of quantitative information.1138 In a similar way, the energy of the reaction driving the actuation of any organ constituted by macromolecular motors must follow the same sensing equation and a fraction of this energy will act on the concomitant neuron terminals, generating the nervous pulse informing the brain. The confirmation of this point can help to solve the pending point of how the nervous pulses are generated by the body organs to inform the brain, paving the way to predict and solve muscular and biological malfunctions related to problems on the organ/brain communication.

8.5. Biological Functional Asymmetry: Why Protein Channels Only Allow One-Way Ionic Flow

Scientist still have not discovered the physical–chemical reasons behind the fact that many biological functions are asymmetric: muscles only work by contraction, nervous pulses only move from dendrites to axons, ionic channels only allow one-way current flow (even against the concentration gradient), enzymatic allosteric reactions are one-way reactions, and so on. As a fortunate exception, respiration (hemoglobin–oxygen allosteric reactions) is a two-way reaction.

Now we can quantify the energy consumed by both, direct and reverse reaction 1 using our materrial models. Whatever the used conducting polymer or the electrolytic media, by consumption of the same oxidation and reduction charge (charge reversibility) the evolution of the electrical energies consumed to open/close the material channels always presents a great asymmetry or hysteresis.112,159 This great energetic asymmetry of the reverse-reaction-driven conformational processes (conformational relaxation–swelling vs shrinking–closing conformational contraction) could pave the way to describe, from Equation (10) and the concomitant for the reduction reaction, biological asymmetry. Translated to biological macromolecular machines, this mean that among the two reactions (forward and backward) involving different electrochemical molecular motors, evolution has selected and improved the most efficient from an energetic point of view to develop the required asymmetric biological function.

9. Technological Perspectives

In parallel the construction, characterization, and theoretical description of new bioreplicating devices and computers
constituted by electrochemical macromolecular sensing motors should provide feedback quantitative knowledge to support brain function’s description.

9.1. Artificial Chemical Synapse

The polymer oxidation/reduction (reaction (1) backward) inside the water potential window (Figure 1a) constitutes a biocompatible electron/ion-sensing-transducer (transduces an electronic signal from computers to ionic signals generated by actuation of macromolecular motors, which can interact with ionic protein channels in dendrites, and vice versa) required to build artificial chemical synapses for neuron/computer direct communications.[160] Different materials give electron–anion, electron–cation, or electron–molecule transducers constituting a new open door to advance in the practically empty room of computer-neuron quantitative communication. Using different electroionic components, new devices can be constructed replicating present electronic devices but using different ion carriers instead of the only electron carriers in present microelectronic devices. As the final aim, most realistic neuronal networks can be developed in the future replicating synaptic communication.

9.2. Smart Membranes

One of the main coming human problems is water availability for both drinking and agriculture. Nowadays membranes and their energetic (economic) requirements limit water decontamination and desalination. Present technologies use nanoporous membranes with constant pore diameters, which are very far from natural membranes using opening/closing ion channels. Our model materials follow Faradaic processes (reaction (1)). Any intermediate oxidation state, which means any intermediate material swelling state with any average transmembrane channel diameter (Figure 1), can be attained under control of the consumed oxidation charge. The process is reversible and the average diameter of the interchain pores can be diminished, under control of the electrochemical reduction charge. In addition, we have model materials allowing a prevalent flow of anions and other materials with a prevalent conduction of cations.[54,161,162] These facts will allow the development of smarter and more bioreplicating artificial membranes with a reversible control through the oxidation/reduction charge of the average diameter of the ionic channels, the transmembrane ionic diffusivity, and the transmembrane ionic migration rates for different specific ions.[163–165] Smarter membranes can provide cheaper and faster desalination processes.

9.3. Artificial Muscles, Actuators, and Robots with Artificial Proprioception

Likewise, the reversible Faradaic control of the film volume variation replicates muscle’s actuation allowing the development of artificial muscles working by cooperative actuation of the constitutive molecular motors, as they do natural muscles.[129,155,166–169] The availability of sensing muscles, previously described, and a computer paves the way toward the development of an old engineering dream: the construction of artificial tools and robots with primitive self-awareness or proprioception.

9.4. Smart Batteries or Supercapacitors

Figure 1c,d,f,g show a 3D electrode at the molecular level. At the swollen, oxidized, or charged state each chain stores n positive charges. The 2D electrical double-layer characteristic of any electrochemical process (from any electrochemical device) as described by current textbooks has disappeared. Positive charges along every chain are compensated by counterions surrounding it: this is a monodimensional electrical double layer along each polymeric chain. The charged material is a 3D electrical double layer constituted by the ensemble of the monodimensional electrical double layers of the chains from the polymer film. This means that for those electrodes taking part of batteries all the charges stored on the electrode chains are simultaneously available at any discharge (reaction (1) backward) time: as it happens with capacitors. This fact constitutes a braking point related to traditional electrodes; e.g., for a battery metal electrode, even using metal nanostructures, any metal atom inside the structure can only give its electrons by oxidation when the advance of the 2D double layer from the oxidized nanostructure surface attains that atom. Thus, those materials constituted by electrochemical macromolecular motors open a new way to get fast and ultrafast batteries: the charge/discharge processes follow reaction (1) forward and backward, respectively. Their fast charge/discharge processes and the fact that the stationary oxidized state behaves as a 3D electrical double layer pushed the scientific community to consider them as supercapacitors. The actuation of the macromolecular motors (relaxation, swelling, contraction, compaction) can be the rate-limiting steps for the battery charge/discharge, requiring deeper investigation for its technological implementation. During charge/discharge, they must follow reaction (1) and Equation (10) and consequently they must work as sensing batteries informing by themselves about the charge and energetic states, or about the kinetic limitations, at any working time.

In addition, all those devices and technologies based on natural or artificial chemical and electrochemical molecular or macromolecular motors will have a great energetic advantage related to current thermal motors: natural and artificial macromolecular motors work under constant temperature (that of the body or of the reacting media), far away from the Carnot’s low efficiency servitude imposed on current thermal motors working in a temperature gradient.[170,171]

10. Conclusion

Electrochemical reactions in liquid electrolytes of films of conducting polymers and other electroactive materials provide dense gels constituted by multisensing and multistep macromolecular motors, ions, and solvents.

The reaction-driven actuation of the macromolecular motors opens ionic channels across the material, replicating ion protein channels in cells and, specifically, in neuron membranes.

The material response to potential cycles replicates both the ion protein channel opening/closing cycle driven by a transmembrane potential cycle and the generated ionic pulse.
If the action potential in brain neurons is originated by cooperative actuation of ion protein channels in the neuron membrane and the action potential originates the synaptic connection transferring information between neurons, we can state, as a new hypothesis, that this information (or a good fraction of it) is stored as a different electro-chemo-mechanical (conformational compacted) energetic level in each protein channel, being read and transferred to the action potential by every ionic pulse.

At the moment, our control of individual ion protein channels is not enough to allow a full physical–chemical characterization and theoretical description of the stored–read information packs. Used as model materials, the electrochemical characterization of conducting polymers provides the identification and quantification of different stored–read information packs.

The study of model materials constituted by trillions of electrochemical multistep macromolecular motors suggests that ion (K⁺, Na⁺, Cl−, and Ca²⁺, the most involved during neuronal actuation) protein channels from the neuron membrane could store most of the brain information as conformational closed–contracted energetic states.

The basic amount of long-term conformational contracted energy should be different for every ion channel protein and defined by the local physical chemical conditions at the channel birth time: long-term stored information.

Whatever the initial compacted energetic state, any cyclic transmembrane potential pulse opens the protein channel and the energy of the generated ionic pulse reads and carries this information, being the initial conformational energetic state restored during the channel closing at the end of the potential cycle.

Local variations of the electrical, mechanical, thermal, or chemical conditions should include small temporal and reversible variations of the conformational energy stored by the channel protein during the closing process: short-term and nonpermanent information storage.

The shape of the generated ionic pulse (current, charge, and energy at different pulse times) carries the quantitative information of the two stored energetic conformational components: permanent (long-term) and temporal (short-term).

The temporal energetic information related to the local physical and chemical conditions (self-sensing package of mechanical, chemical, thermal, and electrical information) is read, erased, and substituted by new temporal information reflecting the new local energetic conditions when the protein channel closes.

The channel protein should constitute the basic unit for information storage in neurons (BUISN).

The ionic pulse should constitute a carrier unit of neuronal information, being the initial conformational energetic state restored during the channel closing at the end of the potential cycle.

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At the moment, our control of individual ion protein channels is not enough to allow a full physical–chemical characterization and theoretical description of the stored–read information packs. Used as model materials, the electrochemical characterization of conducting polymers provides the identification and quantification of different stored–read information packs.

The study of model materials constituted by trillions of electrochemical multistep macromolecular motors suggests that ion (K⁺, Na⁺, Cl−, and Ca²⁺, the most involved during neuronal actuation) protein channels from the neuron membrane could store most of the brain information as conformational closed–contracted energetic states.

The basic amount of long-term conformational contracted energy should be different for every ion channel protein and defined by the local physical chemical conditions at the channel birth time: long-term stored information.

Whatever the initial compacted energetic state, any cyclic transmembrane potential pulse opens the protein channel and the energy of the generated ionic pulse reads and carries this information, being the initial conformational energetic state restored during the channel closing at the end of the potential cycle.

Local variations of the electrical, mechanical, thermal, or chemical conditions should include small temporal and reversible variations of the conformational energy stored by the channel protein during the closing process: short-term and nonpermanent information storage.

The shape of the generated ionic pulse (current, charge, and energy at different pulse times) carries the quantitative information of the two stored energetic conformational components: permanent (long-term) and temporal (short-term).

The temporal energetic information related to the local physical and chemical conditions (self-sensing package of mechanical, chemical, thermal, and electrical information) is read, erased, and substituted by new temporal information reflecting the new local energetic conditions when the protein channel closes.

The channel protein should constitute the basic unit for information storage in neurons (BUISN).

The ionic pulse should constitute a carrier unit of neuronal information, being the initial conformational energetic state restored during the channel closing at the end of the potential cycle.

The channel protein should constitute the basic unit for information storage in neurons (BUISN).

The electrochemically stimulated conformational relaxation model and the structural chemical kinetic model developed from the empirical electrochemical study of the model materials allow a good theoretical description of the different packages of quantitative information driven by any ionic pulse generated by actuation of an electrochemical macromolecular motor. The basic equations of the chemical and electrochemical reaction rate provide the quantitative description of the sensing equations.

The conformational energy of the brain closed and packed ion protein channels quantifies the basic permanent information stored by the brain, spinal cord, or other parts of the nervous system.

Any permanent change of the long-term conformational chemical structure of the ion channel by strong and irreversible intramolecular or intermolecular interactions (crosslinking degree, ion trapping, or other strong protein–molecule interactions) should mean long-term changes of both the stored information and the permanent information memory, in some cases related to brain functional diseases.

The full conformational energy stored by brain protein channels after a lifetime and the specific treatment of this information by the different brain regions should quantify and define both brain functions and the individual rational and irrational personality (life and dreams) of any animal or human being.

This long-term stored conformational energy and the concomitant individual personality should shift every day by formation of new ionic channels, by growth of new neurons with the concomitant new synaptic connections, or by permanent conformational changes in the old ionic channels.

Strong local energetic perturbations (thermal, chemical, mechanical, or electrical; Equation 10) or strong interactions with a new molecule or ion (chemical perturbation) can perturb or inhibit the actuation of the ion channel proteins with a concomitant effect on the nervous communication transmission. If these physical–chemical processes are reversible, the concomitant inhibition or perturbation of the neuronal communication should finish by reversing the process when the original conditions are recovered.

The corroboration of the presence of the different packages of mechanical, chemical, electrical, and thermal information carried by any CUNI could open a way toward the description and quantification of both the action potential and the synapse to attain a basic quantitative model of neuronal connectivity. Then we could explore how different parts of the brain store and treat the information packs to give brain functions (images, memory, consciousness, proprioception, thoughts, self-reflection, dreams, and so on) or malfunctions.

A parallel construction and exploration of new soft, wet, electrochemically driven, more intelligent, and bioreplicating machines and computers based on model materials constituted by electro-chemo-conformational molecular machines replicating basic units of neuronal information could provide feedback information to describe brain functions and malfunctions.

Those hypotheses could open new experimental possibilities for those neuroscientists trying to understand neuronal connectivity or trying to describe and quantify brain functions and how those functions are correlated with specific brain structural changes.

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Conflict of Interest

The author declare no conflict of interest.
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**Toribio F. Otero** is a chemist from Oviedo University (1974). He received his Ph.D. degree in chemistry (electrochemistry) in 1978 (supervised at the Rocasolano Institute, CSIC) from the Madrid Complutense University and became a full professor of physical chemistry and macromolecules at the University of the Basque Country, in 1989. Since 2000, he has been working at the Technical University of Cartagena. His research interest combines electrochemistry, polymer science, and material science applied to model materials for the replication and theoretical description of biological organs (artificial muscles, smart membranes, smart skins, etc.) and biological functions (self-awareness, proprioception, ectotherm muscles, or brain functionalities).