Journal of Neural Engineering

PAPER

Finite-element modeling of neuromodulation via controlled delivery of potassium ions using conductive polymer-coated microelectrodes

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RECEIVED
25 April 2023

REVISED
20 November 2023

ACCEPTED FOR PUBLICATION
2 February 2024

PUBLISHED
1 March 2024

Keywords: ionic neuromodulation, potassium ions, conductive polymers, ionophores, ion delivery

Supplementary material for this article is available online

Abstract

Objective. The controlled delivery of potassium is an interesting neuromodulation modality, being potassium ions involved in shaping neuron excitability, synaptic transmission, network synchronization, and playing a key role in pathological conditions like epilepsy and spreading depression. Despite many successful examples of pre-clinical devices able to influence the extracellular potassium concentration, computational frameworks capturing the corresponding impact on neuronal activity are still missing. *Approach*. We present a finite-element model describing a PEDOT:PSS-coated microelectrode (herein, simply *ionic actuator*) able to release potassium and thus modulate the activity of a cortical neuron in an *in-vitro*-like setting. The dynamics of ions in the ionic actuator, the neural membrane, and the cellular fluids are solved self-consistently. *Main results*. We showcase the capability of the model to describe on a physical basis the modulation of the intrinsic excitability of the cell and of the synaptic transmission following the electro-ionic stimulation produced by the actuator. We consider three case studies for the ionic actuator with different levels of selectivity to potassium: ideal selectivity, no selectivity, and selectivity achieved by embedding ionophores in the polymer. *Significance*. This work is the first step toward a comprehensive computational framework aimed to investigate novel neuromodulation devices targeting specific ionic species, as well as to optimize their design and performance, in terms of the induced modulation of neural activity.

1. Introduction

Extracellular potassium is a crucial modulator of neuronal activity [1, 2]. An increase in its concentration $[K^+]$ lowers the outward K^+ fluxes in the ion channels, thereby depolarizing the membrane potential and increasing the intrinsic excitability of the cell [3]. As a result of depolarization, synaptic transmission at excitatory synapses is facilitated, since the postsynaptic current at the glutamatergic receptors is enhanced and the release of neurotransmitters is promoted by a major presynaptic inflow of calcium through voltage-gated Ca^{2+} channels [4–6]. At the network level, potassium accumulation and diffusion generate non-synaptic coupling between neurons, which in turn shapes network activity and may induce synchronization [7]. Perturbations of $[K^+]$ are interesting also from a neurological perspective, since they are linked to many pathological conditions such as epilepsy [8, 9] or spreading depression [10, 11]. Therefore, the control of $[K^+]$, which we will thereafter refer to as *ionic stimulation*, is drawing attention as a possible innovative pathway toward neuromodulation [12]. This has been

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implemented by several novel devices, herein referred to as *ionic actuators*, capable of perturbing the extracellular concentration of potassium at spatiotemporal scales approaching those of neuron activity [13–15].

Ionic stimulation obtained with ionic actuators fits in the broader realm of drug-delivery devices applied to neuromodulation. A prominent class of such technology relies on the properties of conductive polymers (CPs) [16], also known as organic mixed ionic and electronic conductors (OMIECs) [17]. CP-coated electrodes can modulate the local ionic concentration upon application of an electrical stimulus which translates into the injection of holes[6] (or electrons) in the polymer backbone and is followed by the release of pre-charged cations (or anions) in the target electrolyte. The pre-charging can be achieved using the electrostatic forces provided by fixed moieties in the CP blend or when the charged drugs act as dopants [18–20]. In the purely electrostatic CP loading, selectivity can be achieved by adding ionophores [21–23], using ion-selective membranes [24] or cell membrane bilayers with specific ion-channel expressions [25]. Alternative architectures that stem from the field of iontronics [26], bypass the selectivity problem by employing multiple electrolyte reservoirs where ions/drugs are stored, delivered or drained [13–15]. However, this approach poses evident challenges in the design and implementation of the microfluidics, requires high voltages and is thus not easy to miniaturize.

Multiphysics computational models are pivotal to aid the design and deployment of ionic actuators as neuroengineering devices, as they reduce the need for *in-vitro*/animal studies and the prototyping cost and development time. Indeed, they allow to improve the understanding of the device operation, by providing insight into underlying phenomena not directly accessible by experiments. Moreover, they enable the investigation of large regions in the parametric space, paving the way for optimum design of the neuromodulation devices. Modeling the dynamics of ionic actuators requires an accurate description of the ions' electrodiffusion. Given the relatively large dimensions of these devices, the Poisson–Nernst–Planck (PNP) model [27] is a good candidate to capture both drift and diffusion transport mechanisms, as well as charge screening effects in the space-time domain. The PNP model can also be adapted to CPs [28], and has been employed in computational works focusing on the characterization and optimization of iontronic devices [29–31] or ISM-cuff electrodes [32]. Notwithstanding, to the extent of our knowledge, computational frameworks accounting for both ionic actuators and their effect on neuronal membranes are still missing in the literature. This is in contrast with other neuroengineering modalities, e.g. electrical stimulation, where similar modeling frameworks are employed [33, 34].

The main difficulty of coupling the description of ionic actuators and neuronal activity resides in the workhorse models employed in computational neuroscience: the volume conductor description of the cellular fluids [35], and the cable theory framework of membrane dynamics [36]. Indeed, the former assumes the neuron milieu to be ohmic, while the latter relies on a circuit-level description of the transmembrane fluxes. As a result, the modeled electric currents have no direct connection with the underlying ionic fluxes. This is not an issue when modeling, e.g. the electric interaction with electrodes for stimulation [33, 34] and recording [37, 38], but becomes pivotal in presence of ionic actuators (see Methods). A small body of literature applied the PNP framework to describe ionic transport phenomena occurring in nervous tissues [39–42], mainly focusing on the study of slow potentials and microdomains. We point out that these frameworks exploit the quasistatic approximation of Maxwell equations [35], thereby neglecting capacitive and inductive effects in the cellular fluids. Also, there exists a family of models describing ion dynamics in the nervous milieu under the assumption of only diffusive fluxes [43–48]. However, this is in general not justifiable for non-biological electrogenic sources like ionic actuators, since that approach neglects possible components of electric stimulation arising from ion release/uptake.

In this work, we propose the first *in-silico* framework that describes the coupled dynamics of a ionic actuator, ion transport in the intra- and extra-cellular fluids (ICF, ECF), and the electrogenic processes at the neural membrane. These models are solved in a self-consistent fashion according to the electrodiffusive level of detail. As a case study, we use a PEDOT:PSS-coated microelectrode releasing K^+ placed below a cortical neuron soma with dome geometry. This configuration enables us to examine how the action of the ionic actuator affects neural activity, both through the perturbation of the extracellular potassium concentration (*ionic stimulation*) and of the electrical potential (*electric stimulation*). First, we showcase the extreme cases of an ionic actuator with either ideal selectivity or no selectivity to K^+. In the ideal case, the sole action of the ionic actuator is sufficient to drive ionically the neuron into tonic firing or depolarization block. In the non-selective case, mainly electric stimulation is delivered since the polymer is not able to collect enough potassium from the extra-cellular fluid. Second, we study a possible functionalization of the actuator's selectivity by resorting to ionophores. Simulations show that the optimized ionic actuator enhances the neuron sensitivity to

[6] More precisely, the injection of holes is associated with the creation of polarons and bipolarons in the polymer. In this paper, we use the term *holes* to ease the discussion.

concurrent electrical stimulation as well as facilitates excitatory synaptic transmission.

2. Methods

The computational framework used in this work (figure 1) couples the dynamics of the ionic actuator, the ICF, the ECF, and the neural membrane. It combines modeling efforts from the literature separately accounting for the CP-electrolyte interaction [28], and ion transport in cellular fluids in presence of the neural membrane's electrogenic activity [39, 43]. The simulation domains with the corresponding physics are represented by a frame and a set of equations in figure 1. Arrows connecting frames report the equations that couple different domains. Generalizations of the computational framework to account for ionophores and synapses are shown in figure 2. A description of the abbreviations, physical variables, and parameters used is reported in the supplementary materials in tables S1–S3, respectively. The model is implemented in COMSOL Multiphysics [49] (technical details are reported in the supplementary note 1). In the following, we briefly describe the model equations, the reference physical and geometrical parameters, as well as the case studies examined. The model verification is addressed in the supplementary note 2.

2.1. Model equations

2.1.1. Intra- and extra-cellular fluids

The ECF and ICF are modeled as electrolytes using the PNP equations (equations (1)–(3)). The electrostatic potential of the ions, ψ_c, is obtained by solving the Poisson equation (equation (1)), which depends on the local space and time-dependent net charge density due to all the ionic species in the aqueous phase. For simplicity, we restrict the analysis to the main ionic agents responsible for the generation of action potentials (APs) at the neural membrane, namely K^+, Na^+, Cl^-. The bulk concentrations are taken from [43], in agreement with typical (artificial) cerebrospinal fluids [1]. A generic anion A^-, assumed fixed and uniformly distributed for simplicity, is added to provide electroneutrality (i.e. $[K^+]+[Na^+]-[Cl^-]-[A^-]=0$) in the bulk of the solutions. Mass conservation of each mobile species is enforced with the continuity equations (equations (2)). Therefore, time-dependent variations of ionic concentrations are given by drift and diffusion fluxes and described using the Nernst-Planck transport equations (equations (3)). Note that, equations (1)–(3) are solved in both the extra and intracellular domains. The presence of an extracellular reference electrode (RE) is mimicked through boundary conditions in the ECF's bulk that set the electric potential to ground and the ionic concentrations to their baseline values. Since no limit on the RE's current is imposed, such boundary conditions also account for the action of a counter electrode (CE).

2.1.2. Neural membrane

The transmembrane fluxes through ion channels are modeled using the Hodgkin–Huxley (HH) formalism (equations (6)–(8)), implemented at each mesh point of the cell membrane. The HH model of this work has been introduced in [43] and later used to describe an interneuron of the rat CA1 hippocampus [50, 51]. It includes a transient sodium current (subscript T) and a delayed rectifying potassium current (subscript DR), which are voltage-gated and responsible for the generation of APs (equations (7a)–(7b)). Moreover, our implementation has a leakage current (subscript L) specific for each ion species (equations (7c)–(7e)), differently to the original HH model [52]. Equation (6) collects three first-order differential equations modeling the dynamics of the gating variables for the potassium (n) and sodium (m, h) voltage-gated channels, which depend on the (in)activation curves n_∞, m_∞, h_∞, and time constants τ_n, τ_m, τ_h, respectively. Equation (8) reports the total transmembrane current density for each ion species, which depends (through equation (7)) on the maximum conductances of the ion channels, the gating variables, and the difference between the membrane and reversal potentials (see section 2.1.3). In order to preserve the rest potential V_r of the chosen HH model at the steady state, each current density in equation (8) is shifted by its value $I_{\mathrm{X}_i,\mathrm{r}}$ at V_r, where $\mathrm{X}_i \in \{K^+, Na^+, Cl^-\}$, and therefore is null under steady-state conditions. We note that alternative choices for the steady state are possible. For instance, in [39] the authors block the voltage-gated channels and let the system achieve the thermodynamic equilibrium. Nevertheless, since sub-threshold fluxes are orders of magnitude smaller than the ones that shape neural firing, these choices are expected to mildly impact the system's behavior. Since our investigations focus on temporal scales of tens to hundreds of milliseconds (see Results), we do not account for homeostatic mechanisms responsible for the regulation of ion concentrations, such as ion transporters at the neural membrane or spatial buffering by glial cells [2]. The interaction of these mechanisms with ion dynamics is expected to become relevant at the scale of seconds or longer [43–48].

2.1.3. Coupling HH and PNP models

The currents through ion channels are imposed as flux boundary conditions in and out of the cell (equation (10)), according to the ion currents given by equation (8). The dielectric effects of the membrane are modeled as an ideal capacitor with parallel plates via a thin layer approximation. Namely, they are accounted for through boundary conditions on the electric displacement field that depends on the membrane capacitance C_m and the membrane potential

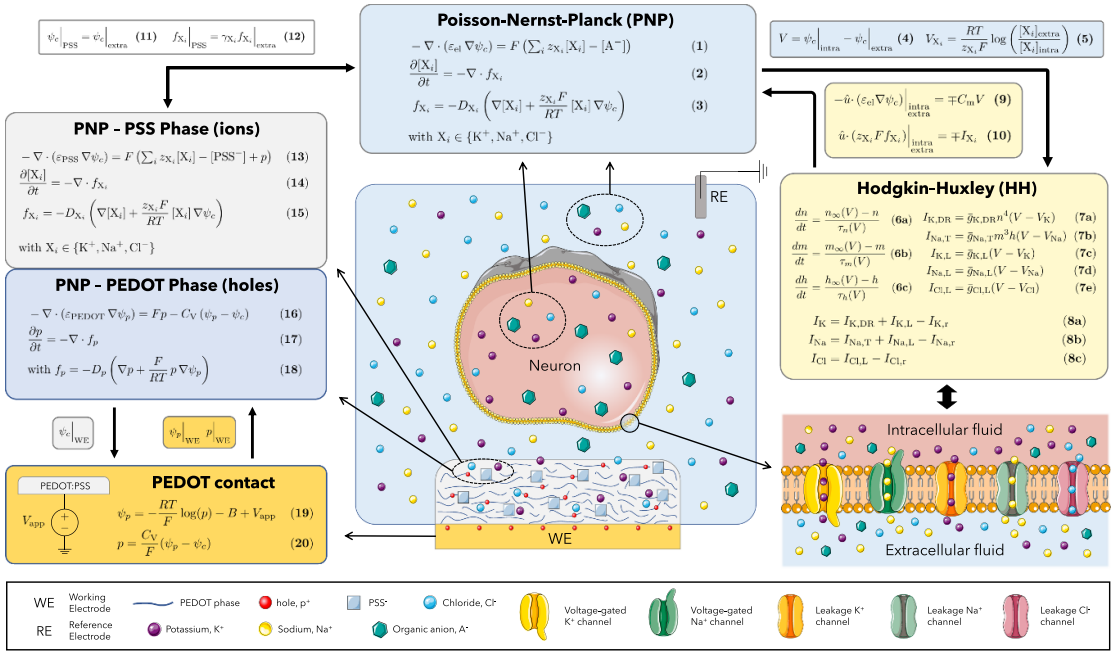


Figure 1. Sketch of the neuron cell (center) containing the intracellular fluid (ICF) and surrounded by the extracellular fluid (ECF), contacted by an external reference electrode (RE). Below the neuron, the CP-based ionic actuator is contacted by a metal (e.g. gold) electrode operating as working electrode (WE). The operation mechanism consists of electronic doping of the PEDOT phase that induces an ion flux pointing outwards from the CP. The equations used for each physics in the simulation domain are represented by frames placed around the main sketch. Frames are connected with arrows that indicate the coupling equations implemented in COMSOL Multiphysics. A description of the physical variables and parameters is reported in tables S2 and S3, respectively. Part of the image is adapted from Servier Medical Art. CC BY 4.0.

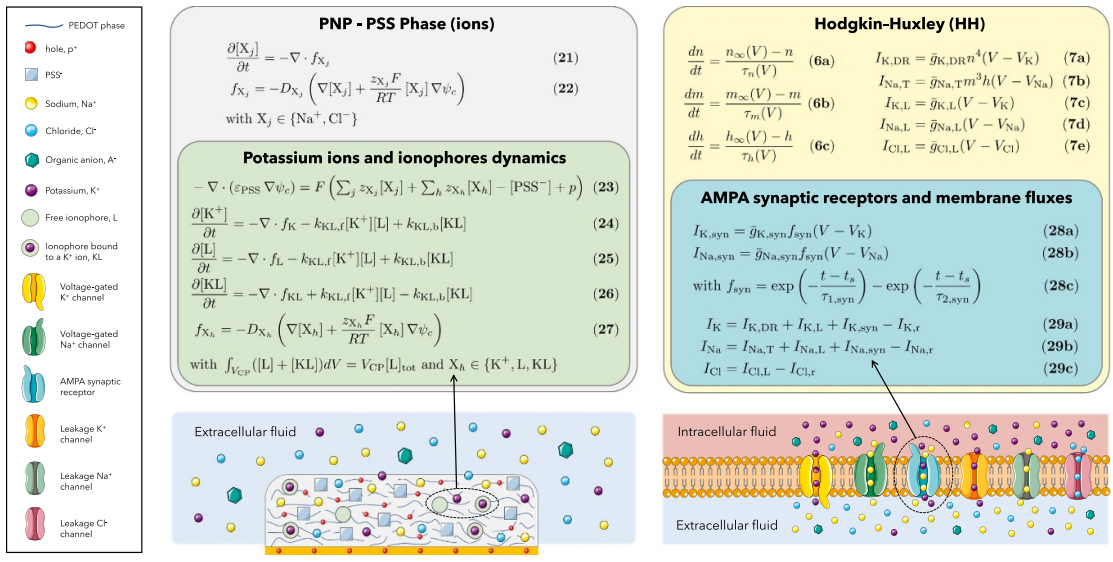


Figure 2. Sketch illustrating the changes made to the modeling framework shown in figure 1 to account for the dynamics of ionophores (left) and AMPA excitatory synapses (right). Green and blue insets highlight the new or updated equations in the PNP-PSS model of the CP (grey frame, as in figure 1) and the HH model of the neural membrane (yellow frame, as in figure 1). A description of the physical variables and parameters is reported in tables S2 and S3, respectively. Part of the image is adapted from Servier Medical Art. CC BY 4.0.

V (equation (9)). These conditions are responsible for the electrical double layer (EDL) formation at the two sides of the membrane, and avoid the need to explicitly solve the Poisson equation in the membrane domain (as done, e.g. in [39]), thereby reducing the computational cost. The HH model extracts the membrane potential V by sampling the electrostatic potential predicted by the PNP at the intra- and extracellular side of the neural membrane (equation (4)). Differently from previous works [39], the runtime calculation of the reversal potentials V_K, V_{Na}, V_{Cl} is done by sampling the ionic concentrations at a distance $d_s = 6$ nm from the neural membrane, i.e. a distance 5 times larger than the Debye length [27] in the

ECF and ICF (equation (5)). This strategy is adopted to avoid distortion of the ion concentrations induced by charge screening effects in the EDL.

2.1.4. Ionic actuator

The ionic actuator consists of a film of conjugated polymer-polyelectrolyte blend (hereafter simply referred to conductive polymer, CP), that is, a two-phase domain where both ionic and electronic transport take place simultaneously (see figure 1). We consider a PEDOT:PSS blend as the reference CP and use the model proposed in [28]. According to [28], the polyelectrolyte PSS phase and the PEDOT phase can be modeled by coupling two PNP sets of equations: in the PNP of the PSS phase, the concentration of holes is added to the space charge density of the Poisson equation so that ions are electrostatically influenced by the holes' spatial distribution (see equation (13)); differently, in the PNP of the PEDOT phase the electrostatic potential of holes, ψ_p, in the Poisson equation (equation (16)) depends on ψ_c in the form of a capacitive coupling, namely, through the volumetric capacitance C_V (with units of F cm^{-3}). This phenomenological term quantifies the extent of entanglement between the two phases and can be seen as the result of a three-dimensional EDL [53, 54]. Mass conservation of ions and holes in their respective phase is also ensured by the continuity equations (equations (14) and (17)), where electrodiffusive fluxes are described with the Nernst–Planck equation (equations (15) and (18)). Note that, for the sake of simplicity, we do neglect reactions occurring at the CP/electrolyte interface [55], such as oxygen reduction reactions often seen in PEDOT:PSS CPs [56]. This phenomenon should translate into an additional faradaic current drawn by the WE when using a negative bias but should not sensibly impact the capacitive mechanism that enables the ionic injection in the extracellular fluid.

2.1.5. Coupling between polyelectrolyte and extracellular fluid

Since polyelectrolyte and electrolyte phases are both ionic phases, the PSS/ECF interface must ensure continuity of the electrostatic potential (see equation (11)). Fluxes of ions, however, may experience affinity changes due to, e.g. ionophores incorporated in CP [21, 22] or from ion-selective barriers [25]. For the sake of generality, we equipped our model with virtual affinity coefficients γ_K, γ_{Na}, γ_{Cl} at the PSS/ECF interface equal to either 0 or 1 (see equation (12)) to introduce ideal selectivity of the CP to specific ions (see section 2.2).

2.1.6. Ionophores

While the parameters γ_{X_i}, $X_i \in \{K^+, Na^+, Cl^-\}$, are used as phenomenological terms to induce ideal selectivity, ionophores are employed as a more realistic way to describe a selective ionic actuator [21, 22]. With respect to the ideal CP, the physics of an ionophore-containing CP (described in figure 2, left panel) also includes the continuity equations (equations (25) and (26)) for the free ionophores, L, as well as the selective complexes formed with potassium ions, KL. Forward and backward reaction terms are included in these equations and the continuity equation for K^+ ions (equation (24)) to account for the binding and unbinding mechanisms of ionophores and potassium ions [57]. Electrodiffusive fluxes are described by the Nerst–Planck equation (equation (27)). Note that ionophores are confined in the CP domain and can be regarded as fixed or mobile depending on the value of their diffusivity coefficient. Moreover, in this work we assume the ionophore molecules as neutral species so that only their complexed form (positively charged) contributes to the Poisson equation (equation (23)). The continuity equations and the electrodiffusive fluxes for Na^+ and Cl^- are the same as in equations (14) and (15) but, for the sake of clarity, they are also reported in equations (21) and (22) to explicitly separate the K^+ dynamics.

2.1.7. Synapses

A model of excitatory synapse (described in figure 2, right panel) is included in the neural membrane when testing the neuromodulation capability of the CP beyond to purely induce APs (see section 3.4). The model is taken from [58] and accounts for the K^+ and Na^+ fluxes through an AMPA postsynaptic receptor (equation (28)). We consider only single synaptic events for each simulation. The excitatory postsynaptic currents (EPSCs) are described with a template profile for the ion postsynaptic conductances, and are modulated by the membrane and reversal potentials. The total transmembrane currents for each ion species are updated accordingly (equation (29)). Differently to [58], we neglect the small calcium component to avoid the additional computational cost of modeling the Ca^{2+} electrodiffusion in the cellular fluids.

2.2. Case studies for the ionic actuator

In the present work, we consider 3 case studies of CP with different levels of selectivity towards K^+ in terms of storage and release.

- *Ideally-selective CP* (isCP): Na^+ ions cannot enter the CP. This is accomplished by setting $\gamma_{Na} = 0$ while $\gamma_K = \gamma_{Cl} = 1$. The physical parameters of the CP are taken from the literature [28, 53, 55] and ionophores are not embedded in the CP backbone. As a result, the CP in the undoped state is precharged almost completely with K^+, which compensates the fixed moieties PSS^-.

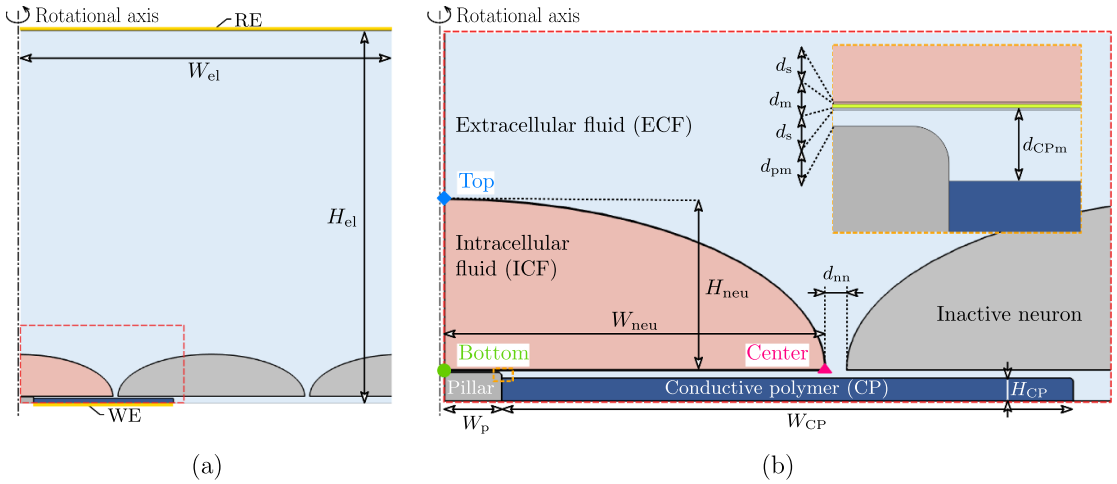


Figure 3. (a) Section of the 2D-axisymmetric geometry used in this work. The active neuron is shown in pink and the CP in blue. Domains in grey are considered inactive and are not included in the simulation space. Metal contacts (WE and RE) with applied potentials are shown by thick yellow lines. (b) Zoom of the active neuron domain, highlighting some relevant points at the neuron membrane: 'Top' (blue), 'Center' (red), and 'Bottom' (green) that will be employed in the figures in the Results section. Orange dashed lines (inset) report an additional zoom of the CP-Neuronal cleft. Additional description of the geometrical parameters and their reference values are reported in table S5.

- *Non-selective CP* (nsCP): the CP is permeable to all of the ions ($\gamma_{Na} = \gamma_K = \gamma_{Cl} = 1$). The physical parameters of the CP are taken from the literature [28, 53, 55] and ionophores are not embedded in the CP backbone. As a result, the CP in the undoped state is pre-charged by both K^+ and Na^+, in same proportions as in the ECF (where $[Na^+] \gg [K^+]$).
- *Ionophores-induced selective CP* (ionoCP): the CP is permeable to all of the ions as in the previous case, but it is endowed with ionophores, that enhance the proportion of K^+ ions inside the CP. However, their binding affinity resists to the ion release into the ECF. To get the best from this trade-off, we tailor the chemical parameters of the CP and of the ionophores by resorting to a simplified phase boundary model for the CP with ionophores and its interaction with the ECF (see supplementary note 3).

If not otherwise specified, we use the values reported in table S3 for the physical parameters. For the convenience of the reader, we report in table S4 the parameters and the correspondent values adopted to instantiate the isCP, nsCP, ionoCP case studies.

2.3. Geometry

The proposed modeling approach allows us to spatio-temporally resolve ionic gradients and potential drops in the continuous space including the double layer charge at the interfaces. As such, this model demands for a refined space discretization capable to reproduce sub-nanometer features. To reduce computational cost we consider a 2D-axisymmetric geometrical domain that cuts down the model complexity to the one of a 2D model but restricts geometry to axial symmetry [59]. The reference simulation structure used in this work is shown in figure 3(a). It includes an active neuron cell (light red) shaped as a halved oblate ellipsoid (dome) laying on a ring-shaped ionic actuator (dark blue) immersed in an electrolyte bath (light blue). Lateral neurons (grey, on the right) are non-active and are included by means of encumbrance to resemble realistic neighboring cells in a cultured setting. Obviously, their dome shape cannot be enforced in the 2D-axisymmetrical model so they are essentially rings limiting the ion transport in the vertical direction as in a realistic culture. An oxide pillar (grey, on the bottom left) is included to keep the neuron at a given distance from the polymer, leaving an electrolyte cleft between the two. A zoom-in view of the active neuron boundaries is reported in figure 3(b). If not otherwise specified, we use the values in table S5 for the geometrical parameters.

3. Results

3.1. Ideally-selective CP (isCP)

Figure 4 shows the working principle of ion actuation in the isCP case study. Initially, the ionic actuator is biased at a negative potential (dedoped state), $V_{app} = -1$ V, which corresponds to a very small hole concentration, p, in the CP so that the PSS^- charges are mostly compensated by the stored K^+ ions. By ramping the applied potential, holes are injected into the film (or, in other words, electrons are transferred from the PEDOT into the metal contact) and potassium ions are released in the ECF producing a constant ionic current in accordance with the volumetric capacitive behavior of the CP. The cations diffuse towards the neuron and increase the local extracellular concentration, $[K^+]$, in the

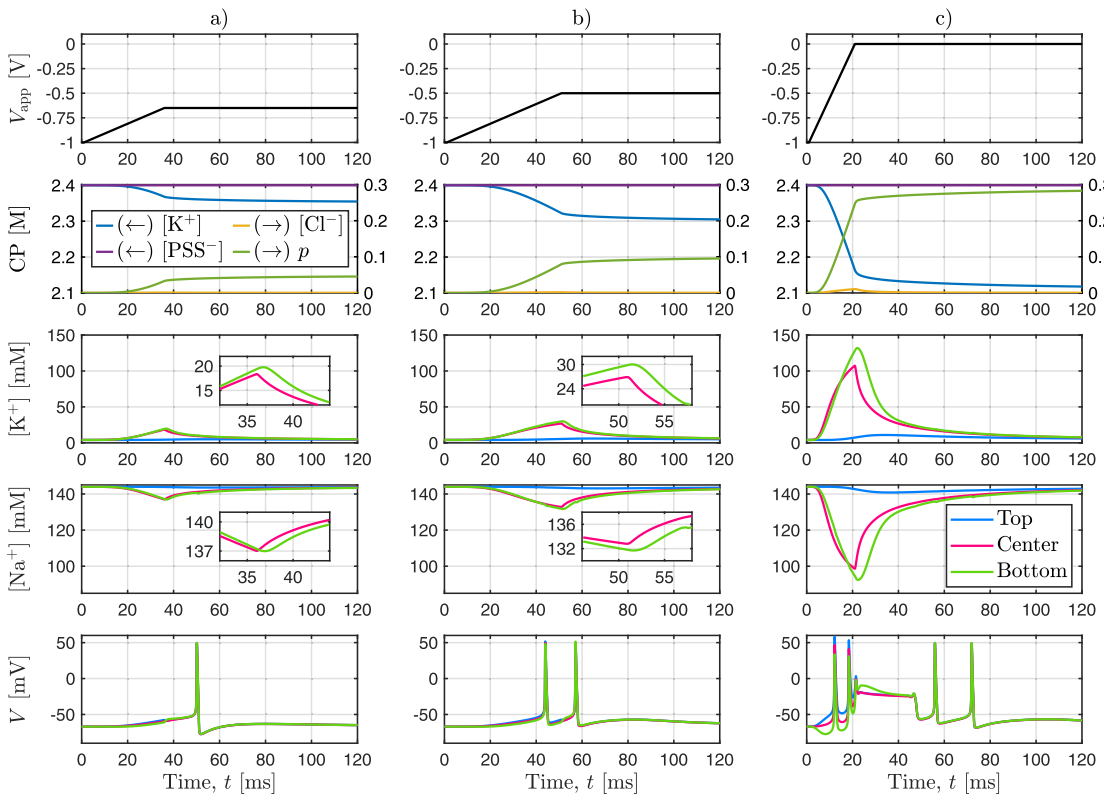


Figure 4. Ideally-selective CP (isCP): examples of ionic neuromodulation transients. Different profiles for the applied potential to the CP are considered: (a) $V_{app,max} = -0.65$ V, $\nu = 10$ V s^{-1}, (b) $V_{app,max} = -0.5$ V, $\nu = 10$ V s^{-1}, (c) $V_{app,max} = 0$ V, $\nu = 50$ V s^{-1}. The rows show, in order: (1) the potential applied to the metal contact below the CP, (2) the concentrations of ions and holes inside the CP, the extracellular concentrations for (3) K^+ and (4) Na^+, and (5) the membrane potential. The labels 'top', 'center' and 'bottom' refer to the points marked in figure 3(b). In the second row, two different scales are adopted for $[K^+]$, $[PSS^-]$ and $[Cl^-]$, p, respectively (see arrows in the legend).

proximity of the cell membrane resulting in membrane depolarization. As shown in figure 4(a), a $V_{app,max} = -0.65$ V produces $\Delta[K^+] = 20$ mM and is able to induce an *ionic* AP. By increasing the maximum value of the applied voltage, one can further increase the released dose of K^+ and hence the local $[K^+]$, thereby eliciting multiple APs. An example is shown in figure 4(b), where $V_{app,max} = -0.5$ V induces two consecutive ionic APs. The ionic flux emitted by the CP during the release is proportional to the slope of the ramp stimulus $V_{app}(t)$, namely $\nu = dV_{app}(t)/dt$. Therefore, higher ν yields larger transient perturbations of the local concentration of K^+. This is shown in figure 4(c), where the neuron reaches a configuration of depolarization block [60] due to the large perturbation of $[K^+]$. One should note that, since the CP is assumed perfectly selective to K^+ ions ($\gamma_{Na^+} = 0$), the increase of $[K^+]$ induced by the ionic actuator produces a decrease of $[Na^+]$ and an increase of $[Cl^-]$ (not shown), owing to electroneutrality. While changes in sodium concentration also contribute to membrane depolarization, their effect is quite limited compared to potassium. This is highlighted in figure S1, where we show the reversal potentials as a function of the changes in the extracellular ion concentration. We remark that the initial value of the applied potential $V_{app} = -1$ V to keep the polymer in a dedoped state depends on the choice of the CP (PEDOT-PSS), the metal contact, and the reference electrode. Therefore, it may vary with different instances of model parameters. Given the purely capacitive nature of CPs assumed in this work, and since we do not model redox reactions between the polymer and the extracellular fluid, no current flows from the WE to RE under constant applied potential.

We point out that, during K^+ release, the bottom side of the neuron is hyperpolarized, while the upper one is depolarized (see the last row in figure 4); and the extent of such perturbations is enhanced by larger ν. This is due to the drift component of the ionic flux released by the CP, which acts as anodal source of electrical stimulation [61]. Incidentally, this may raise the question that the electrical component may be the main neuromodulation drive of the firing patterns observed in figure 4. To rule out this hypothesis, we repeated the same simulations while keeping the reversal potentials fixed to their baseline values (see figure S2). Since no APs are elicited in this case, we can confirm that the ionic neuromodulation, and thus the release of potassium ions, is responsible for the neural activity observed in figure 4. Figure S2 also suggests that the slope of the actuation potential must

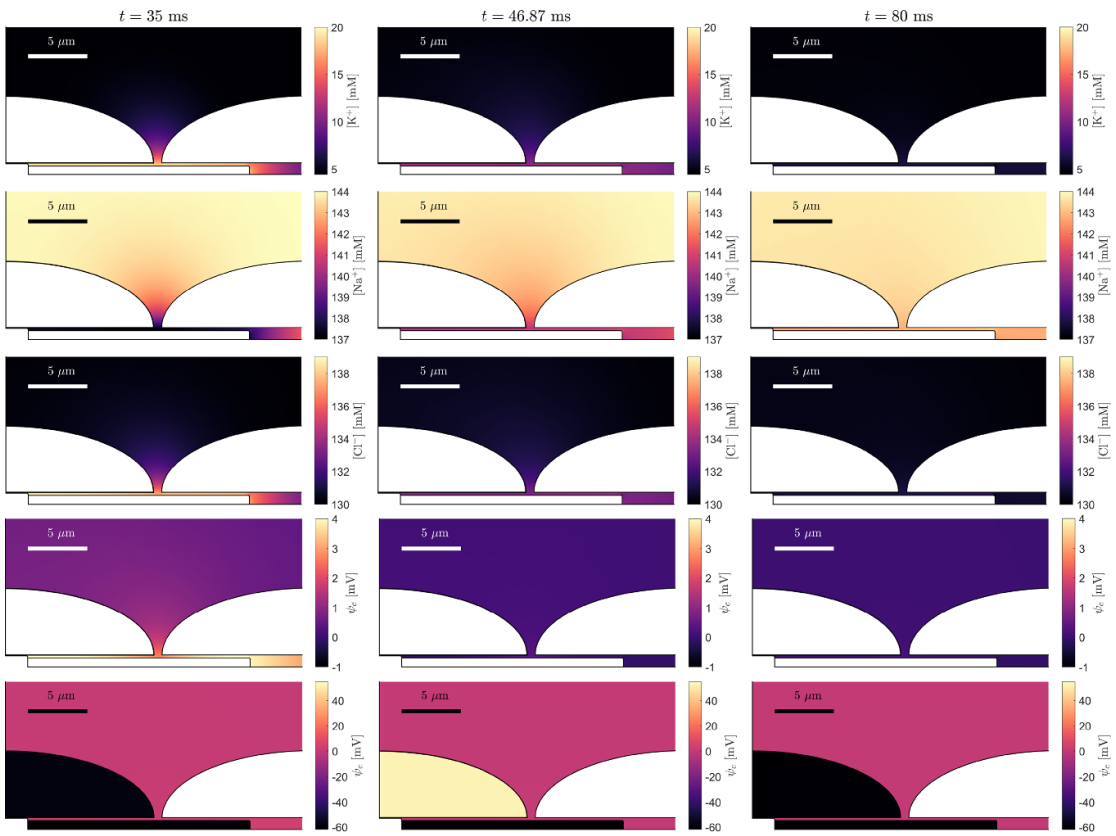


Figure 5. Ideally-selective CP (isCP): 2D-axisymmetric cutplanes illustrating the spatial distributions of different physical variables taken during the transient simulation in figure 4(a). Three time snapshots are considered: (left) at the end of K^+ release ($t = 35$ ms), (middle) at the peak of the AP ($t = 46.87$ ms), and (right) during the post-AP re-equilibration of ions in the ECF ($t = 80$ ms). The rows show, in order: the extracellular concentrations of (1) K^+, (2) Na^+, and (3) Cl^-, the electric potential (4) in the ECF only and (5) in both the ICF and ECF. Note the different color scale in rows (4) and (5).

be small enough to limit the electric field generated by the ionic actuator and therefore ensure a ionic-only stimulation. We point out that, owing to the capacitive nature of the CP, the currents delivered through ramp profiles of $V_{app}(t)$ resemble pulse-shaped waveforms typically used in neuroengineering devices for electrical stimulation [62, 63].

Figure 5 reports different snapshots of the 2D-axisymmetric spatial distributions of ionic concentrations and potentials of the transient in figure 4(a). Three time points are considered: (left) at the end of K^+ release ($t = 35$ ms), (middle) at the peak of the elicited AP ($t = 46.87$ ms), and (right) during the post-AP re-equilibration of ions in the ECF ($t = 80$ ms). A close inspection of the extracellular potential (fourth row) confirms a non-negligible electrical gradient during release (e.g. the total potential drop in the neuron-CP cleft is a few mV at $t = 35$ ms), which is responsible for the aforementioned electric component of neurostimulation.

The ion-release performance of the ionic actuator depends on both CP properties and geometrical factors. In fact, on one side the available ionic dose is strictly related to the number of fixed charges incorporated in the film. For example, figure S3 shows that the maximum releasable dose of K^+ decreases with decreasing $[PSS^-]$ in the CP. Once the CP is depleted from cations, Cl^- anions start entering the CP to balance the excess holes injected by the metal contact. On the other side, the encumbered space around CP helps to maintain the perturbation of $[K^+]$ in the bottom part of the neuron for longer times, thus facilitating ionic APs. This is shown in figure S4 where, for the same V_{app} profile, the change in extracellular $[K^+]$ decreases for larger gaps between the active and lateral neurons (i.e. low surface density of neurons). A similar effect is obtained for larger clefts between the neuron and the CP, as illustrated in figure S5.

3.2. Non-selective CP (nsCP)

Figure 6 illustrates the working principle of ion actuation in the nsCP case study. Since no selectivity to K^+ is enforced, we first tested the CP capability of maintaining a pre-charged dose of K^+ ions, i.e. we assume that the polymer has been initially preconditioned with pure KCl that is then replaced with the extracellular fluid. In figure 6(a) we report the simulation results of such ion-retention study, starting from a CP pre-charged with K^+ and held in the undoped state ($V_{app} = -1$ V). Being permeable also to Na^+,

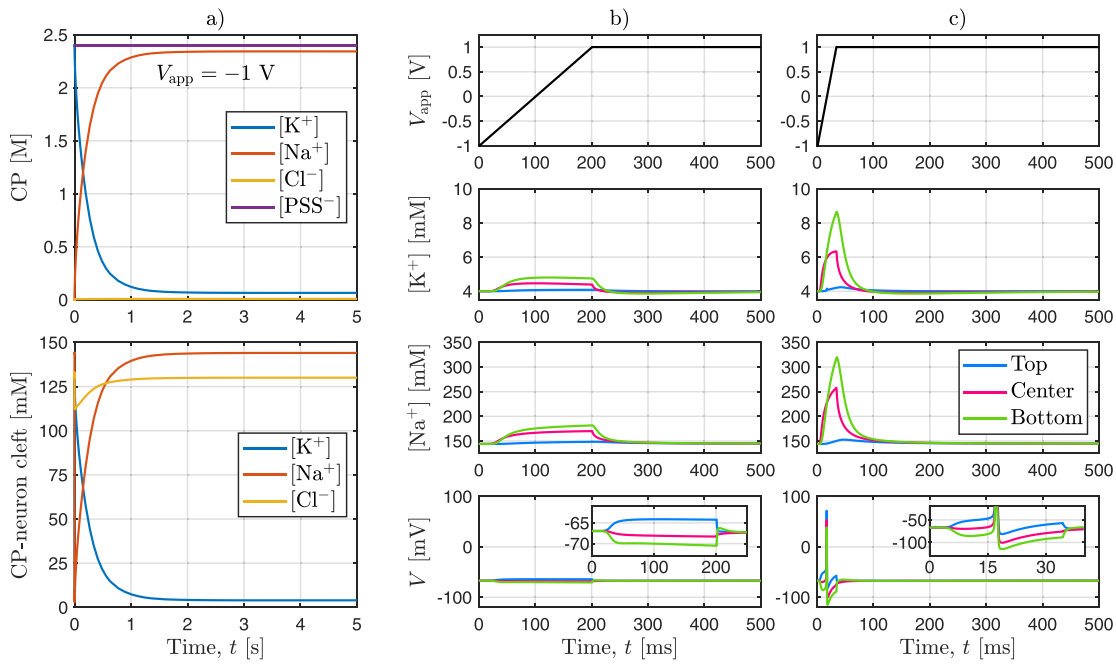


Figure 6. Non-selective CP (nsCP). (a) Ion-retention study of the K^+-preconditioned CP immersed into a physiological fluid while biased at $V_{app} = -1$ V. The top figure shows the time-evolution of the ion concentrations inside the CP, while in the bottom the ones in the CP-neuron cleft. (b) and (c) Examples of ionic neuromodulation transients performed immediately after the ion-retention study. Different slopes for the applied potential are considered (with $V_{app,max} = 1$ V): (a) $\nu = 10\ \mathrm{V\,s^{-1}}$ and (b) $\nu = 60\ \mathrm{V\,s^{-1}}$. The rows show, in order: (1) the potential applied to the CP, the extracellular concentrations for (2) K^+ and (3) Na^+, and (4) the membrane potential.

the CP rapidly evolves to a configuration of thermodynamic equilibrium where K^+ and Na^+ concentrations retain the same ratio as in the ECF, corresponding to $[K^+]_{CP} = 65.1$ mM, $[Na^+]_{CP} = 2.34$ M, and so $[K^+]_{CP}/[Na^+]_{CP} = 2.8\%$. Therefore, the CP fails to maintain most of the pre-charged K^+ dose, which is released in the ECF in an uncontrolled fashion. Compared to the isCP, the available potassium in the nsCP case is hence reduced by a remarkable factor (37 in our case).

Starting from the condition resulting from the transient in figure 6(a), we simulate two examples of ionic actuation with applied stimulus featuring either $\nu = 10\ \mathrm{V\,s^{-1}}$ or $\nu = 60\ \mathrm{V\,s^{-1}}$ (figures 6(b) and (c), respectively). Differently to the isCP case, the injection of holes induces a release of both K^+ and Na^+ ions. Since Na^+ is the dominant ion in the CP, the ion release predominantly affects the local concentration of sodium ions in the ECF. In contrast to what we observed in figure 4 for the isCP, $[K^+]$ here increases locally by only a few mM, despite having applied a larger stimulus, $V_{app,max} = 1$ V versus $-0.65/-0.5$ V in figure 4. Another important finding is that the membrane potential induced by the nsCP is mostly due to the electric field produced by the applied potential rather than by the perturbation of the ionic concentrations (mostly $[Na^+]$). As shown in figure 6(c), an AP can eventually be elicited if ν is increased to, e.g. $\nu = 60\ \mathrm{V\,s^{-1}}$. However, the AP persists with an almost identical time course even when the reversal potentials of the neuron are kept fixed to their baseline values (see figure S6). We will thereafter refer to this kind of stimulation of action potentials as *electric*, i.e. APs not directly induced by the perturbation of the extracellular ionic concentrations.

3.3. Ionophores-induced selective CP (ionoCP)

We chose the ionoCP properties according to optimality criteria based on simulations employing a reduced model of the CP/ECF interaction (see supplementary note 3). The optimization parameters were the equilibrium constant of ionophores β_{KL} and the concentration of fixed charges in the polymer $[PSS^-]$. The backward rate constant was set based on the literature ($k_{KL,b} = 10^{-4}$ 1/s as in [64]), while the forward one is by definition $k_{KL,f} = k_{KL,b} \cdot \beta_{KL}$. The optimum was evaluated adopting as figure of merit the $[K^+]$ change achieved in the finite-volume ECF at steady state (representative of the ionic stimulation achievable by the ionoCP), for a given applied $V_{app,max}$. Figures S7(a)–(c) show $[K^+]$ vs $[PSS^-]$ curves that were obtained for different total concentrations of ionophore in the system, $[L]_{tot}$, and $V_{app,max} = 2$ V. Interestingly, in all cases, the optimum association constant was $\beta_{KL} = 100\ \mathrm{M^{-1}}$. Even though larger concentrations of ionophores induce more ionic release, we chose $[L]_{tot} = 200$ mM corresponding to half of the maximum steric occupancy of a very common K^+-ionophore [65]. Therefore, the optimum from figure S7(b) was

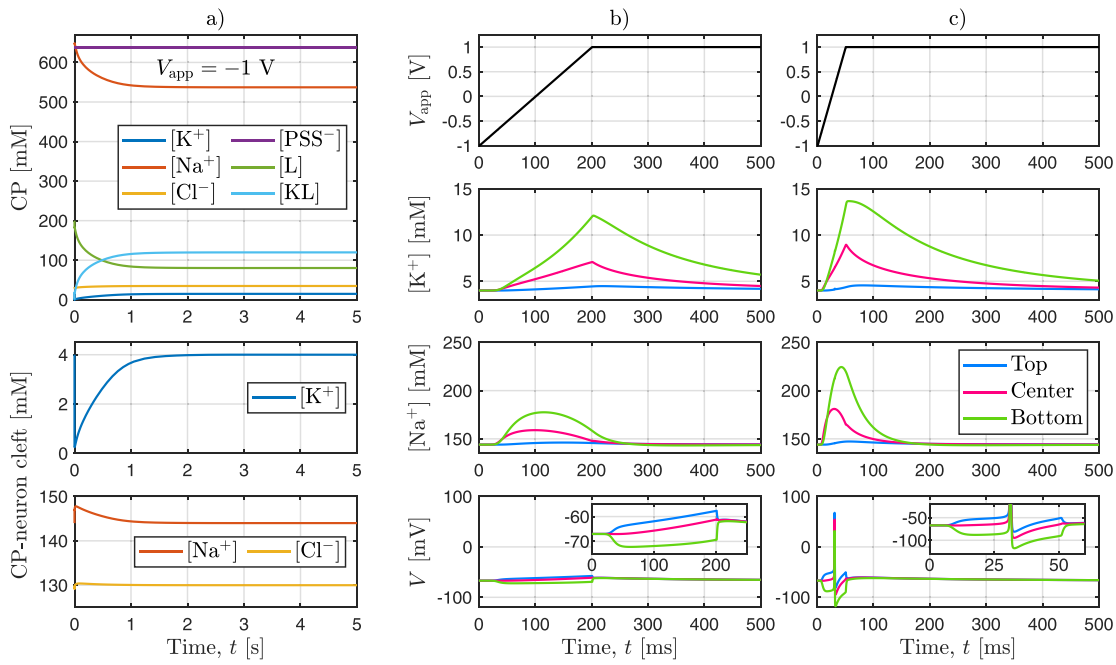


Figure 7. Ionophores-induced selective CP (ionoCP). (a) Re-equilibration study with CP biased at $V_{app} = -1$ V to allow the formation of KL complexes. The first row shows the ion concentrations inside the CP, while the second and third rows the ones in the cleft between the neuron and the CP. (b) and (c) Examples of ionic neuromodulation transients after the re-equilibration study. Different slopes for the applied potential are considered (with $V_{app,max} = 1$ V): (b) $\nu = 10$ V s^{-1} and (c) $\nu = 40$ V s^{-1}. The rows show, in order: (1) the potential applied to the CP, the extracellular concentrations for (2) K^+ and (3) Na^+, and (4) the membrane potential.

used, i.e. $[PSS^-] = 637$ mM. Further analysis regarding the maximum voltage applied at the CP electrode, $V_{app,max}$, revealed that the optimum amount of $[PSS^-]$ depends on this parameter with direct proportionality (figure S7(d)) but changes on the above-defined figure of merit are modest (figure S7(e)).

Figure 7 reports the simulation results for ion actuation in the ionoCP case study with the optimized parameters described above. Here, ionophores L are embedded in the CP and provide selectivity to K^+ ions by forming K^+–L complexes (hereafter, simply KL). The formation process is shown in figure 7(a), where a CP pre-charged with Na^+ is immersed into the extracellular fluid and held at the dedoped state $V_{app} = -1$ V while ionophores bind the free K^+ ions entering from the ECF. At equilibrium, the ratio between potassium (both free and complexed) and sodium ions in the CP results larger than in the ECF (and thus larger than in the nsCP case seen in figure 6). Specifically, we observe $[K^+]_{CP} = 14.9$ mM, $[KL] = 119.8$ mM, $[Na^+]_{CP} = 537.1$ mM, and so $([K^+]_{CP} + [KL])/[Na^+]_{CP} = 25.1\%$ (instead of 2.8% as in the nsCP case).

Figures 7(b) and (c) show two examples of ionic actuation with the ionoCP, for $\nu = 10$ s^{-1} and $\nu = 40$ s^{-1}, respectively ($V_{app,max} = 1$ V). Because of the selectivity induced by the ionophores and their relatively low association constant, a much higher perturbation of $[K^+]$ is obtained with respect to the non-selective case of figure 6. However, the main hallmark of the ionophores' presence is the prolonged release of K^+ due to the unbinding of the KL complexes that continues for several hundreds of ms after the end of the V_{app} ramp (compare figures 7(b) and 6(b)). This is also shown in figure S8, where the local $[K^+]$ at the bottom of the neuron is plotted for different $V_{app,max}$ and for different time snapshots after the end of the release, in both the ionoCP and nsCP cases. Figure 7(c) shows that an AP is obtained by increasing ν to 40 V s^{-1}. Interestingly, a closer analysis revealed that such AP is a mixed ionic/electric AP since it is not elicited if the reversal potentials are kept fixed to their baseline values (see figure S9). In other words, the K^+-induced depolarization lowers the threshold for electrical stimulation necessary to induce firing.

An important feature of the ionoCP device, is the possibility of operating with a single reservoir (i.e. the ECF) as a recyclable source of ions. Figure 8 shows a preliminary investigation of this possibility. Namely, we considered actuation transients with voltage pulses featuring both rise and fall ramps, possibly with different slopes. The falling ramp allows the CP to return to its dedoped state and thus recharged with ions diffusing from the ECF. We extended the simulation time to include many pulses, thereby showing that a full recovery of the baseline equilibrium between CP and ECF is achieved in less than 1 s after the falling ramp. Figure 8 also indicates that the return to baseline of the potential applied to the CP (or, in other words, the CP

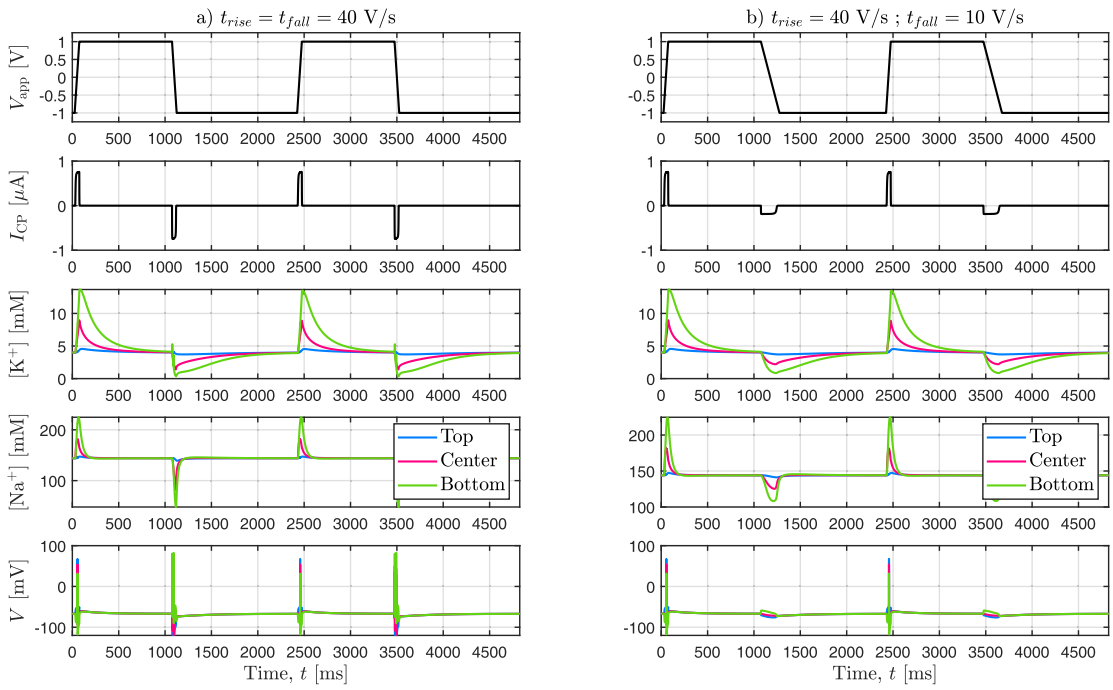


Figure 8. Test of the reversibility of the operation of the ionophores-induced selective CP (ionoCP). Potential pulses with different rise and fall times are applied at the CP during the actuation cycle. From top to bottom, rows indicate: (1) the voltage applied to the CP V_{app}, (2) the current emitted by the CP, $I_{CP} = F\frac{d}{dt}\left(\int_{CP} p\, d\Omega\right)$, the extracellular concentration of (3) [K^+], and (4) [Na^+], and, (5), the membrane potential V. In (a), fast slopes of 40 V s^{-1} are used for both rising and falling edges, causing electrically-induced APs at each front followed by a gradual return to the electrochemical equilibrium. In (b), a slower slope of 10 V s^{-1} is used on the falling edge (i.e. return to baseline) that does not induce APs. Besides, two consecutive pulses are displayed for both cases, showing no perceptible difference in the second pulse compared to the first one in terms of potential waveform and ionic profiles. An interesting observation is that the ionic emission and recharge dynamics are very different, as they reflect two different mechanisms: the first one is the ionic release limited by K^+ diffusion to the bulk of the extracellular fluid, while the second one is the depletion of ions in the proximity of the CP/electrolyte interface, ultimately limited by the diffusion of ions from the bulk to the solution.

recharge of ionic carriers) can be seen as an actuation mechanism as well, since the descending voltage ramp can induce both potential and ion concentration perturbations in the electrolyte. The rate of the recovering step will thus determine the extent of the actuation both in terms of modulation of the ionic concentrations and in terms of the transient electric field in the extracellular domain surrounding the neuron.

The analysis above suggests that, despite not being sufficient to handle a fully ionic neuromodulation, the functionalized ionoCP is still able to enhance the excitability of the neuron and to operate in a reversible fashion. The reader should note that ionophores are here modeled as mobile species in our framework. However, this is not a critical choice since results are very mildly affected by considering such species to be covalently bound to the polymer backbone or with very low diffusion coefficients (see figure S10).

3.4. Ionophores-induced selective CP (ionoCP): effect on AMPA synapses

To further test the neuromodulation capabilities of the ionoCP film, we evaluate the response of the neuron undergoing ionic actuation in the presence of an excitatory synaptic event. First, we determined the synaptic conductances $\bar{g}_{K,syn}$, $\bar{g}_{Na,syn}$ (see figure 2, right) as the minimum values required to elicit APs (see figure S11). Thus, we investigated the efficacy of synaptic transmission for different scaling of the synaptic conductances and for increasing extents of ionic release (see figure 9). We point out that, since the neural membrane is described by a reduced HH model [43], the $\bar{g}_{X_i,syn}$ are regarded as phenomenological terms lumping the postsynaptic conductances of all the AMPA synaptic receptors, rather than the dynamics of a single synapse. In this perspective, variations of $\bar{g}_{X_i,syn}$ qualitatively represent changes in the presynaptic drive to the neuron. Figure 9(a) shows a synaptic event occurring 30 ms after an ionic actuation transient that fails to induce an AP (0.4 $g_{X_i,syn}$, $V_{app,max} = 0$ V). Successful synaptic transmission can be achieved through larger presynaptic drive (0.7 $g_{X_i,syn}$ in figure 9(b)) or more ionic release ($V_{app,max} = 1$ V) in figure 9(c), since the postsynaptic current gets enhanced. Figures 9(a)–(f) illustrate a more extensive study, where elicited APs are mapped in the two-dimensional space of synaptic conductances scaling—extent of ionic

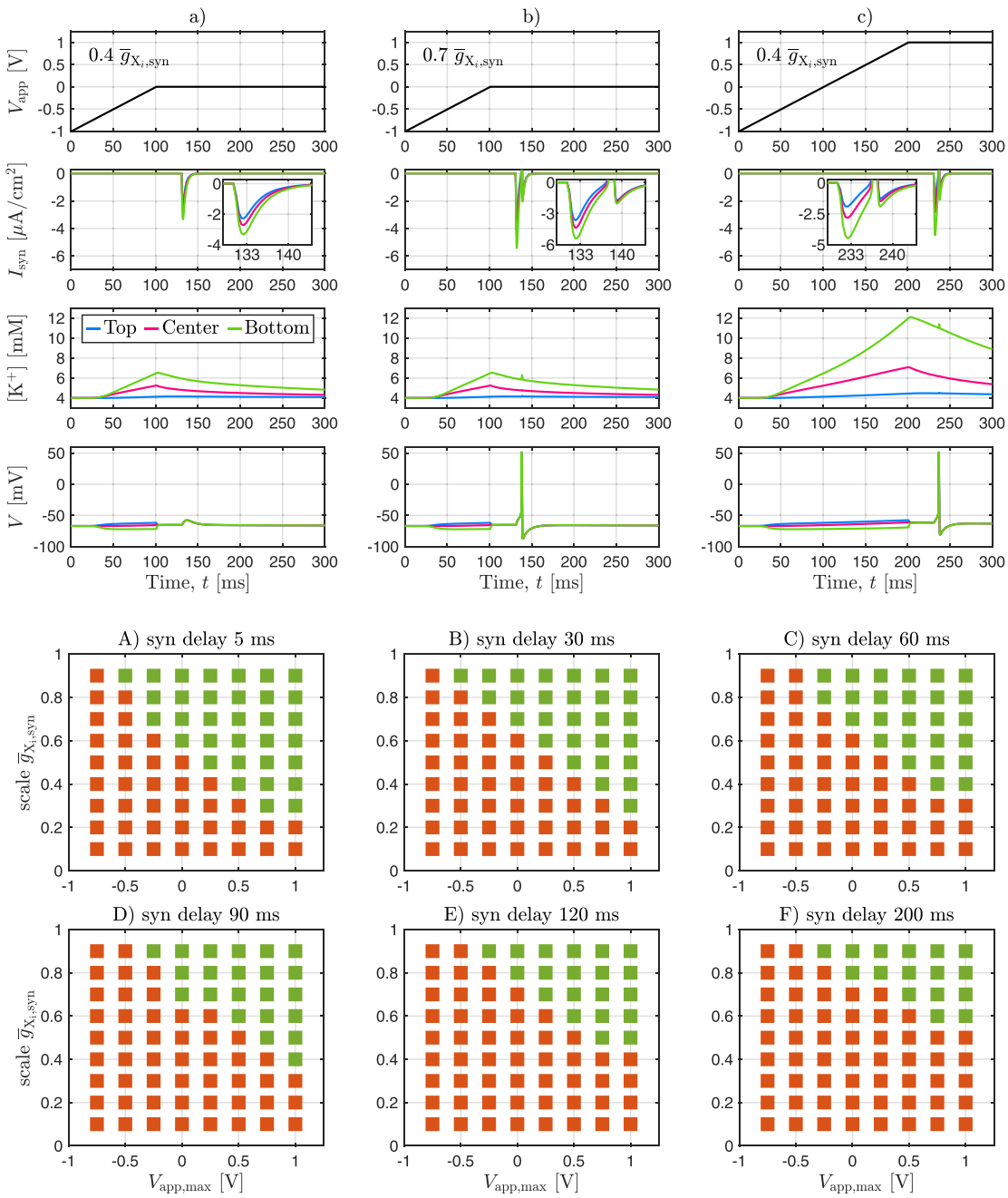


Figure 9. Ionophores-induced selective CP (ionoCP) and synaptic transmission. (Top) Examples of synaptic events taking place 30 ms after the end of the ionic release. The one in (a) fails to induce an AP (0.4 $g_{X_i,syn}$, $V_{app,max} = 0$ (V). Successful synaptic transmission can be achieved by increasing the postsynaptic current with, e.g. (b) a larger presynaptic drive (0.7 $\overline{g}_{X_i,syn.}$) or (c) higher applied potential ($V_{app,max} = 1$ V). The rows show, in order: (1) the potential applied to the CP, (2) the synaptic current $I_{syn} = I_{K,syn} + I_{Na,syn}$ (3) the extracellular concentrations for K^+, and (4) the membrane potential. (Bottom) Systematic evaluation of the synaptic transmission's efficacy in the space of $V_{app,max}$ and the scaling of $\overline{g}_{X_i,syn}$. Each subplot corresponds to a different delay between the synaptic event and the end of ionic release. In order, from A to F: 5, 30, 60, 90, 120, and 200 ms. Green squares: AP elicited. Red squares: no AP elicited.

release, for different delays between ionic stimulation and the synaptic event. These results clearly suggest that excitatory synaptic transmission is facilitated in the presence of the ionic actuators releasing K^+. Moreover, thanks to the slow release granted by ionophores, such facilitation lasts up to hundreds of milliseconds with progressively milder intensity.

4. Discussion

4.1. Modeling of neuromodulation through ionic actuators

In this work, we introduced a finite-element model to describe the interaction between a CP-coated microelectrode and a neuron soma. To the extent of our knowledge, this is the first computational

framework that solves the coupled equations for the dynamics of an ionic actuator, the cellular fluids, and the neural membrane. We used our simulation framework to investigate the controlled delivery of potassium in the extracellular fluid as a neuromodulation mean. We considered three case studies for the CP, with different levels of selectivity to K^+: ideally-selective (isCP), non-selective (nsCP), and ionophores-induced selective (ionoCP).

The isCP case, despite being unrealistic, allowed us to showcase the technological potential of ionic neuromodulation assuming a CP film able to selectively store and release in the ECF only potassium. A local increase of $[K^+]$ allows steering a target neuron to regimes of firing or depolarization block by affecting its intrinsic excitability. These are well-established facts in literature [66], which can be leveraged to elicit or inhibit neural activity, respectively. We note that, regarding inhibition, depolarization block is a mechanism putatively exploited by neurons to limit the overall network activity also *in-vivo* [67]. A FEM modeling framework enables to link such neuromodulation targets to the physical and geometrical parameters of the CP and its surroundings, as well as the stimulation protocols. Examples of such capabilities have been showcased by changing the potential waveform applied to the CP, the maximum releasable dose of potassium, the lateral encumbrance due to other cells, and the size of the CP-neuron cleft. Notwithstanding, similar analyses can be performed for all the other model parameters, e.g. the CP size, the material of the metal contact, or other intrinsic parameters of the CP, such as the volumetric capacitance, in support of thoughtful engineering choices.

At the opposite side of the selectivity spectrum, the nsCP case illustrates how a bare PEDOT:PSS-coated electrode is not effective as ionic neuromodulator. Indeed, it is not able to hold a pre-charged potassium dose, e.g. coming from a preconditioning stage in a different electrolyte. Further, it mainly conveys electric stimuli to target neurons. This is an important sanity check for our simulation deck, since such coatings are routinely used in electric neurostimulation devices to enhance properties such as contact impedance, charge storage capacitance, and biocompatibility [68, 69], and our model confirms that such electrodes can elicit APs through electrical stimulation but not via ionic perturbation.

The ionoCP case is investigated as a possible ionic neuromodulation device endowed with ionophores that confer selectivity. Indeed, the possibility to embed ionophores in the polymeric backbones has already been proven in the literature [21–23], even though they were employed for ion-sensing devices rather than for ion delivery. A second important challenge addressed by our solution is the operation in a single reservoir, i.e. the ECF, which holds the promise to act as a recyclable source of ions to perform unlimited stimulation, reconciling miniaturization without handling multiple reservoirs as in other iontronic solutions [13, 70]. Our findings suggest that ionophores with an equilibrium constant around $\beta_{KL} = 100\ M^{-1}$ give the best trade-off between selectivity and release performance. This value is smaller than those used in sensor applications (e.g. $\beta_{KL} = 1026.2 \pm 118.3\ M^{-1}$ in [21]) as too strong complexes are difficult to dissociate during the actuation phase. Notwithstanding, our framework can be utilized to test realistic ionophore species [71, 72], by instantiating the respective parameters. With the optimized ionoCP, we have shown *in-silico* that, despite its performances being highly inferior with respect to the isCP, it is still possible to induce a significant local perturbation of $[K^+]$ up to tens of mM above the extracellular bulk concentration, sufficient to enhance the sensitivity of the neuron to other stimulation means (e.g. electrical stimulation), as well as to facilitate excitatory synaptic transmission. A similar neuromodulation capability was recently proven *ex-vivo* in retina tissue by microfluid delivery of Ames' medium containing 22 mM K^+ on perforated microelectrode arrays [73]. This suggests that induced synaptic facilitation provided by ionic neuromodulation may also represent a mean to trigger synaptic plasticity in networks of neurons.

The above analysis led us to conclude that it is difficult to elicit APs by releasing potassium ions only, unless an ideally selective polymer is available. In case the polymer is not selective or only partially selective, APs are essentially elicited by electrical stimulation if the electrode potential is ramped fast, but this cannot be referred to as *ionic actuation*. Further, ideal selectivity for actuation purposes is very hard to achieve with ionophores. The inclusion of synaptic dynamics showed that effects on neural activity driven by ionic actuation are more pronounced through the synaptic pathway rather than those affecting the intrinsic excitability of the neuron. These analyses, despite being qualitative, prompt the need for a description of neuronal dynamics down to the level of synaptic transmission to correctly predict the effects of ionic actuation. Since synaptic dynamics is intrinsically a network phenomenon, more effort must be made to increase the complexity of the simulation deck, while ensuring a viable computational cost. We remark that our conclusions, despite being obtained *in-silico*, are build upon models that have been extensively validated against experiments. Indeed, the two-phase model for the CP has been shown to effectively fit electrochemical data [28]. Moreover, the HH model [43], coupled with lumped dynamics of ions in the cellular fluid, was able to qualitatively capture the firing patterns of interneurons of the rat CA1 hippocampus in seizure-like and spreading depression-like events [50, 51].

4.2. Simulation platform

Our approach based on COMSOL Multiphysics enables seamless integration with other stimulation or sensing devices that may be relevant in neuromodulation applications, like multielectrode arrays [74]. Moreover, the use of a commercial platform has been motivated by its widespread adoption in the computational communities of neuroengineering [33, 34] and electrochemistry [28–32], and by its capabilities in bridging the gaps between these two disciplines: the former being very knowledgeable in terms of modeling neural activity and excitation but relying on an ohmic description of the neural milieu, while the latter focusing on the electrodiffusive description of cellular fluids but without taking into account the effects on neuronal activity. We point out that this is an alternative approach compared to that of the computational neuroscience community dealing with drift-diffusion phenomena in the neural microenvironment [39, 75–78], which typically embraces open-source software.

4.3. Model limitations and outlook

In this work, we resorted to the PNP model to describe ion electrodiffusion in the cellular fluids. Modeling neural activity with such a level of detail is very computationally demanding and therefore difficult to scale to large spatial domains and more complex geometries. The main reason resides in the building up of electrical double layers at charged interfaces that require very fine spatial meshes with subnanometer resolution. Therefore, studies in the literature employing this formalism have been hitherto limited to simple neural morphologies such as axons [39]. Alternatively, other studies have focused on neural microdomains [41, 42] with small spatial extension, like nodes of Ranvier [40], spines [79], ion channels [80], and synapses [81]. As an example of the aforementioned computational burden, we observed an average simulation time of about 26 min for the studies reported in figure 9(b) (89 transients lasting 300 ms), while about 33 min for those in figure 9(d) (89 transients lasting 400 ms). Simulations were run in parallel on two servers: the first with an Intel® Xeon® X5690 CPU and 189 GB of RAM while the second with an Intel® Xeon® Gold 6136 CPU and 500 GB of RAM. Further details are reported in supplementary note 1. It is thus clear that a reduction in the computational burden is pivotal to pave the way to more realistic descriptions of the *in-vivo* neural milieu, e.g. accounting for detailed neuron morphologies [82] and network interactions [83]. This, in turn, holds the promise to make the presented framework more informative for the design and optimization of ionic actuators, and allows it to handle more complex and realistic cases needed for proper validation against experimental data.

Aiming in this direction, the Kirchhoff–Nernst–Planck (KNP) framework has been developed [58, 75–78, 84]. It sensibly reduces the computational burden by enforcing electroneutrality in the resolved space domain and splitting displacement currents among ionic fluxes at the cell membranes. However, the validity of KNP has been assessed for biological electrogenic sources [85] but not during the operation of ionic actuators. Indeed, to date, computation efforts focusing on the sole ionic actuator rely on the PNP [29–32]. Before deploying the KNP in our setting, its domain of validity must be determined taking into account the tiny clefts and non-physiological ionic concentrations that may stem from the neuron-CP interaction. A preliminary analysis is shown in figure S12, where we report the charge density in the cleft between the CP and the neuron under the ion release by the ionoCP (figure S12(a)) or the nsCP (figure S12(b)). Further, we consider the charge in the cleft during a synaptically-induced AP (figure S12(c)), as an example of physiological electrogenic source. Except for the starting and ending phases of the applied stimulus ramp, at each time point the charge in (b) is similar to that in (c). On the other hand, the charge results more than ten times greater in (a) than in (c). This deviation from electroneutrality persists for the entire duration of ionic release in (a) (hundreds of ms) instead of a single AP's duration in (c) (a few ms). These results suggest that the electroneutrality assumption embraced by the KNP might not hold under the operation of ionic actuators like the ionoCP. A thorough comparison of the PNP model used in this work with a KNP-based model is not in the scope of this work and is left for future investigation.

It is important to remark that in our approach the dynamics of the cellular fluids and the ionic actuator are solved self-consistently. This modeling scheme is rarely pursued, even in established computational frameworks supporting the design of neural interfaces, e.g. for electrical stimulation [86, 87]. Rather, scientists resort to *hybrid models*: first, the extracellular potential is computed with either analytical approximations [88] or finite-element methods (FEMs) [33]; second, the response of nerve cells is assessed by feeding the results of the previous step as input. Similar schemes have been developed also for electrodiffusive models of the neuron-ECF interaction [75]. Assessing the validity of these schemes in the ionic neuromodulation setting may provide further means to reduce the computational cost, thanks to the decoupling of simulations in two problems easier than the original one. To this aim, our model may be instrumental in validating such simplifications. Another advantage of hybrid approaches is to deploy the full potential of simulators of realistic multicompartment models of nerve cells, like NEURON [89], accounting for complex morphological and dynamical features. Unfortunately, our self-consistent framework in COMSOL does not allow us to delegate the solution of the neural membrane

dynamics to third-party software. This limits the integration and reusability of models of neural cells previously published in literature [90].

The electrodiffusive formalism employed in this work, as well as the KNP mentioned above, are intrinsically more accurate than the ohmic formalism, where the cellular fluids are considered volume conductors and diffusion mechanisms are neglected. Given its simplicity and low computational cost, the ohmic formalism is widely used to model the interface between neurons and implanted electrodes, both for stimulation [34] and recording [91] studies. However, the lack of a proper description of the ionic transport limits the validity to cases where the electric field is the main vehicle of action potential recording/-generation. In supplementary note 2 (section 'Limit case: ohmic approximation for cellular fluids') we introduce the main equations of the ohmic formalism and show that, in fact, its predictions agree with our model only in limit cases where the cleft between the CP and the neuron is sufficiently large such that the modulations of the ionic concentrations are relatively small. In this comparison, we employed the nsCP since, among our case studies, is the one that best reproduces electrodes routinely used in scenarios of electrical neural stimulation/recording (see section 4.1).

We built our modeling framework with the aim of having the essential features to serve as a benchmark for testing the neuromodulation capabilities of the ionic actuator. The selected features resulted from a compromise between the computational burden of simulations and the spatio-temporal scales of interest, namely those of a single neuron soma discharging up to a few APs, thereby leading to several simplifications. On the neural milieu's side, we modeled the dynamics of K^+, Na^+, and Cl^- ions, along with the ion channels responsible for the sole generation of action potentials. However, many other ions [1], like Ca^{2+} or Mg^{2+}, and ionic channels [36] affects the neural functioning. Furthermore, we neglected homeostatic mechanisms occurring at neural membranes or glial cells that are pivotal for the regulation of the ionic composition in the neural microenvironment [2] and are expected to counteract the operation of ionic actuators. Nevertheless, the effects of such mechanisms manifest at temporal scales longer than the ones of interest in this work. A possible way to capitalize on the aforementioned efforts to reduce the computational burden would be the inclusion of such mechanisms and gain insight into the effects of ionic actuation at longer temporal scales. Similar considerations apply also to the CP's side, where many non-idealities and parasitic phenomena were neglected. For instance: faradaic conduction in the CP [92], the formation of competing bindings of ionophores with, e.g. Na^+ ions [21], series impedance of the electrodes [59], as well as red-ox reaction between the CP and the cellular fluids [55]. Other model simplifications are the usage of uniform and time-invariant parameter values inside domains, in contrast with time variability and reduced ionic diffusivity due to tortuosity effects in the ECF [93], as well as variability in the density of ion channels in different portions of the membrane [94]. Notwithstanding, our multiphysics framework is amenable for the integration of these features to explore their effects on the device performance.

5. Conclusion

This work combines the multiphysical description of the most essential set of electrochemical and biological processes regarding neurons under ionic and electrical stimulation in a single comprehensive simulation deck. By including accurate models of ion-transport and transmembrane fluxes we demonstrated *in-silico* that the proposed modeling approach can be a powerful tool to predict neuron excitability and to benchmark the performance of novel neuromodulation devices. As an example of application, we simulated the action of an ionic actuator based on OMIECs embedding ionophores and demonstrated its capability to provide single-neuron synaptic facilitation. These efforts are oriented toward versatile integration with iontronic devices aiming at closing the loop of already existing methodologies for neural recording and computation *in-liquido* [95].

Data availability statement

The data cannot be made publicly available upon publication because they are not available in a format that is sufficiently accessible or reusable by other researchers. The data that support the findings of this study are available upon reasonable request from the authors.

Acknowledgment

This work was supported by the European Union's Horizon 2020 Research and Innovation Programme (IN-FET Project) via the Consorzio Nazionale Interuniversitario per la Nanoelettronica (IUNET) under Grant Agreement 862882.

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