This is the peer reviewd version of the followng article:

Finite-element modeling of neuromodulation via controlled delivery of potassium ions using conductive polymer-coated microelectrodes / Verardo, Claudio; Mele, Leandro Julian; Selmi, Luca; Palestri, Pierpaolo. - In: JOURNAL OF NEURAL ENGINEERING. - ISSN 1741-2552. - 21:2(2024), pp. 1-18. [10.1088/1741-2552/ad2581]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

26/12/2024 15:57

¹ Finite-element modeling of neuromodulation via

- ² controlled delivery of potassium ions using
- ³ conductive polymer-coated microelectrodes

4	Claudio Verardo ^{*,1,3} , Leandro Julian Mele ^{*,1,4} , Luca Selmi ² ,
5	Pierpaolo Palestri ^{1,2}
6	¹ Polytechnic Department of Engineering and Architecture, Università degli Studi di
7	Udine, Udine, Italy
8	2 Department of Engineering "Enzo Ferrari", Università degli Studi di Modena e
9	Reggio Emilia, Modena, Italy
10	³ BioRobotics Institute and Department of Excellence in Robotics and AI, Scuola
11	Superiore Sant'Anna, Pisa, Italy
12	⁴ Department of Materials Science and Engineering, Stanford University, Stanford,
13	United States of America
14	* The authors contributed equally to the work.
15	E-mail: pierpaolo.palestri@uniud.it

The controlled delivery of potassium is an interesting neuromodulation Abstract. *Objective*. 16 modality, being potassium ions involved in shaping neuron excitability, synaptic transmission, network 17 synchronization, and playing a key role in pathological conditions like epilepsy and spreading depression. 18 Despite many successful examples of pre-clinical devices able to influence the extracellular potassium 19 concentration, computational frameworks capturing the corresponding impact on neuronal activity 20 are still missing. Approach. We present a finite-element model describing a PEDOT:PSS-coated 21 microelectrode (herein, simply *ionic actuator*) able to release potassium and thus modulate the activity 22 of a cortical neuron in an *in-vitro*-like setting. The dynamics of ions in the ionic actuator, the neural 23 membrane, and the cellular fluids are solved self-consistently. Main results. We showcase the capability 24 of the model to describe on a physical basis the modulation of the intrinsic excitability of the cell and 25 of the synaptic transmission following the electro-ionic stimulation produced by the actuator. We 26 consider three case studies for the ionic actuator with different levels of selectivity to potassium: 27 ideal selectivity, no selectivity, and selectivity achieved by embedding ionophores in the polymer. 28 Significance. This work is the first step toward a comprehensive computational framework aimed 29 to investigate novel neuromodulation devices targeting specific ionic species, as well as to optimize 30 their design and performance, in terms of the induced modulation of neural activity. 31

32 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 38 calcium through voltage-gated Ca^{2+} channels [4]–[6]. At the network level, potassium 39 accumulation and diffusion generate non-synaptic coupling between neurons, which 40 in turn shapes network activity and may induce synchronization [7]. Perturbations 41 of $[K^+]$ are interesting also from a neurological perspective, since they are linked to 42 many pathological conditions such as epilepsy [8], [9] or spreading depression [10], [11]. 43 Therefore, the control of $[K^+]$, which we will thereafter refer to as *ionic stimulation*, is 44 drawing attention as a possible innovative pathway toward neuromodulation [12]. This 45 has been implemented by several novel devices, herein referred to as *ionic actuators*, 46 capable of perturbing the extracellular concentration of potassium at spatiotemporal 47 scales approaching those of neuron activity [13]-[15]. 48

Ionic stimulation obtained with ionic actuators fits in the broader realm of drug-49 delivery devices applied to neuromodulation. A prominent class of such technology relies 50 on the properties of conductive polymers (CPs) [16], also known as organic mixed ionic 51 and electronic conductors (OMIECs) [17]. CP-coated electrodes can modulate the local 52 ionic concentration upon application of an electrical stimulus which translates into the 53 injection of holes‡ (or electrons) in the polymer backbone and is followed by the release 54 of pre-charged cations (or anions) in the target electrolyte. The pre-charging can be 55 achieved using the electrostatic forces provided by fixed moieties in the CP blend or 56 when the charged drugs act as dopants [18]–[20]. In the purely electrostatic CP loading, 57 selectivity can be achieved by adding ionophores [21]-[23], using ion-selective membranes 58 [24] or cell membrane bilayers with specific ion-channel expressions [25]. Alternative 59 architectures that stem from the field of iontronics [26], bypass the selectivity problem 60 by employing multiple electrolyte reservoirs where ions/drugs are stored, delivered or 61 drained [13]–[15]. However, this approach poses evident challenges in the design and 62 implementation of the microfluidics, requires high voltages and is thus not easy to 63 miniaturize. 64

Multiphysics computational models are pivotal to aid the design and deployment 65 of ionic actuators as neuroengineering devices, as they reduce the need for *in*-66 vitro/animal studies and the prototyping cost and development time. Indeed, they 67 allow to improve the understanding of the device operation, by providing insight into 68 underlying phenomena not directly accessible by experiments. Moreover, they enable the 69 investigation of large regions in the parametric space, paying the way for optimum design 70 of the neuromodulation devices. Modeling the dynamics of ionic actuators requires an 71 accurate description of the ions' electrodiffusion. Given the relatively large dimensions 72 of these devices, the Poisson-Nernst-Planck (PNP) model [27] is a good candidate to 73 capture both drift and diffusion transport mechanisms, as well as charge screening effects 74 in the space-time domain. The PNP model can also be adapted to CPs [28], and has been 75 employed in computational works focusing on the characterization and optimization of 76 iontronic devices [29]–[31] or ISM-cuff electrodes [32]. Notwithstanding, to the extent of 77

[‡] 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.

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 82 activity resides in the workhorse models employed in computational neuroscience: the 83 volume conductor description of the cellular fluids [35], and the cable theory framework 84 of membrane dynamics [36]. Indeed, the former assumes the neuron milieu to be ohmic, 85 while the latter relies on a circuit-level description of the transmembrane fluxes. As a 86 result, the modeled electric currents have no direct connection with the underlying ionic 87 fluxes. This is not an issue when modeling, e.g., the electric interaction with electrodes 88 for stimulation [33], [34] and recording [37], [38], but becomes pivotal in presence of 89 ionic actuators (see Methods). A small body of literature applied the PNP framework 90 to describe ionic transport phenomena occurring in nervous tissues [39]–[42], mainly 91 focusing on the study of slow potentials and microdomains. We point out that these 92 frameworks exploit the quasistatic approximation of Maxwell equations [35], thereby 93 neglecting capacitive and inductive effects in the cellular fluids. Also, there exists a 94 family of models describing ion dynamics in the nervous milieu under the assumption 95 of only diffusive fluxes [43]–[48]. However, this is in general not justifiable for non-96 biological electrogenic sources like ionic actuators, since that approach neglects possible 97 components of electric stimulation arising from ion release/uptake. 98

In this work, we propose the first *in-silico* framework that describes the coupled 99 dynamics of a ionic actuator, ion transport in the intra- and extra-cellular fluids (ICF, 100 ECF), and the electrogenic processes at the neural membrane. These models are solved 101 in a self-consistent fashion according to the electrodiffusive level of detail. As a case 102 study, we use a PEDOT:PSS-coated microelectrode releasing K⁺ placed below a cortical 103 neuron soma with dome geometry. This configuration enables us to examine how the 104 action of the ionic actuator affects neural activity, both through the perturbation of the 105 extracellular potassium concentration (*ionic stimulation*) and of the electrical potential 106 (*electric stimulation*). First, we showcase the extreme cases of an ionic actuator with 107 either ideal selectivity or no selectivity to K^+ . In the ideal case, the sole action 108 of the ionic actuator is sufficient to drive ionically the neuron into tonic firing or 109 depolarization block. In the non-selective case, mainly electric stimulation is delivered 110 since the polymer is not able to collect enough potassium from the extra-cellular fluid. 111 Second, we study a possible functionalization of the actuator's selectivity by resorting 112 to ionophores. Simulations show that the optimized ionic actuator enhances the neuron 113 sensitivity to concurrent electrical stimulation as well as to facilitate excitatory synaptic 114 transmission. 115



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 3.0.

116 2. Methods

The computational framework used in this work (Fig. 1) couples the dynamics 117 of the ionic actuator, the ICF, the ECF, and the neural membrane. It combines 118 modeling efforts from the literature separately accounting for the CP-electrolyte 119 interaction [28], and ion transport in cellular fluids in presence of the neural membrane's 120 electrogenic activity [39], [43]. The simulation domains with the corresponding physics 121 are represented by a frame and a set of equations in Fig. 1. Arrows connecting 122 frames report the equations that couple different domains. Generalizations of the 123 computational framework to account for ionophores and synapses are shown in Fig. 2. 124 A description of the abbreviations, physical variables, and parameters used is reported 125 in the supplementary materials in Tables S1, S2, and S3, respectively. The model 126 is implemented in COMSOL Multiphysics [49] (technical details are reported in the 127 Supplementary Note 1). In the following, we briefly describe the model equations, the 128 reference physical and geometrical parameters, as well as the case studies examined. 129 The model verification is addressed in the Supplementary Note 2. 130



Figure 2. Sketch illustrating the changes made to the modeling framework shown in Fig. 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 Fig. 1) and the HH model of the neural membrane (yellow frame, as in Fig. 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 3.0.

131 2.1. Model equations

2.1.1. Intra- and extra-cellular fluids The ECF and ICF are modeled as electrolytes 132 using the PNP equations (Eqs. 1-3). The electrostatic potential of the ions, ψ_c , is 133 obtained by solving the Poisson equation (Eq. 1), which depends on the local space and 134 time-dependent net charge density due to all the ionic species in the aqueous phase. For 135 simplicity, we restrict the analysis to the main ionic agents responsible for the generation 136 of action potentials (APs) at the neural membrane, namely K⁺, Na⁺, Cl⁻. The bulk 137 concentrations are taken from [43], in agreement with typical (artificial) cerebrospinal 138 fluids [1]. A generic anion A⁻, assumed fixed and uniformly distributed for simplicity, 139 is added to provide electroneutrality (i.e., $[K^+] + [Na^+] - [Cl^-] - [A^-] = 0$) in the bulk of 140 the solutions. Mass conservation of each mobile species is enforced with the continuity 141 equations (Eqs. 2). Therefore, time-dependent variations of ionic concentrations are 142 given by drift and diffusion fluxes and described using the Nernst-Planck transport 143 equations (Eqs. 3). Note that, Eqs. 1-3 are solved in both the extra and intracellular 144 domains. The presence of an extracellular reference electrode (RE) is mimicked through 145 boundary conditions in the ECF's bulk that set the electric potential to ground and the 146 ionic concentrations to their baseline values. Since no limit on the RE's current is 147 imposed, such boundary conditions also account for the action of a counter electrode 148 (CE).149

2.1.2. Neural membrane The transmembrane fluxes through ion channels are modeled 150 using the Hodgkin-Huxley (HH) formalism (Eqs. 6-8), implemented at each mesh point 151 of the cell membrane. The HH model of this work has been introduced in [43] and 152 later used to describe an interneuron of the rat CA1 hippocampus [50], [51]. It includes 153 a transient sodium current (subscript T) and a delayed rectifying potassium current 154 (subscript DR), which are voltage-gated and responsible for the generation of APs (Eqs. 155 7a-b). Moreover, our implementation has a leakage current (subscript L) specific for each 156 ion species (Eqs. 7c-e), differently to the original HH model [52]. Equation 6 collects 157 three first-order differential equations modeling the dynamics of the gating variables 158 for the potassium (n) and sodium (m, h) voltage-gated channels, which depend on the 159 (in)activation curves n_{∞} , m_{∞} , h_{∞} , and time constants τ_n , τ_m , τ_h , respectively. Equation 160 8 reports the total transmembrane current density for each ion species, which depends 161 (through Eq. 7) on the maximum conductances of the ion channels, the gating variables, 162 and the difference between the membrane and reversal potentials (see Section 2.1.3). In 163 order to preserve the rest potential $V_{\rm r}$ of the chosen HH model at the steady state, each 164 current density in Eq. 8 is shifted by its value $I_{X_i,r}$ at V_r , where $X_i \in \{K^+, Na^+, Cl^-\}$, 165 and therefore is null under steady-state conditions. We note that alternative choices for 166 the steady state are possible. For instance, in [39] the authors block the voltage-gated 167 channels and let the system achieve the thermodynamic equilibrium. Nevertheless, since 168 sub-threshold fluxes are orders of magnitude smaller than the ones that shape neural 169 firing, these choices are expected to mildly impact the system's behavior. Since our 170 investigations focus on temporal scales of tens to hundreds of milliseconds (see Results), 171 we do not account for homeostatic mechanisms responsible for the regulation of ion 172 concentration, such as ion transporters at the neural membrane or spatial buffering by 173 glial cells [2]. The interaction of these mechanisms with ion dynamics is expected to 174 become relevant at the scale of seconds or longer [43]–[48]. 175

2.1.3. Coupling HH and PNP models The currents through ion channels are imposed 176 as flux boundary conditions in and out of the cell (Eq. 10), according to the ion currents 177 given by Eq. 8. The dielectric effects of the membrane are modeled as an ideal capacitor 178 with parallel plates via a thin layer approximation. Namely, they are accounted for 179 through boundary conditions on the electric displacement field that depends on the 180 membrane capacitance $C_{\rm m}$ and the membrane potential V (Eq. 9). These conditions 181 are responsible for the electrical double layer (EDL) formation at the two sides of the 182 membrane, and avoid the need to explicitly solve the Poisson equation in the membrane 183 domain (as done, e.g., in [39]), thereby reducing the computational cost. The HH model 184 extracts the membrane potential V by sampling the electrostatic potential predicted by 185 the PNP at the intra- and extra-cellular side of the neural membrane (Eq. 4). Differently 186 from previous works [39], the runtime calculation of the reversal potentials $V_{\rm K}$, $V_{\rm Na}$, $V_{\rm Cl}$ 187 is done by sampling the ionic concentrations at a distance $d_s = 6$ nm from the neural 188 membrane, i.e., a distance 5 times larger than the Debye length [27] in the ECF and ICF 189 (Eq. 5). This strategy is adopted to avoid distortion of the ion concentrations induced 190

¹⁹¹ by charge screening effects in the EDL.

2.1.4. Ionic actuator The ionic actuator consists of a film of conjugated polymer-192 polyelectrolyte blend (hereafter simply referred to conductive polymer, CP), that is, a 193 two-phase domain where both ionic and electronic transport take place simultaneously 194 (see Fig. 1). We consider a PEDOT:PSS blend as the reference CP and use the model 195 proposed in [28]. According to [28], the polyelectrolyte PSS phase and the PEDOT 196 phase can be modeled by coupling two PNP sets of equations: in the PNP of the PSS 197 phase, the concentration of holes is added to the space charge density of the Poisson 198 equation so that ions are electrostatically influenced by the holes' spatial distribution 199 (see Eq. 13); differently, in the PNP of the PEDOT phase the electrostatic potential of 200 holes, ψ_p , in the Poisson equation (Eq. 16) depends on ψ_c in the form of a capacitive 201 coupling, namely, through the volumetric capacitance C_V (with units of F/cm³). This 202 phenomenological term quantifies the extent of entanglement between the two phases 203 and can be seen as the result of a three-dimensional EDL [53], [54]. Mass conservation of 204 ions and holes in their respective phase is also ensured by the continuity equations (Eqs. 205 14 and 17), where electrodiffusive fluxes are described with the Nernst-Planck equation 206 (Eqs. 15 and 18). Note that, for the sake of simplicity, we do neglect reactions occurring 207 at the CP/electrolyte interface [55], such as oxygen reduction reactions (ORRs) often 208 seen in PEDOT:PSS CPs [56]. This phenomenon should translate into an additional 209 faradaic current drawn by the WE when using a negative bias but should not sensibly 210 impact the capacitive mechanism that enables the ionic injection in the extracellular 211 fluid. 212

213 2.1.5. Coupling between polyelectrolyte and extracellular fluid Since polyelectrolyte and 214 electrolyte phases are both ionic phases, the PSS/ECF interface must ensure continuity 215 of the electrostatic potential (see Eq. 11). Fluxes of ions, however, may experience 216 affinity changes due to, e.g., ionophores incorporated in CP [21], [22] or from ion-217 selective barriers [25]. For the sake of generality, we equipped our model with virtual 218 affinity coefficients $\gamma_{\rm K}$, $\gamma_{\rm Na}$, $\gamma_{\rm Cl}$ at the PSS/ECF interface equal to either 0 or 1 (see 219 Eq. 12) to introduce ideal selectivity of the CP to specific ions (see Section 2.2).

Ionophores While the parameters γ_{X_i} , $X_i \in \{K^+, Na^+, Cl^-\}$, are used as 2.1.6. 220 phenomenological terms to induce ideal selectivity, ionophores are employed as a more 221 realistic way to describe a selective ionic actuator [21], [22]. With respect to the ideal 222 CP, the physics of an ionophore-containing CP (described in Fig. 2, left panel) also 223 includes the continuity equations (Eqs. 25, 26) for the free ionophores, L, as well as the 224 selective complexes formed with potassium ions, KL. Forward and backward reaction 225 terms are included in these equations and the continuity equation for K^+ ions (Eq. 24) 226 to account for the binding and unbinding mechanisms of ionophores and potassium ions 227 [57]. Electrodiffusive fluxes are described by the Nerst-Planck equation (Eq. 27). Note 228 that ionophores are confined in the CP domain and can be regarded as fixed or mobile 229

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 (Eq. 23). The continuity equations and the electrodiffusive fluxes for Na⁺ and Cl⁻ are the same as in Eqs. 14-15 but, for the sake of clarity, they are also reported in Eqs. 21-22 to explicitly separate the K⁺ dynamics.

2.1.7. Synapses A model of excitatory synapse (described in Fig. 2, right panel) is 235 included in the neural membrane when testing the neuromodulation capability of the 236 CP beyond to purely induce APs (see Section 3.4). The model is taken from [58] and 237 accounts for the K^+ and Na^+ fluxes through an AMPA postsynaptic receptor (Eq. 238 26). We consider only single synaptic events for each simulation. The excitatory 239 postsynaptic currents (EPSCs) are described with a template profile for the ion 240 postsynaptic conductances, and are modulated by the membrane and reversal potentials. 241 The total transmembrane currents for each ion species are updated accordingly (Eq. 242 27). Differently to [58], we neglect the small calcium component to avoid the additional 243 computational cost of modeling the Ca^{2+} electrodiffusion in the cellular fluids. 244

245 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 pre-charged almost completely with K⁺, which compensates the fixed moieties PSS⁻.

• 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.



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.

268 2.3. Geometry

The proposed modeling approach allows us to spatio-temporally resolve ionic gradients 269 and potential drops in the continuous space including the double layer charge at the 270 interfaces. As such, this model demands for a refined space discretization capable to 271 reproduce sub-nanometer features. To reduce computational cost we consider a 2D-272 axisymmetric geometrical domain that cuts down the model complexity to the one of 273 a 2D model but restricts geometry to axial symmetry [59]. The reference simulation 274 structure used in this work is shown in Fig. 3.a. It includes an active neuron cell (light 275 red) shaped as a halved oblate ellipsoid (dome) laying on a ring-shaped ionic actuator 276 (dark blue) immersed in an electrolyte bath (light blue). Lateral neurons (grey, on the 277 right) are non-active and are included by means of encumbrance to resemble realistic 278 neighboring cells in a cultured setting. Obviously, their dome shape cannot be enforced 279 in the 2D-axisymmetrical model so they are essentially rings limiting the ion transport 280 in the vertical direction as in a realistic culture. An oxide pillar (grey, on the bottom 281 left) is included to keep the neuron at a given distance from the polymer, leaving an 282 electrolyte cleft between the two. A zoom-in view of the active neuron boundaries is 283 reported in Fig. 3.b. If not otherwise specified, we use the values in Table S5 for the 284 geometrical parameters. 285

286 3. Results

287 3.1. Ideally-selective CP (isCP)

Figure 4 shows the working principle of ion actuation in the isCP case study. Initially, 288 the ionic actuator is biased at a negative potential (dedoped state), $V_{app} = -1$ V, which 289 corresponds to a very small hole concentration, p, in the CP so that the PSS⁻ charges are 290 mostly compensated by the stored K^+ ions. By ramping the applied potential, holes are 291 injected into the film (or, in other words, electrons are transferred from the PEDOT into 292 the metal contact) and potassium ions are released in the ECF producing a constant 293 ionic current in accordance with the volumetric capacitive behavior of the CP. The 294 cations diffuse towards the neuron and increase the local extracellular concentration, 295 [K⁺], in the proximity of the cell membrane resulting in membrane depolarization. As 296 shown in Fig. 4.a, a $V_{\text{app,max}} = -0.65$ V produces $\Delta[K^+] = 20$ mM and is able to induce 297 an *ionic* AP. By increasing the maximum value of the applied voltage, one can further 298 increase the released dose of K^+ and hence the local $[K^+]$, thereby eliciting multiple APs. 299 An example is shown in Fig. 4.b, where $V_{app,max} = -0.5$ V induces two consecutive ionic 300 APs. The ionic flux emitted by the CP during the release is proportional to the slope 301 of the ramp stimulus $V_{\rm app}(t)$, namely $v = dV_{\rm app}(t)/dt$. Therefore, higher v yields larger 302 transient perturbations of the local concentration of K^+ . This is shown in Fig. 4.c, 303 where the neuron reaches a configuration of depolarization block [60] due to the large 304 perturbation of [K⁺]. One should note that, since the CP is assumed perfectly selective 305 to K^+ ions ($\gamma_{Na^+} = 0$), the increase of [K⁺] induced by the ionic actuator produces a 306 decrease of $[Na^+]$ and an increase of $[Cl^-]$ (not shown), owing to electroneutrality. While 307 changes in sodium concentration also contribute to membrane depolarization, their effect 308 is quite limited compared to potassium. This is highlighted in Fig. S1, where we show 309 the reversal potentials as a function of the changes in the extracellular ion concentration. 310 We remark that the initial value of the applied potential $V_{app} = -1$ V to keep the polymer 311 in a dedoped state depends on the choice of the CP (PEDOT-PSS), the metal contact, 312 and the reference electrode. Therefore, it may vary with different instances of model 313 parameters. Given the purely capacitive nature of CPs assumed in this work, and since 314 we do not model redox reactions between the polymer and the extracellular fluid, no 315 current flows from the WE to RE under constant applied potential. 316

We point out that, during K^+ release, the bottom side of the neuron is 317 hyperpolarized, while the upper one is depolarized (see the last row in Fig. 4); and 318 the extent of such perturbations is enhanced by larger v. This is due to the drift 319 component of the ionic flux released by the CP, which acts as anodal source of electrical 320 stimulation [61]. Incidentally, this may raise the question that the electrical component 321 may be the main neuromodulation drive of the firing patterns observed in Fig. 4. To 322 rule out this hypothesis, we repeated the same simulations while keeping the reversal 323 potentials fixed to their baseline values (see Fig. S2). Since no APs are elicited in this 324 case, we can confirm that the ionic neuromodulation, and thus the release of potassium 325 ions, is responsible for the neural activity observed in Fig. 4. Fig. S2 also suggests 326



Figure 4. Ideally-selective CP (isCP): examples of ionic neuromodulation transients. Different profiles for the applied potential to the CP are considered: a) $V_{\text{app,max}} = -0.65 \text{ V}$, v = 10 V/s, b) $V_{\text{app,max}} = -0.5 \text{ V}$, v = 10 V/s, c) $V_{\text{app,max}} = 0 \text{ V}$, v = 50 V/s. 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 Fig. 3.b. In the second row, two different scales are adopted for [K⁺], [PSS⁻] and [Cl⁻], p, respectively (see arrows in the legend).

that the slope of the actuation potential must 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 $V_{\rm app}(t)$ 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 332 of ionic concentrations and potentials of the transient in Fig. 4.a. Three time points 333 are considered: (left) at the end of K^+ release (t = 35 ms), (middle) at the peak of the 334 elicited AP (t = 46.87 ms), and (right) during the post-AP re-equilibration of ions in the 335 ECF (t = 80 ms). A close inspection of the extracellular potential (fourth row) confirms 336 a non-negligible electrical gradient during release (e.g., the total potential drop in the 337 neuron-CP cleft is a few mV at t = 35 ms), which is responsible for the aforementioned 338 electric component of neurostimulation. 339

³⁴⁰ The ion-release performance of the ionic actuator depends on both CP properties



Figure 5. Ideally-selective CP (isCP): 2D-axisymmetric cutplanes illustrating the spatial distributions of different physical variables taken during the transient simulation in Fig. 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).

and geometrical factors. In fact, on one side the available ionic dose is strictly related to 341 the number of fixed charges incorporated in the film. For example, Fig. S3 shows that 342 the maximum releasable dose of K^+ decreases with decreasing [PSS⁻] in the CP. Once 343 the CP is depleted from cations, Cl⁻ anions start entering the CP to balance the excess 344 holes injected by the metal contact. On the other side, the encumbered space around 345 CP helps to maintain the perturbation of $[K^+]$ in the bottom part of the neuron for 346 longer times, thus facilitating ionic APs. This is shown in Fig. S4 where, for the same 347 V_{app} profile, the change in extracellular [K⁺] decreases for larger gaps between the active 348 and lateral neurons (i.e., low surface density of neurons). A similar effect is obtained 349 for larger clefts between the neuron and the CP, as illustrated in Fig. S5. 350



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-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) v = 10 V/s and b) v = 60 V/s. 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.

$_{351}$ 3.2. Non-selective CP (nsCP)

Figure 6 illustrates the working principle of ion actuation in the nsCP case study. 352 Since no selectivity to K^+ is enforced, we first tested the CP capability of maintaining 353 a pre-charged dose of K^+ ions, i.e., we assume that the polymer has been initially 354 preconditioned with pure KCl that is then replaced with the extracellular fluid. In Fig. 355 6.a we report the simulation results of such ion-retention study, starting from a CP 356 pre-charged with K^+ and held in the undoped state ($V_{app} = -1$ V). Being permeable 357 also to Na⁺, the CP rapidly evolves to a configuration of thermodynamic equilibrium 358 where K^+ and Na^+ concentrations retain the same ratio as in the ECF, corresponding 359 to $[K^+]_{CP} = 65.1 \text{ mM}, [Na^+]_{CP} = 2.34 \text{ M}, \text{ and so } [K^+]_{CP} / [Na^+]_{CP} = 2.8\%$. Therefore, the 360 CP fails to maintain most of the pre-charged K^+ dose, which is released in the ECF in 361 an uncontrolled fashion. Compared to the isCP, the available potassium in the nsCP 362 case is hence reduced by a remarkable factor (37 in our case). 363

Starting from the condition resulting from the transient in Fig. 6.a, we simulate two examples of ionic actuation with applied stimulus featuring either v = 10 V/s or v = 60V/s (Fig. 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,



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-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) v = 10 V/s and c) v = 40 V/s. 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 ion release predominantly affects the local concentration of sodium ions in the ECF. 368 In contrast to what we observed in Fig. 4 for the isCP, $[K^+]$ here increases locally by 369 only a few mM, despite having applied a larger stimulus, $V_{app,max} = 1$ V versus -0.65/-0.5 370 V in Fig. 4. Another important finding is that the membrane potential induced by the 371 nsCP is mostly due to the electric field produced by the applied potential rather than 372 by the perturbation of the ionic concentrations (mostly $[Na^+]$). As shown in Fig. 6.c, 373 an AP can eventually be elicited if v is increased to, e.g., v = 60 V/s. However, the AP 374 persists with an almost identical time course even when the reversal potentials of the 375 neuron are kept fixed to their baseline values (see Fig. S6). We will thereafter refer to 376 this kind of stimulation of action potentials as *electric*, i.e., APs not directly induced by 377 the perturbation of the extracellular ionic concentrations. 378

379 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 ($k_{\rm KL,b} = 10^{-4}$ 1/s as in [64]), while the forward one is by 384 definition $k_{\text{KL,f}} = k_{\text{KL,b}} \cdot \beta_{\text{KL}}$. The optimum was evaluated adopting as figure of merit 385 the $[K^+]$ change achieved in the finite-volume ECF at steady state (representative of 386 the ionic stimulation achievable by the ionoCP), for a given applied $V_{\text{app,max}}$. Fig. 387 S7.a-c show $[K^+]$ vs $[PSS^-]$ curves that were obtained for different total concentrations 388 of ionophore in the system, $[L]_{tot}$, and $V_{app,max} = 2$ V. Interestingly, in all cases, the 389 optimum association constant was $\beta_{\rm KL} = 100 {\rm M}^{-1}$. Even though larger concentrations 390 of ionophores induce more ionic release, we chose [L]_{tot} = 200 mM corresponding to half 391 of the maximum steric occupancy of a very common K^+ -ionophore [65]. Therefore, the 392 optimum from Fig. S7.b was used, i.e., [PSS⁻]= 637 mM. Further analysis regarding 393 the maximum voltage applied at the CP electrode, $V_{app,max}$, revealed that the optimum 394 amount of [PSS⁻] depends on this parameter with direct proportionality (Fig. S7.d) 305 but changes on the above-defined figure of merit are modest (Fig. S7.e). 396

Figure 7 reports the simulation results for ion actuation in the ionoCP case study 397 with the optimized parameters described above. Here, ionophores L are embedded 398 in the CP and provide selectivity to K^+ ions by forming K^+ -L complexes (hereafter, 399 simply KL). The formation process is shown in Fig. 7.a, where a CP pre-charged with 400 $\mathrm{Na^+}$ is immersed into the extra cellular fluid and held at the dedoped state V_app = -1401 V while ionophores bind the free K^+ ions entering from the ECF. At equilibrium, 402 the ratio between potassium (both free and complexed) and sodium ions in the CP 403 results larger than in the ECF (and thus larger than in the nsCP case seen in Fig. 6). 404 Specifically, we observe $[K^+]_{CP} = 14.9 \text{ mM}$, [KL] = 119.8 mM, $[Na^+]_{CP} = 537.1 \text{ mM}$, and 405 so $([K^+]_{CP} + [KL])/[Na^+]_{CP} = 25.1\%$ (instead of 2.8% as in the nsCP case). 406

Figure 7.b and c show two examples of ionic actuation with the ionoCP, for v = 10407 V/s and v = 40 V/s, respectively ($V_{app,max} = 1$ V). Because of the selectivity induced by 408 the ionophores and their relatively low association constant, a much higher perturbation 409 of $[K^+]$ is obtained with respect to the non-selective case of Fig. 6. However, the main 410 hallmark of the ionophores' presence is the prolonged release of K⁺ due to the unbinding 411 of the KL complexes that continues for several hundreds of ms after the end of the V_{app} 412 ramp (compare Fig. 7.b and Fig. 6.b). This is also shown in Fig. S8, where the local 413 $[K^+]$ at the bottom of the neuron is plotted for different $V_{app,max}$ and for different time 414 snapshots after the end of the release, in both the ionoCP and nsCP cases. Fig. 7.c 415 shows that an AP is obtained by increasing v to 40 V/s. Interestingly, a closer analysis 416 revealed that such AP is a mixed ionic/electric AP since it is not elicited if the reversal 417 potentials are kept fixed to their baseline values (see Fig. S9). In other words, the 418 K⁺-induced depolarization lowers the threshold for electrical stimulation necessary to 419 induce firing. 420

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



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, $I_{CP} = F \frac{d}{dt} (\int_{CP} p \, d\Omega)$, the extracellular concentration of 3) [K⁺], and 4) [Na⁺], and, 5), the membrane potential V. In a), fast slopes of 40 V/s 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 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.

ions diffusing from the ECF. We extended the simulation time to include many pulses, 426 thereby showing that a full recovery of the baseline equilibrium between CP and ECF is 427 achieved in less than 1 s after the falling ramp. Figure 8 also indicates that the return to 428 baseline of the potential applied to the CP (or, in other words, the CP recharge of ionic 429 carriers) can be seen as an actuation mechanism as well, since the descending voltage 430 ramp can induce both potential and ion concentration perturbations in the electrolyte. 431 The rate of the recovering step will thus determine the extent of the actuation both in 432 terms of modulation of the ionic concentrations and in terms of the transient electric 433 field in the extracellular domain surrounding the neuron. 434

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 Fig. S10).

441 3.4. Ionophores-induced selective CP (ionoCP): effect on AMPA synapses

To further test the neuromodulation capabilities of the ionoCP film, we evaluate the 442 response of the neuron undergoing ionic actuation in the presence of an excitatory 443 synaptic event. First, we determined the synaptic conductances $\bar{g}_{K,syn}$, $\bar{g}_{Na,syn}$ (see 444 Fig. 2, right) as the minimum values required to elicit APs (see Fig. S11). Thus, we 445 investigated the efficacy of synaptic transmission for different scaling of the synaptic 446 conductances and for increasing extents of ionic release (see Fig. 9). We point out 447 that, since the neural membrane is described by a reduced HH model [43], the $\overline{g}_{X_{i,syn}}$ 448 are regarded as phenomenological terms lumping the postsynaptic conductances of all 449 the AMPA synaptic receptors, rather than the dynamics of a single synapse. In this 450 perspective, variations of $\overline{g}_{X_i,syn}$ qualitatively represent changes in the presynaptic drive 451 to the neuron. Figure 9.a shows a synaptic event occurring 30 ms after an ionic actuation 452 transient that fails to induce an AP (0.4 $g_{X_i,syn}$, $V_{app,max} = 0$ V). Successful synaptic 453 transmission can be achieved through larger presynaptic drive (0.7 $g_{X_i,syn}$ in Fig. 9.b) 454 or more ionic release ($V_{app,max} = 1$ V) in Fig. 9.c, since the postsynaptic current gets 455 enhanced. Figures 9.A-F illustrate a more extensive study, where elicited APs are 456 mapped in the two-dimensional space of synaptic conductances scaling – extent of ionic 457 release, for different delays between ionic stimulation and the synaptic event. These 458 results clearly suggest that excitatory synaptic transmission is facilitated in the presence 459 of the ionic actuators releasing K^+ . Moreover, thanks to the slow release granted by 460 ionophores, such facilitation lasts up to hundreds of milliseconds with progressively 461 milder intensity. 462

463 4. Discussion

464 4.1. Modeling of neuromodulation through ionic actuators

In this work, we introduced a finite-element model to describe the interaction between 465 a CP-coated microelectrode and a neuron soma. To the extent of our knowledge, this is 466 the first computational framework that solves the coupled equations for the dynamics of 467 an ionic actuator, the cellular fluids, and the neural membrane. We used our simulation 468 framework to investigate the controlled delivery of potassium in the extracellular fluid 469 as a neuromodulation mean. We considered three case studies for the CP, with different 470 levels of selectivity to K⁺: ideally-selective (isCP), non-selective (nsCP), and ionophores-471 induced selective (ionoCP). 472

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



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 $\bar{g}_{X_i,syn}$) 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 $\bar{g}_{X_i,syn}$. 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.

neuron to regimes of firing or depolarization block by affecting its intrinsic excitability. 476 These are well-established facts in literature [66], which can be leveraged to elicit or 477 inhibit neural activity, respectively. We note that, regarding inhibition, depolarization 478 block is a mechanism putatively exploited by neurons to limit the overall network activity 479 also in-vivo [67]. A FEM modeling framework enables to link such neuromodulation 480 targets to the physical and geometrical parameters of the CP and its surroundings, as 481 well as the stimulation protocols. Examples of such capabilities have been showcased 482 by changing the potential waveform applied to the CP, the maximum releasable dose 483 of potassium, the lateral encumbrance due to other cells, and the size of the CP-484 neuron cleft. Notwithstanding, similar analyses can be performed for all the other 485 model parameters, e.g., the CP size, the material of the metal contact, or other intrinsic 486 parameters of the CP, such as the volumetric capacitance, in support of thoughtful 487 engineering choices. 488

At the opposite side of the selectivity spectrum, the nsCP case illustrates how a 489 bare PEDOT:PSS-coated electrode is not effective as ionic neuromodulator. Indeed, it 490 is not able to hold a pre-charged potassium dose, e.g., coming from a preconditioning 491 stage in a different electrolyte. Further, it mainly conveys electric stimuli to target 492 neurons. This is an important sanity check for our simulation deck, since such coatings 493 are routinely used in electric neurostimulation devices to enhance properties such as 494 contact impedance, charge storage capacitance, and biocompatibility [68], [69], and our 495 model confirms that such electrodes can elicit APs through electrical stimulation but 496 not via ionic perturbation. 497

The ionoCP case is investigated as a possible ionic neuromodulation device endowed 498 with ionophores that confer selectivity. Indeed, the possibility to embed ionophores in 499 the polymeric backbones has already been proven in the literature [21]-[23], even though 500 they were employed for ion-sensing devices rather than for ion delivery. A second 501 important challenge addressed by our solution is the operation in a single reservoir, 502 i.e., the ECF, which holds the promise to act as a recyclable source of ions to perform 503 unlimited stimulation, reconciling miniaturization without handling multiple reservoirs 504 as in other iontronic solutions [13], [70]. Our findings suggest that ionophores with an 505 equilibrium constant around $\beta_{\rm KL} = 100 \text{ M}^{-1}$ give the best trade-off between selectivity 506 and release performance. This value is smaller than those used in sensor applications 507 (e.g., $\beta_{\rm KL} = 1026.2 \pm 118.3 \,{\rm M}^{-1}$ in [21]) as too strong complexes are difficult to dissociate 508 during the actuation phase. Notwithstanding, our framework can be utilized to test 509 realistic ionophore species [71], [72], by instantiating the respective parameters. With 510 the optimized ionoCP, we have shown *in-silico* that, despite its performances being 511 highly inferior with respect to the isCP, it is still possible to induce a significant local 512 perturbation of $[K^+]$ up to tens of mM above the extracellular bulk concentration, 513 sufficient to enhance the sensitivity of the neuron to other stimulation means (e.g., 514 electrical stimulation), as well as to facilitate excitatory synaptic transmission. A similar 515 neuromodulation capability was recently proven *ex-vivo* in retina tissue by microfluid 516 delivery of Ames' medium containing 22 mM K⁺ on perforated microelectrode arrays 517

⁵¹⁸ [73]. This suggests that induced synaptic facilitation provided by ionic neuromodulation ⁵¹⁹ 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 520 potassium ions only, unless an ideally selective polymer is available. In case the polymer 521 is not selective or only partially selective, APs are essentially elicited by electrical 522 stimulation if the electrode potential is ramped fast, but this cannot be referred to 523 as *ionic actuation*. Further, ideal selectivity for actuation purposes is very hard to 524 achieve with ionophores. The inclusion of synaptic dynamics showed that effects on 525 neural activity driven by ionic actuation are more pronounced through the synaptic 526 pathway rather than those affecting the intrinsic excitability of the neuron. These 527 analyses, despite being qualitative, prompt the need for a description of neuronal 528 dynamics down to the level of synaptic transmission to correctly predict the effects of 529 ionic actuation. Since synaptic dynamics is intrinsically a network phenomenon, more 530 effort must be made to increase the complexity of the simulation deck, while ensuring a 531 viable computational cost. We remark that our conclusions, despite being obtained *in*-532 silico, are build upon models that have been extensively validated against experiments. 533 Indeed, the two-phase model for the CP has been shown to effectively fit electrochemical 534 data [28]. Moreover, the HH model [43], coupled with lumped dynamics of ions in the 535 cellular fluid, was able to qualitatively capture the firing patterns of interneurons of the 536 rat CA1 hippocampus in seizure-like and spreading depression-like events [50], [51]. 537

538 4.2. Simulation platform

Our approach based on COMSOL Multiphysics enables seamless integration with other 539 stimulation or sensing devices that may be relevant in neuromodulation applications, 540 like multielectrode arrays (MEAs) [74]. Moreover, the use of a commercial platform 541 has been motivated by its widespread adoption in the computational communities of 542 neuroengineering [33], [34] and electrochemistry [28]–[32], and by its capabilities in 543 bridging the gaps between these two disciplines: the former being very knowledgeable in 544 terms of modeling neural activity and excitation but relying on an ohmic description of 545 the neural milieu, while the latter focusing on the electrodiffusive description of cellular 546 fluids but without taking into account the effects on neuronal activity. We point out 547 that this is an alternative approach compared to that of the computational neuroscience 548 community dealing with drift-diffusion phenomena in the neural microenvironment [39], 549 [75]–[78], which typically embraces open-source software. 550

551 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 557 to simple neural morphologies such as axons [39]. Alternatively, other studies have 558 focused on neural microdomains [41], [42] with small spatial extension, like nodes of 559 Ranvier [40], spines [79], ion channels [80], and synapses [81]. As an example of the 560 aforementioned computational burden, we observed an average simulation time of about 561 26 minutes for the studies reported in Fig. 9.B (89 transients lasting 300 ms), while 562 about 33 minutes for those in Fig. 9.D (89 transients lasting 400 ms). Simulations were 563 run in parallel on two servers: the first with an Intel[®] Xeon[®] X5690 CPU and 189 GB 564 of RAM while the second with an Intel[®] Xeon[®] Gold 6136 CPU and 500 GB of RAM. 565 Further details are reported in Supplementary Note 1. It is thus clear that a reduction in 566 the computational burden is pivotal to pave the way to more realistic descriptions of the 567 *in-vivo* neural milieu, e.g., accounting for detailed neuron morphologies [82] and network 568 interactions [83]. This, in turn, holds the promise to make the presented framework more 569 informative for the design and optimization of ionic actuators, and allows it to handle 570 more complex and realistic cases needed for proper validation against experimental data. 571 Aiming in this direction, the Kirchhoff-Nernst-Planck (KNP) framework has been 572 developed [58], [75]–[78], [84]. It sensibly reduces the computational burden by enforcing 573 electroneutrality in the resolved space domain and splitting displacement currents among 574 ionic fluxes at the cell membranes. However, the validity of KNP has been assessed 575 for biological electrogenic sources [85] but not during the operation of ionic actuators. 576 Indeed, to date, computation efforts focusing on the sole ionic actuator rely on the 577 PNP [29]–[32]. Before deploying the KNP in our setting, its domain of validity must be 578 determined taking into account the tiny clefts and non-physiological ionic concentrations 579 that may stem from the neuron-CP interaction. A preliminary analysis is shown in Fig. 580 S12, where we report the charge density in the cleft between the CP and the neuron 581 under the ion release by the ionoCP (Fig. S12.a) or the nsCP (Fig. S12.b). Further, 582 we consider the charge in the cleft during a synaptically-induced AP (Fig. S12.c), as an 583 example of physiological electrogenic source. Except for the starting and ending phases 584 of the applied stimulus ramp, at each time point the charge in (b) is similar to that in 585 (c). On the other hand, the charge results more than ten times greater in (a) than in 586 (c). This deviation from electroneutrality persists for the entire duration of ionic release 587 in (a) (hundreds of ms) instead of a single AP's duration in (c) (a few ms). These 588 results suggest that the electroneutrality assumption embraced by the KNP might not 589 hold under the operation of ionic actuators like the ionoCP. A thorough comparison of 590 the PNP model used in this work with a KNP-based model is not in the scope of this 591 work and is left for future investigation. 592

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 [37] or finite-element methods (FEM) [38]; second, the response of nerve cells is assessed by

feeding the results of the previous step as input. Similar schemes have been developed 599 also for electrodiffusive models of the neuron-ECF interaction [75]. Assessing the 600 validity of these schemes in the ionic neuromodulation setting may provide further 601 means to reduce the computational cost, thanks to the decoupling of simulations in two 602 problems easier than the original one. To this aim, our model may be instrumental in 603 validating such simplifications. Another advantage of hybrid approaches is to deploy 604 the full potential of simulators of realistic multicompartment models of nerve cells, 605 like NEURON [88], accounting for complex morphological and dynamical features. 606 Unfortunately, our self-consistent framework in COMSOL does not allow us to delegate 607 the solution of the neural membrane dynamics to third-party software. This limits the 608 integration and reusability of models of neural cells previously published in literature 609 [89]. 610

The electrodiffusive formalism employed in this work, as well as the KNP mentioned 611 above, are intrinsically more accurate than the ohmic formalism, where the cellular 612 fluids are considered volume conductors and diffusion mechanisms are neglected. Given 613 its simplicity and low computational cost, the ohmic formalism is widely used to 614 model the interface between neurons and implanted electrodes, both for stimulation 615 [34] and recording [90] studies. However, the lack of a proper description of the ionic 616 transport limits the validity to cases where the electric field is the main vehicle of 617 action potential recording/generation. In Supplementary Note 2 (Sec. "Limit case: 618 ohmic approximation for cellular fluids") we introduce the main equations of the ohmic 619 formalism and show that, in fact, its predictions agree with our model only in limit 620 cases where the cleft between the CP and the neuron is sufficiently large such that 621 the modulations of the ionic concentrations are relatively small. In this comparison, 622 we employed the nsCP since, among our case studies, is the one that best reproduces 623 electrodes routinely used in scenarios of electrical neural stimulation/recording (see Sec. 624 4.1). 625

We built our modeling framework with the aim of having the essential features to 626 serve as a benchmark for testing the neuromodulation capabilities of the ionic actuator. 627 The selected features resulted from a compromise between the computational burden of 628 simulations and the spatio-temporal scales of interest, namely those of a single neuron 629 some discharging up to a few APs, thereby leading to several simplifications. On the 630 neural milieu's side, we modeled the dynamics of K^+ , Na^+ , and Cl^- ions, along with 631 the ion channels responsible for the sole generation of action potentials. However, many 632 other ions [1], like Ca^{2+} or Mg^{2+} , and ionic channels [36] affects the neural functioning. 633 Furthermore, we neglected homeostatic mechanisms occurring at neural membranes or 634 glial cells that are pivotal for the regulation of the ionic composition in the neural 635 microenvironment [2] and are expected to counteract the operation of ionic actuators. 636 Nevertheless, the effects of such mechanisms manifest at temporal scales longer than 637 the ones of interest in this work. A possible way to capitalize on the aforementioned 638 efforts to reduce the computational burden would be the inclusion of such mechanisms 639 and gain insight into the effects of ionic actuation at longer temporal scales. Similar 640

considerations apply also to the CP's side, where many non-idealities and parasitic 641 phenomena were neglected. For instance: faradaic conduction in the CP [91], the 642 formation of competing bindings of ionophores with, e.g., Na⁺ ions [21], series impedance 643 of the electrodes [59], as well as red-ox reaction between the CP and the cellular fluids 644 [55]. Other model simplifications are the usage of uniform and time-invariant parameter 645 values inside domains, in contrast with time variability and reduced ionic diffusivity due 646 to tortuosity effects in the ECF [92], as well as variability in the density of ion channels in 647 different portions of the membrane [93]. Notwithstanding, our multiphysics framework 648 is amenable for the integration of these features to explore their effects on the device 649 performance. 650

51 5. Conclusion

This work combines the multiphysical description of the most essential set of 652 electrochemical and biological processes regarding neurons under ionic and electrical 653 stimulation in a single comprehensive simulation deck. By including accurate models of 654 ion-transport and transmembrane fluxes we demonstrated *in-silico* that the proposed 655 modeling approach can be a powerful tool to predict neuron excitability and to 656 benchmark the performance of novel neuromodulation devices. As an example of 657 application, we simulated the action of an ionic actuator based on organic mixed 658 ionic-electronic conductors (OMIECs) embedding ionophores and demonstrated its 659 capability to provide single-neuron synaptic facilitation. These efforts are oriented 660 toward versatile integration with iontronic devices aiming at closing the loop of already 661 existing methodologies for neural recording and computation *in-liquido* [94]. 662

663 Acknowledgments

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 (IU. NET) Consortium under Grant Agreement 862882.

667 References

- R. Rasmussen, J. O'Donnell, F. Ding, and M. Nedergaard, "Interstitial ions: A key
 regulator of state-dependent neural activity?" *Progress in Neurobiology*, vol. 193,
 2020. DOI: 10.1016/j.pneurobio.2020.101802.
- [2] G. G. Somjen, Ions in the Brain: Normal Function, Seizures, and Stroke. Oxford
 University Press, 2004, ISBN: 9780195151718.
- ⁶⁷³ [3] B. Frankenhaeuser and A. L. Hodgkin, "The after-effects of impulses in the giant
 ⁶⁷⁴ nerve fibres of Loligo.," *The Journal of physiology*, vol. 131, no. 2, 1956. DOI:
 ⁶⁷⁵ 10.1113/jphysiol.1956.sp005467.

23

- M. Balestrino, P. G. Aitken, and G. G. Somjen, "The effects of moderate changes of extracellular K+ and Ca2+ on synaptic and neural function in the CA1 region of the hippocampal slice," *Brain Research*, vol. 377, no. 2, 1986. DOI: 10.1016/0006-8993(86)90863-2.
- [5] P. Y. Shih, L. P. Savtchenko, N. Kamasawa, et al., "Retrograde Synaptic Signaling
 Mediated by K+ Efflux through Postsynaptic NMDA Receptors," Cell Reports,
 vol. 5, no. 4, 2013. DOI: 10.1016/j.celrep.2013.10.026.
- [6] L. M. Grover and T. J. Teyler, "Effects of extracellular potassium concentration and postsynaptic membrane potential on calcium-induced potentiation in area CA1 of rat hippocampus," *Brain Research*, vol. 506, no. 1, 1990. DOI: 10.1016/ 0006-8993(90)91198-P.
- [7] D. M. Durand, E. H. Park, and A. L. Jensen, "Potassium diffusive coupling in neural networks," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 365, no. 1551, 2010. DOI: 10.1098/rstb.2010.0050.
- [8] J. V. Raimondo, R. J. Burman, A. A. Katz, and C. J. Akerman, "Ion dynamics during seizures," *Frontiers in Cellular Neuroscience*, vol. 9, no. OCT, 2015. DOI: 10.3389/fncel.2015.00419.
- [9] S. F. Traynelis and R. Dingledine, "Potassium-induced spontaneous electrographic
 seizures in the rat hippocampal slice," *Journal of Neurophysiology*, vol. 59, no. 1,
 1988. DOI: 10.1152/jn.1988.59.1.259.
- [10] D. Pietrobon and M. A. Moskowitz, "Chaos and commotion in the wake of
 cortical spreading depression and spreading depolarizations," *Nature Reviews Neuroscience*, vol. 15, no. 6, 2014. DOI: 10.1038/nrn3770.
- [11] A. J. Hansen and T. Zeuthen, "Extracellular ion concentrations during spreading depression and ischemia in the rat brain cortex," *Acta Physiologica Scandinavica*, vol. 113, no. 4, 1981. DOI: 10.1111/j.1748-1716.1981.tb06920.x.
- [12] G. Ullah and S. J. Schiff, "Tracking and control of neuronal Hodgkin-Huxley dynamics," *Physical Review E Statistical, Nonlinear, and Soft Matter Physics*, vol. 79, no. 4, 2009. DOI: 10.1103/PhysRevE.79.040901.
- J. Isaksson, P. Kjäll, D. Nilsson, N. Robinson, M. Berggren, and A. RichterDahlfors, "Electronic control of Ca2+ signalling in neuronal cells using an organic
 electronic ion pump," *Nature Materials*, vol. 6, no. 9, 2007. DOI: 10.1038/
 nmat1963.
- [14] I. Uguz, C. M. Proctor, V. F. Curto, et al., "A Microfluidic Ion Pump for In Vivo
 Drug Delivery," Advanced Materials, vol. 29, no. 27, 2017. DOI: 10.1002/adma.
 201701217.
- [15] C. M. Proctor, I. Uguz, A. Slezia, et al., "An Electrocorticography Device with an Integrated Microfluidic Ion Pump for Simultaneous Neural Recording and Electrophoretic Drug Delivery In Vivo," Advanced Biosystems, vol. 3, no. 2, 2019.
 DOI: 10.1002/adbi.201800270.

- [16] M. Berggren, E. D. Głowacki, D. T. Simon, E. Stavrinidou, and K. Tybrandt, "In
 Vivo Organic Bioelectronics for Neuromodulation," *Chemical Reviews*, vol. 122, no. 4, pp. 4826–4846, 2022. DOI: 10.1021/acs.chemrev.1c00390.
- [17] B. D. Paulsen, K. Tybrandt, E. Stavrinidou, and J. Rivnay, "Organic mixed ionic-electronic conductors," *Nature Materials*, vol. 19, no. 1, 2020. DOI: 10.1038/
 s41563-019-0435-z.
- [18] Z. J. Du, G. Q. Bi, and X. T. Cui, "Electrically Controlled Neurochemical Release from Dual-Layer Conducting Polymer Films for Precise Modulation of Neural Network Activity in Rat Barrel Cortex," *Advanced Functional Materials*, vol. 28, no. 12, 2018. DOI: 10.1002/adfm.201703988.
- [19] K. M. Woeppel, X. S. Zheng, Z. M. Schulte, N. L. Rosi, and X. T. Cui,
 "Nanoparticle Doped PEDOT for Enhanced Electrode Coatings and Drug
 Delivery," Advanced Healthcare Materials, vol. 8, no. 21, 2019. DOI: 10.1002/
 adhm.201900622.
- [20] C. Tan, N. Kushwah, and X. T. Cui, "Electrically controlled neurochemical delivery from microelectrodes for focal and transient modulation of cellular behavior," *Biosensors*, vol. 11, no. 9, 2021. DOI: 10.3390/bios11090348.
- A. Villarroel Marquez, G. Salinas, M. Abarkan, et al., "Design of Potassium Selective Mixed Ion/Electron Conducting Polymers," *Macromolecular Rapid Communications*, vol. 41, no. 12, 2020. DOI: 10.1002/marc.202000134.
- [22] S. Wustoni, C. Combe, D. Ohayon, M. H. Akhtar, I. McCulloch, and S. Inal,
 "Membrane-Free Detection of Metal Cations with an Organic Electrochemical Transistor," *Advanced Functional Materials*, vol. 29, no. 44, 2019. DOI: 10.1002/ adfm.201904403.
- M. Jeszke, K. Trzciński, J. Karczewski, and E. Luboch, "Investigation of poly(3,4ethylenedioxythiophene) deposition method influence on properties of ion-selective
 electrodes based on bis(benzo-15-crown-5) derivatives," *Electrochimica Acta*,
 vol. 246, 2017. DOI: 10.1016/j.electacta.2017.05.197.
- M. Sessolo, J. Rivnay, E. Bandiello, G. G. Malliaras, and H. J. Bolink, "Ion-selective organic electrochemical transistors," *Advanced Materials*, vol. 26, no. 28, pp. 4803–4807, 2014. DOI: 10.1002/adma.201400731.
- R. M. Owens, S. Daniel, A. M. Pappa, *et al.*, "Optical and electronic ion channel monitoring from native human membranes," *ACS Nano*, vol. 14, no. 10, 2020. DOI: 10.1021/acsnano.0c01330.
- T. Arbring Sjöström, M. Berggren, E. O. Gabrielsson, et al., "A Decade of Iontronic Delivery Devices," Advanced Materials Technologies, vol. 3, no. 5, 2018.
 DOI: 10.1002/admt.201700360.
- ⁷⁵³ [27] A. J. Bard, L. R. Faulkner, and H. S. White, *Electrochemical methods:*⁷⁵⁴ *fundamentals and applications*, 2nd ed. John Wiley & Sons Inc., 2001, ISBN:
 ⁷⁵⁵ 9780471043720.

- K. Tybrandt, I. V. Zozoulenko, and M. Berggren, "Chemical potential-electric double layer coupling in conjugated polymer-polyelectrolyte blends," *Science advances*, vol. 3, no. 12, eaao3659, 2017. DOI: 10.1126/sciadv.aao3659.
- [29] K. Tybrandt, "Exploring the potential of ionic bipolar diodes for chemical neural interfaces," Soft Matter, vol. 13, no. 44, 2017. DOI: 10.1039/c7sm01732d.
- [30] T. A. Sjöström, A. Jonsson, E. O. Gabrielsson, M. Berggren, D. T. Simon, and K.
 Tybrandt, "Miniaturized Ionic Polarization Diodes for Neurotransmitter Release
 at Synaptic Speeds," Advanced Materials Technologies, vol. 5, no. 3, 2020. DOI:
 10.1002/admt.201900750.
- T. Arbring Sjöström, A. I. Ivanov, C. Bernard, et al., "Design and Operation of Hybrid Microfluidic Iontronic Probes for Regulated Drug Delivery," Advanced Materials Technologies, vol. 6, no. 2, 2021. DOI: 10.1002/admt.202001006.
- [32] M. T. Flavin, M. A. Paul, A. S. Lim, et al., "Electrochemical modulation enhances the selectivity of peripheral neurostimulation in vivo," *Proceedings of the National Academy of Sciences*, vol. 119, no. 23, Jun. 2022. DOI: 10.1073/PNAS.2117764119.
- [33] S. Romeni, G. Valle, A. Mazzoni, and S. Micera, "Tutorial: a computational framework for the design and optimization of peripheral neural interfaces," *Nature Protocols*, vol. 15, no. 10, 2020. DOI: 10.1038/s41596-020-0377-6.
- A. Fellner, A. Heshmat, P. Werginz, and F. Rattay, "A finite element method framework to model extracellular neural stimulation," *Journal of Neural Engineering*, vol. 19, no. 2, p. 022001, Apr. 2022. DOI: 10.1088/1741-2552/
 AC6060.
- [35] R. Plonsey and R. C. Barr, *Bioelectricity: A quantitative approach*. Springer, 2007,
 ISBN: 9780387488646. DOI: 10.1007/978-0-387-48865-3.
- [36] D. Sterratt, B. Graham, A. Gillies, and D. Willshaw, *Principles of computational modelling in neuroscience*. Cambridge University Press, 2011. DOI: 10.1017/
 CB09780511975899.
- [37] H. Lindén, E. Hagen, S. Leski, E. S. Norheim, K. H. Pettersen, and G. T. Einevoll,
 "LFPy: A tool for biophysical simulation of extracellular potentials generated by
 detailed model neurons," *Frontiers in Neuroinformatics*, vol. 7, no. JAN, 2014.
 DOI: 10.3389/fninf.2013.00041.
- [38] C. H. Lubba, Y. Le Guen, S. Jarvis, et al., "PyPNS: Multiscale Simulation of a Peripheral Nerve in Python," *Neuroinformatics*, vol. 17, no. 1, 2019. DOI: 10. 1007/s12021-018-9383-z.
- J. Pods, J. Schönke, and P. Bastian, "Electrodiffusion models of neurons and extracellular space using the poisson-nernst-planck equations - Numerical simulation of the intra- and extracellular potential for an axon model," *Biophysical Journal*, vol. 105, no. 1, 2013. DOI: 10.1016/j.bpj.2013.05.041.

- [40] C. L. Lopreore, T. M. Bartol, J. S. Coggan, et al., "Computational modeling of three-dimensional electrodiffusion in biological systems: Application to the node of Ranvier," *Biophysical Journal*, vol. 95, no. 6, 2008. DOI: 10.1529/biophysj. 108.132167.
- [41] D. Holcman and R. Yuste, "The new nanophysiology: Regulation of ionic flow in neuronal subcompartments," *Nature Reviews Neuroscience*, vol. 16, no. 11, 2015.
 DOI: 10.1038/nrn4022.
- [42] L. P. Savtchenko, M. M. Poo, and D. A. Rusakov, "Electrodiffusion phenomena in neuroscience: A neglected companion," *Nature Reviews Neuroscience*, vol. 18, no. 10, 2017. DOI: 10.1038/nrn.2017.101.
- [43] J. R. Cressman, G. Ullah, J. Ziburkus, S. J. Schiff, and E. Barreto, "The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: I. single neuron dynamics," *Journal of computational neuroscience*, vol. 26, no. 2, pp. 159–170, 2009. DOI: 10.1007/s10827-008-0132-4.
- E. Barreto and J. R. Cressman, "Ion concentration dynamics as a mechanism for neuronal bursting," *Journal of Biological Physics*, vol. 37, no. 3, 2011. DOI: 10.1007/s10867-010-9212-6.
- ⁸¹² [45] Y. Wei, G. Ullah, and S. J. Schiff, "Unification of neuronal spikes, seizures, and
 ⁸¹³ spreading depression," *Journal of Neuroscience*, vol. 34, no. 35, 2014. DOI: 10.
 ⁸¹⁴ 1523/JNEUROSCI.0516-14.2014.
- ⁸¹⁵ [46] M. Kalia, H. G. Meijer, S. A. van Gils, M. J. van Putten, and C. R. Rose,
 ⁸¹⁶ "Ion dynamics at the energy-deprived tripartite synapse," *PLoS Computational* ⁸¹⁷ *Biology*, vol. 17, no. 6, 2021. DOI: 10.1371/journal.pcbi.1009019.
- [47] S. A. Contreras, J. H. Schleimer, A. T. Gulledge, and S. Schreiber, "Activitymediated accumulation of potassium induces a switch in firing pattern and neuronal excitability type," *PLoS Computational Biology*, vol. 17, no. 5, 2021.
 ⁸²¹ DOI: 10.1371/journal.pcbi.1008510.
- H. Kager, W. J. Wadman, and G. G. Somjen, "Simulated seizures and spreading depression in a neuron model incorporating interstitial space and ion concentrations," *Journal of Neurophysiology*, vol. 84, no. 1, 2000. DOI: 10.1152/ jn.2000.84.1.495.
- [49] Comsol multiphysics user manual, COMSOL Inc., Sweden, 2022.
- ⁸²⁷ [50] G. Ullah and S. J. Schiff, "Assimilating seizure dynamics," *PLoS Computational* ⁸²⁸ *Biology*, vol. 6, no. 5, 2010. DOI: 10.1371/journal.pcbi.1000776.
- Y. Wei, G. Ullah, J. Ingram, and S. J. Schiff, "Oxygen and seizure dynamics: II.
 Computational modeling," *Journal of Neurophysiology*, vol. 112, no. 2, 2014. DOI:
 10.1152/jn.00541.2013.

- [52] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *The Journal* of *Physiology*, vol. 117, no. 4, pp. 500–544, Aug. 1952. DOI: 10.1113/jphysiol. 1952.sp004764.
- J. Rivnay, P. Leleux, M. Ferro, *et al.*, "High-performance transistors for
 bioelectronics through tuning of channel thickness," *Science Advances*, vol. 1,
 no. 4, pp. 1–6, 2015. DOI: 10.1126/sciadv.1400251.
- ⁸³⁹ [54] A. V. Volkov, K. Wijeratne, E. Mitraka, et al., "Understanding the Capacitance of PEDOT:PSS," Advanced Functional Materials, vol. 27, no. 28, pp. 1–10, 2017.
 ⁸⁴¹ DOI: 10.1002/adfm.201700329.
- M. O. Bamgbopa, J. Edberg, I. Engquist, M. Berggren, and K. Tybrandt,
 "Understanding the characteristics of conducting polymer-redox biopolymer
 supercapacitors," *Journal of Materials Chemistry A*, vol. 7, no. 41, pp. 23973–23980, 2019. DOI: 10.1039/c9ta07030c.
- ⁸⁴⁶ [56] J. Ehlich, L. Migliaccio, I. Sahalianov, et al., "Direct measurement of
 ⁸⁴⁷ oxygen reduction reactions at neurostimulation electrodes," Journal of Neural
 ⁸⁴⁸ Engineering, vol. 19, no. 3, 2022. DOI: 10.1088/1741-2552/ac77c0.
- L. J. Mele, P. Palestri, M. A. Alam, and L. Selmi, "Selectivity, sensitivity and detection range in ion-selective membrane-based electrochemical potentiometric sensors analyzed with poisson-boltzmann equilibrium model," *IEEE Sensors Journal*, vol. 22, no. 15, pp. 15010–15021, 2022. DOI: 10.1109/JSEN.2022.
 3185168.
- M. J. Sætra, G. T. Einevoll, and G. Halnes, "An electrodiffusive neuronextracellular-glia model for exploring the genesis of slow potentials in the brain," *PLoS Computational Biology*, vol. 17, no. 7, 2021. DOI: 10.1371/journal.pcbi. 1008143.
- L. J. Mele, C. Verardo, and P. Palestri, "Reproducing capacitive cyclic voltammetric curves by simulation: When are simplified geometries appropriate?" *Electrochemistry Communications*, vol. 142, p. 107378, 2022. DOI: 10.1016/j.
 elecom.2022.107378.
- ⁸⁶² [60] M. Bikson, P. J. Hahn, J. E. Fox, and J. G. Jefferys, "Depolarization
 ⁸⁶³ block of neurons during maintenance of electrographic seizures," *Journal of*⁸⁶⁴ Neurophysiology, vol. 90, no. 4, 2003. DOI: 10.1152/jn.00467.2003.
- ⁸⁶⁵ [61] S. Joucla and B. Yvert, "Modeling extracellular electrical neural stimulation: From
 ⁸⁶⁶ basic understanding to MEA-based applications," *Journal of Physiology Paris*,
 ⁸⁶⁷ vol. 106, no. 3-4, 2012. DOI: 10.1016/j.jphysparis.2011.10.003.
- ⁸⁶⁸ [62] J. K. Krauss, N. Lipsman, T. Aziz, *et al.*, "Technology of deep brain stimulation:
 ⁸⁶⁹ current status and future directions," *Nature Reviews Neurology*, vol. 17, no. 2,
 ⁸⁷⁰ 2021. DOI: 10.1038/s41582-020-00426-z.

- ⁸⁷¹ [63] A. Fitchett, S. Mastitskaya, and K. Aristovich, "Selective Neuromodulation of the
 ⁸⁷² Vagus Nerve," *Frontiers in Neuroscience*, vol. 15, 2021. DOI: 10.3389/fnins.
 ⁸⁷³ 2021.685872.
- ⁸⁷⁴ [64] J. J. Jasielec, T. Sokalski, R. Filipek, and A. Lewenstam, "Neutral-Carrier Ion-⁸⁷⁵ Selective Electrodes Assessed by the Nernst-Planck-Poisson Model," *Analytical* ⁸⁷⁶ *Chemistry*, vol. 87, no. 17, 2015. DOI: 10.1021/acs.analchem.5b00065.
- K. Neupert-Laves and M. Dobler, "The crystal structure of a k+ complex of valinomycin," *Helvetica chimica acta*, vol. 58, no. 2, pp. 432–442, 1975. DOI: 10.
 1002/hlca.19750580212.
- K. Aihara and G. Matsumoto, "Two stable steady states in the Hodgkin-Huxley axons," *Biophysical Journal*, vol. 41, no. 1, 1983. DOI: 10.1016/S0006-3495(83)
 84408-7.
- ⁸⁸³ [67] D. Bianchi, A. Marasco, A. Limongiello, *et al.*, "On the mechanisms underlying the
 ⁸⁸⁴ depolarization block in the spiking dynamics of CA1 pyramidal neurons," *Journal*⁸⁸⁵ of Computational Neuroscience, vol. 33, no. 2, 2012. DOI: 10.1007/s10827-012⁸⁸⁶ 0383-y.
- ⁸⁸⁷ [68] M. Bianchi, A. De Salvo, M. Asplund, et al., "Poly(3,4-ethylenedioxythiophene)⁸⁸⁸ Based Neural Interfaces for Recording and Stimulation: Fundamental Aspects and
 ⁸⁸⁹ In Vivo Applications," Advanced Science, vol. 9, no. 12, 2022. DOI: 10.1002/advs.
 ⁸⁹⁰ 202104701.
- ⁸⁹¹ [69] A. Williamson, M. Ferro, P. Leleux, et al., "Localized Neuron Stimulation with
 Organic Electrochemical Transistors on Delaminating Depth Probes," Advanced
 Materials, vol. 27, no. 30, pp. 4405–4410, 2015. DOI: 10.1002/adma.201500218.
- [70] A. Jonsson, S. Inal, L. Uguz, et al., "Bioelectronic neural pixel: Chemical stimulation and electrical sensing at the same site," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 113, no. 34, pp. 9440–9445, 2016. DOI: 10.1073/pnas.1604231113.
- P. Bühlmann, E. Pretsch, and E. Bakker, "Carrier-based ion-selective electrodes and bulk optodes. 2. Ionophores for potentiometric and optical sensors," *Chemical Reviews*, vol. 98, no. 4, 1998. DOI: 10.1021/cr970113+.
- Y. Qin, Y. Mi, and E. Bakker, "Determination of complex formation constants of 18 neutral alkali and alkaline earth metal ionophores in poly(vinyl chloride) sensing membranes plasticized with bis(2-ethylhexyl)sebacate and o-nitrophenyloctylether," Analytica Chimica Acta, vol. 421, no. 2, 2000. DOI: 10. 1016/S0003-2670(00)01038-2.
- A. Esteban-Linares, X. Zhang, H. H. Lee, et al., "Graphene-based microfluidic
 perforated microelectrode arrays for retinal electrophysiological studies," Lab on
 a Chip, 2023, ISSN: 1473-0189. DOI: 10.1039/D3LC00064H.

F. Leva, C. Verardo, L. J. Mele, P. Palestri, and L. Selmi, "Multiphysics Finite-Element Modeling of the Neuron/Electrode Electrodiffusive Interaction," 2022 *IEEE Sensors*, pp. 1–4, Oct. 2022. DOI: 10.1109/SENSORS52175.2022.9967049.

- [75] A. Solbrå, A. W. Bergersen, J. van den Brink, A. Malthe-Sørenssen, G. T. Einevoll, and G. Halnes, "A Kirchhoff-Nernst-Planck framework for modeling large scale extracellular electrodiffusion surrounding morphologically detailed neurons," *PLoS Computational Biology*, vol. 14, no. 10, 2018. DOI: 10.1371/journal.pcbi.
 1006510.
- ⁹¹⁷ [76] A. J. Ellingsrud, A. Solbrå, G. T. Einevoll, G. Halnes, and M. E. Rognes, "Finite
 ⁹¹⁸ Element Simulation of Ionic Electrodiffusion in Cellular Geometries," *Frontiers in* ⁹¹⁹ Neuroinformatics, vol. 14, 2020. DOI: 10.3389/fninf.2020.00011.
- A. Tuttle, J. R. Diaz, and Y. Mori, "A computational study on the role of glutamate and NMDA receptors on cortical spreading depression using a multidomain electrodiffusion model," *PLoS Computational Biology*, vol. 15, no. 12, 2019. DOI: 10.1371/journal.pcbi.1007455.
- Y. Mori and C. S. Peskin, "A numerical method for cellular electrophysiology based on the electrodiffusion equations with internal boundary conditions at membranes," *Communications in Applied Mathematics and Computational Science*, vol. 4, no. 1, 2009. DOI: 10.2140/camcos.2009.4.85.
- ⁹²⁸ [79] T. Lagache, K. Jayant, and R. Yuste, "Electrodiffusion models of synaptic
 ⁹²⁹ potentials in dendritic spines," *Journal of Computational Neuroscience*, vol. 47,
 ⁹³⁰ no. 1, 2019. DOI: 10.1007/s10827-019-00725-5.
- [80] R. D. Coalson and M. G. Kurnikova, "Poisson-Nernst-Planck theory approach to
 the calculation of current through biological ion channels," *IEEE Transactions on Nanobioscience*, vol. 4, no. 1, 2005. DOI: 10.1109/TNB.2004.842495.
- [81] C. L. Gardner, J. R. Jones, S. M. Baer, and S. M. Crook, "Drift-diffusion simulation of the ephaptic effect in the triad synapse of the retina," *Journal of Computational Neuroscience*, vol. 38, no. 1, 2015. DOI: 10.1007/s10827-014-0531-7.
- [82] E. Hay, S. Hill, F. Schürmann, H. Markram, and I. Segev, "Models of neocortical layer 5b pyramidal cells capturing a wide range of dendritic and perisomatic active properties," *PLoS Computational Biology*, vol. 7, no. 7, 2011. DOI: 10.1371/ journal.pcbi.1002107.
- ⁹⁴² [83] H. Markram, E. Muller, S. Ramaswamy, et al., "Reconstruction and Simulation
 ⁹⁴³ of Neocortical Microcircuitry," Cell, vol. 163, no. 2, 2015. DOI: 10.1016/j.cell.
 ⁹⁴⁴ 2015.09.029.
- M. J. Sætra, G. T. Einevoll, and G. Halnes, "An electrodiffusive, ion conserving
 Pinsky-Rinzel model with homeostatic mechanisms," *PLoS Computational Biology*, vol. 16, no. 4, 2020. DOI: 10.1371/journal.pcbi.1007661.

- ⁹⁴⁸ [85] J. Pods, "A comparison of computational models for the extracellular potential of neurons," *Journal of Integrative Neuroscience*, vol. 16, no. 1, 2017. DOI: 10.3233/ 950 JIN-170009.
- ⁹⁵¹ [86] A. Agudelo-Toro and A. Neef, "Computationally efficient simulation of electrical activity at cell membranes interacting with self-generated and externally imposed electric fields," *Journal of Neural Engineering*, vol. 10, no. 2, 2013. DOI: 10.1088/
 ⁹⁵⁴ 1741-2560/10/2/026019.
- ⁹⁵⁵ [87] S. Joucla, A. Glière, and B. Yvert, "Current approaches to model extracellular
 ⁹⁵⁶ electrical neural microstimulation," *Frontiers in Computational Neuroscience*,
 ⁹⁵⁷ vol. 8, no. FEB, 2014. DOI: 10.3389/fncom.2014.00013.
- [88] N. T. Carnevale and M. L. Hines, *The NEURON book*. Cambridge University
 Press, 2006. DOI: 10.1017/CB09780511541612.
- R. A. McDougal, T. M. Morse, T. Carnevale, et al., "Twenty years of ModelDB and beyond: building essential modeling tools for the future of neuroscience," Journal of Computational Neuroscience, vol. 42, no. 1, 2017. DOI: 10.1007/s10827-016-0623-7.
- R. Bestel, U. Van Rienen, C. Thielemann, and R. Appali, "Influence of Neuronal Morphology on the Shape of Extracellular Recordings with Microelectrode Arrays: A Finite Element Analysis," *IEEE Transactions on Biomedical Engineering*, vol. 68, no. 4, 2021. DOI: 10.1109/TBME.2020.3026635.
- ⁹⁶⁸ [91] M. Berggren and G. G. Malliaras, "How conducting polymer electrodes operate,"
 ⁹⁶⁹ Science, vol. 364, no. 6437, 2019. DOI: 10.1126/science.aaw9295.
- E. Syková and C. Nicholson, "Diffusion in brain extracellular space," *Physiological Reviews*, vol. 88, no. 4, 2008, ISSN: 00319333. DOI: 10.1152/physrev.00027.2007.
- J. R. Buitenweg, W. L. Rutten, and E. Marani, "Modeled channel distributions explain extracellular recordings from cultured neurons sealed to microelectrodes," *IEEE Transactions on Biomedical Engineering*, vol. 49, no. 12, pp. 1580–1590, 2002.
- M. Cucchi, D. Parker, E. Stavrinidou, P. Gkoupidenis, and H. Kleemann,
 "In Liquido Computation with Electrochemical Transistors and Mixed Conductors for Intelligent Bioelectronics," *Advanced Materials*, 2023. DOI: 10.1002/adma.
 202209516.

Supplementary material

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

Claudio Verardo, Leandro Julian Mele, Luca Selmi, Pierpaolo Palestri

This file includes:

- Supplementary Tables S1-S5.
- Supplementary Figures S1-S12.
- Supplementary Note 1: COMSOL implementation details.
- Supplementary Note 2: model verification.
- Supplementary Note 3: reduced ionoCP-ECF model.

Symbol	Description
FEM	Finite-element model
CP	Conductive polymer
isCP	Ideally-selective CP
nsCP	Non-selective CP
ionoCP	Ionophores-induced selective CP
PEDOT-PSS	poly(3,4-ethylenedioxythiophene) polystyrene sulfonate
OMIEC	Organic mixed ionic-electronic conductors
PNP	Poisson-Nernst-Planck
KNP	Kirchhoff-Nernst-Planck
ICF	Intracellular fluid
ECF	Extracellular fluid
AP	Action potential
HH	Hodgkin-Huxley
EDL	Electrical double layer
ORR	Oxygen reduction reactions
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptor
EPSC	Excitatory postsynaptic current
WE	Working electrode
RE	Reference electrode
CE	Counter electrode
MEA	Multielectrode array

Table S1.Abbreviations used in the text.

Table S2. Physical variables solved in the model (Figs. 1, 2 in the main body).

Symbol	Description		Units			
		ECF	ICF	Neural Membrane	CP	
$\overline{\psi_c}$	electric potential (ions)	\checkmark	\checkmark		\checkmark	mV
ψ_p	electric potential (holes)				\checkmark	mV
$[K^+]$	K^+ concentration	\checkmark	\checkmark		\checkmark	mM
$[Na^+]$	Na^+ concentration	\checkmark	\checkmark		\checkmark	mM
[Cl ⁻]	Cl^- concentration	\checkmark	\checkmark		\checkmark	mM
p	holes concentration				\checkmark	mM
$f_{\rm K}$	K ⁺ flux	\checkmark	\checkmark		\checkmark	$mol/(m^2s)$
$f_{\rm Na}$	Na ⁺ flux	\checkmark	\checkmark		\checkmark	$mol/(m^2s)$
$f_{\rm Cl}$	Cl^- flux	\checkmark	\checkmark		\checkmark	$mol/(m^2s)$
f_p	holes flux				\checkmark	$mol/(m^2s)$
$V_{\rm app}$	potential applied to the PEDOT contact				\checkmark	Ϋ́Υ Ϋ́
V^{++}	membrane potential			\checkmark		mV
$V_{\rm K}$	K ⁺ reversal potential			\checkmark		mV
$V_{\rm Na}$	Na ⁺ reversal potential			\checkmark		mV
$V_{\rm Cl}$	Cl ⁻ reversal potential			\checkmark		mV
$I_{\rm K,DR}$	current K ⁺ voltage-gated channel			\checkmark		$\mu { m A/cm^2}$
$I_{\rm Na,T}$	current Na ⁺ voltage-gated channel			\checkmark		$\mu A/cm^2$
$I_{\rm K,L}$	current K ⁺ leakage channel			\checkmark		$\mu A/cm^2$
$I_{\rm Na,L}$	current Na ⁺ leakage channel			\checkmark		$\mu A/cm^2$
$I_{\rm Cl,L}$	current Cl ⁻ leakage channel			\checkmark		$\mu A/cm^2$
IK	total current K ⁺ channels			\checkmark		$\mu A/cm^2$
INa	total current Na ⁺ channels			\checkmark		$\mu A/cm^2$
Ici	total current Cl^- channels			\checkmark		$\mu A/cm^2$
n	$I_{\rm K DB}$ activating gating variable			\checkmark		-
m	$I_{\text{Na,T}}$ activating gating variable			\checkmark		-
h	$I_{\rm Na,T}$ inactivating gating variable			\checkmark		-
[L]	concentration of free ionophores				\checkmark	mM
[KL]	concentration of ionophores bound to K ⁺ ions				\checkmark	mM
$f_{ m L}$	L flux				\checkmark	$mol/(m^2s)$
$f_{\rm KL}$	KL flux				\checkmark	$mol/(m^2s)$
$I_{\rm K,syn}$	K ⁺ current through AMPA synapse			\checkmark		$\mu A/cm^2$
$I_{\rm Na,syn}$	Na ⁺ current through AMPA synapse			\checkmark		$\mu A/cm^2$

Symbol	Description		Value/expressio	Units	Ref.	
	* 	ECF	ÍCF	CP		
Т	temperature	309.15	309.15	309.15	Κ	[1]
RT/F	thermal voltage	26.64	26.64	26.64	mV	[1]
$\varepsilon_{\rm el}$	cellular fluids dielectric constant	$80\varepsilon_0$	$80\varepsilon_0$	-	F/m	
$\varepsilon_{\mathrm{PSS}}$	dielectric constant PSS phase	-	-	$80\varepsilon_0$	F/m	
$\varepsilon_{\rm PEDOT}$	dielectric constant PEDOT phase	-	-	$40\varepsilon_0$	F/m	$\lfloor 2 \rfloor$
$z_{ m K}$	K ⁺ ion valence	+1	+1	+1	-	
$z_{ m Na}$	Na ⁺ ion valence	+1	+1	+1	-	
$z_{ m Cl}$	Cl ⁻ ion valence	-1	-1	-1	-	
$D_{\rm K}$	K ⁺ ion diffusivity	$2.19 \cdot 10^{-9}$	$2.19 \cdot 10^{-9}$	$5.08 \cdot 10^{-10}$	m^2/s	[3], [4]
D_{Na}	Na ⁺ ion diffusivity	$1.50 \cdot 10^{-9}$	$1.50 \cdot 10^{-9}$	$3.34 \cdot 10^{-10}$	m^2/s	[3], [4]
$D_{\rm Cl}$	Cl ⁻ ion diffusivity	$2.28\cdot10^{-9}$	$2.28 \cdot 10^{-9}$	$5.08 \cdot 10^{-10}$	m^2/s	[3], [4]
D_p	holes diffusivity	-	-	$D_p(p)^{\mathrm{a}}$	m^{2}/s	[4]
$[K^+]_B$	K ⁺ bulk concentration	4	140	-	\dot{mM}	[1]
[Na [∓]] _B	Na ⁺ bulk concentration	144	18	-	mM	[1]
$[Cl^-]_B$	Cl ⁻ bulk concentration	130	6	-	mM	[1]
$[A^-]$	organic anion concentration	18 ^b	152 ^b	-	mM	
[PSS ⁻]	PSS fixed charges (polyanion)	-	-	Table S4	mM	[4]
$C_{\rm V}$	volumetric capacitance	-	-	39	F/cm^3	[5]
B	Au-Ag/AgCl workfunction difference	-	-	-0.7	Ϋ́ Υ	[4]
$\gamma_{ m K}$	CP-ECF virtual selectivity to K ⁺	-	-	1	-	
$\gamma_{\rm Na}$	CP-ECF virtual selectivity to Na ⁺	-	-	Table S4	-	
$\gamma_{\rm Cl}$	CP-ECF virtual selectivity to Cl ⁻	-	-	1	-	
$L_{\rm D}$	Debye length	0.8 ^c	1.1 ^c	-	nm	[3]
$z_{ m L}$	L valence	-	-	0	-	
$z_{\rm KL}$	KL valence	-	-	+1	- 2 /	
$D_{\rm L}$	L diffusivity	-	-	$D_{\rm K}/100$	m^2/s	
$D_{\rm KL}$	KL diffusivity	-	-	$D_{\rm K}/100$	m^2/s	
β_{KL}	association constant K ⁺ -L binding	-	-	100	1/M	
$k_{ m KL,b}$	backward rate constant K ⁺ -L binding	-	-	10^{4}	1/s	[6]
$k_{\rm KL,f}$	forward rate constant K ⁺ -L binding	-	-	$k_{\rm KL,b} \cdot \beta_{\rm KL}$	1/(M s)	
$[L]_{tot}$	total concentration of L and KL	-	-	Table S4	mM	
			Neural Membra	ane	. 0	[.]
C_{m}	membrane capacitance		1		$\mu F/cm^2$	[1]
$\overline{g}_{\mathrm{K,DR}}$	$I_{\rm K,DR}$ max conductance		40		$\rm mS/cm^2$	[1]
$\overline{g}_{\mathrm{Na,T}}$	$I_{\rm Na,T}$ max conductance		100		$\rm mS/cm^2$	[1]
$\overline{g}_{\mathrm{K,L}}$	$I_{\rm K,L}$ conductance		0.05		$\rm mS/cm^2$	[1]
$\overline{g}_{\mathrm{Na,L}}$	$I_{\rm Na,L}$ conductance		0.0175		$\rm mS/cm^2$	[1]
$\overline{g}_{\rm Cl,L}$	$I_{\rm Cl,L}$ conductance		0.05		mS/cm^2	[1]
ϕ	temperature correction factor		3		-	[1]
α_n	n forward rate constant		$-0.01(V+34)\phi$		ms^{-1}	[1]
ß	n backward rate constant		$\exp(-0.1(V+34))$)−1 ⊦44 \	mc^{-1}	[1]
ρ_n			$0.125\phi \exp(-\frac{8}{8})$	<u>,0</u>)	1115	[1]
α_m	<i>m</i> forward rate constant		$\frac{-0.1(V+30)\phi}{\exp(-0.1(V+30))}$)-1	ms^{-1}	[1]
β_m	m backward rate constant		$4\phi \exp(-\frac{V+55}{18})$	<u>5</u>)	ms^{-1}	[1]
α_h	h forward rate constant		$0.07\phi \exp(-\frac{V+V}{20})$	$\frac{44}{2}$)	ms^{-1}	[1]
β_h	h backward rate constant		φ 20	<u> </u>	ms^{-1}	[1]
n	n activation curve		$\exp\left(-0.1(V+14)\right)$ $\alpha_n(V)$)+1	_	[1]
n_{∞}			$\overline{\alpha_n(V)} + \beta_n(V)$	<u>)</u>		[1]
$ au_n$	n time constant		$\overline{\alpha_n(V)} + \beta_n(V)$	D	$^{\mathrm{ms}}$	[1]
m_{∞}	m activation curve		$\frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)}$	7	-	[1]
$ au_m$	m time constant		$\frac{\alpha_m(v) + \beta_m(v)}{1}$) .	ms	[1]
ь.	h inactivation aumo		$\alpha_m(V) + \beta_m(V)$)		[1]
n_{∞}	<i>n</i> machivation curve		$\overline{\alpha_h(V)} + \beta_h(V)$)	-	[1]
$ au_h$	h time constant		$\frac{1}{\alpha_{L}(V)+\beta_{L}(V)}$	5	\mathbf{ms}	[1]
$V_{\rm r}$	resting membrane potential		-67.0	,	mV	
$I_{\rm K,r}$	current of K ⁺ channels at rest	$(I_{\rm K}$	$_{\rm DR} + I_{\rm K,L}) _{V=V}$	r = 1.41	$\mu A/cm^2$	
I _{Na} r	current of Na ⁺ channels at rest	(I_{Na})	$T + I_{NaL}) _{V=V}$	= -2.16	$\mu A/cm^2$	
I_{C1r}	current of Cl ⁻ channels at rest	(ita	$(I_{C1 L}) _{V=V} = 0$	0.75	$\mu A/cm^2$	
GN	Na ⁺ total conductance of AMPA synapse		2.22		nS	
$G_{\rm Na,syn}$	K^+ total conductance of ΔMPA synapse		1 00 d		nS	
GK,syn	No ⁺ conductorial of AMDA compared		4.90 ~	0.20		
$g_{\rm Na,syn}$	Na conductance of AMPA synapse	($G_{Na,syn}/A_{neu} =$	0.30	mS/cm ²	
$g_{\rm K,syn}$	κ conductance of AMPA synapse		$G_{\rm K,syn}/A_{\rm neu} = 0$	0.67	$\rm mS/cm^2$	r 1
$ au_{1,\mathrm{syn}}$	slow time constant of AMPA synapse		3		ms	[7]
$\frac{\tau_{2,\text{syn}}}{D}$	tast time constant of AMPA synapse	1	1		ms	[7]
κ gas con	stant, F Faraday constant, ε_0 vacuum die	iectric consta	ant.			

Table S3. Physical parameters and reference values used in the model (Figs. 1, 2 in the main body).

A gas constant, F raraday constant, ε_0 vacuum dielectric constant ^a $D_p(p) = 2.05 \cdot 10^{-5}(1.05 - 1.08/(1 + \exp((p - 71.0)/22.8))).$ ^b Set to provide electroneutrality in the bulk of ECF/ICS. ^c $L_{\rm D} = \sqrt{\varepsilon_{\rm el}RT \cdot (F^2 \sum_i z_i^2 [X_i]_{\rm B})^{-1}}$ with $X_i \in \{K^+, Na^+, Cl^-\}.$ ^d Set to have $I_{\rm K,syn} = 0.5|I_{\rm Na,syn}|$ at $V = V_{\rm r}$ as in [7].

Table S4. Parameters from Table S3 that are varied in order to instantiate the case studies considered in the main text (see Section 2.2): ideally-selective CP (isCP), non-selective CP (nsCP), ionophores-induced selective CP (ionoCP). We point out that $[L]_{tot} = 0$ corresponds to not including ionophores.

Symbol	Description	Value/expression			Units	Ref.
		isCP	nsCP	ionoCP		
$\gamma_{\rm Na}$	CP-ECF virtual selectivity to Na ⁺	0	1	1	-	
$[L]_{tot}$	total concentration of L and KL	0	0	200	mM	
$[PSS^-]$	PSS fixed charges (polyanion)	2400	2400	637	mM	[4]

Table S5. Geometrical parameters and reference values used in this work (see Fig. 3).

Symbol	Description	Value	Units
$W_{\rm el}$	electrolyte radius	40	μm
$H_{\rm el}$	electrolyte height	40	$\mu \mathrm{m}$
$W_{\mathbf{p}}$	pillar radius	1.5	$\mu \mathrm{m}$
$H_{\rm p}^{-}$	pillar thickness	750	nm
$d_{ m pm}$	pillar-neuron cleft	50	nm
$W_{\rm CP}$	CP length	15	$\mu\mathrm{m}$
$H_{\rm CP}$	CP thickness	600	nm
$A_{\rm CP}$	CP surface area	905.9	μm^2
$V_{\rm CP}$	CP volume	508.7	μm^3
$d_{ m m}$	membrane thickness	10	nm
$d_{ m s}$	sampling distance	6	nm
W_{neu}	neuron base radius	10	$\mu \mathrm{m}$
$H_{\rm neu}$	neuron height	4.5	$\mu \mathrm{m}$
$A_{\rm neu}$	neuron surface area	730.7	μm^2
V_{neu}	neuron volume	942.5	μm^3
$d_{ m nn}$	cleft between active and inactive neurons	541	nm
$d_{\rm CPm}$	CP-neuron cleft	200	nm



Figure S1. Reversal potentials $V_{\rm K}$, $V_{\rm Na}$, $V_{\rm Cl}$ evaluated in ranges of extracellular concentrations considered in the main text, according to the Nernst equation. The intracellular concentrations are kept to their baseline values (see Table S3). The baseline values for the reversal potentials are highlighted with circles. The potassium's reversal potential is the most sensitive to perturbation of the ionic milieu.



Figure S2. Ideally-selective CP (isCP). The same ionic stimulation transients of Fig. 4 are shown but with neuron reversal potentials fixed to their baseline values (see Fig. S1). Sanity check to confirm that the neural activity observed in Fig. 4 is mainly caused by the ionic component of neurostimulation (i.e., the released K^+). The hyperpolarization (respectively, depolarization) observed at the bottom (respectively, top) of the neuron are caused by the electric field induced in the ECF during ion release. The extents of such perturbations of membrane potential depend on the slope of the potential applied to the CP (compare columns a), b) with c)). From top to bottom, rows indicate: 1) the applied stimulus V_{app} , the extracellular concentrations of 2) [K⁺] and 3) [Na⁺] in different points of the ECF and 4) the membrane potential V.



Figure S3. Ideally-selective CP (isCP). Examples of ionic stimulation performed with different concentrations of embedded fixed charges in the CP. a) $[PSS^-] = 2.4 \text{ M}$ (used as reference value as in the main text). b) $[PSS^-] = 1.2 \text{ M}$ (50% of the reference value). c) $[PSS^-] = 0.6 \text{ M}$ (25% of the reference value). Compared to Fig. 4, the ramps of applied potential are much longer (v = 10 V/s and $V_{\text{app,max}} = 7 \text{ V}$) in order to induce a complete depletion of potassium ions in the CP. We observe that higher concentrations of $[PSS^-]$ translate into longer time frames of K⁺ release. From top to bottom, rows indicate: 1) the applied stimulus V_{app} , 2) the ion, hole and fixed charge concentrations inside the CP, the extracellular concentrations of 3) $[K^+]$ and 4) $[Na^+]$ in different points of the ECF, and 5) the membrane potential V. Interestingly, with such voltage ramp, larger than those used in the main body of the paper, the neuron response resembles seizure-like events (SLEs), with decreasing APs amplitudes and possible termination in configurations of depolarization block (see last row). The neuron recovers from such SLEs when all the K⁺ stored in the CP has been released.



Figure S4. Ideally-selective CP (isCP). The ionic stimulation transient of Fig. 4.a is repeated for different extents of neuron's lateral encumbrance. Namely, distances of the lateral inactive neurons d_{nn} (see Fig. 3): a) 541 nm (used as reference value in the main text), b) 1.95 μ m, and c) infinite (i.e., without lateral neurons). Configurations a), and b) correspond to geometries with neuronal area occupation of 90% and 70%, respectively. The area occupation is defined as the ratio between the 2D neuron area $A_{neu}^{2D} = \pi W_{neu}^2$ and the 2D area of its proximal extracellular microenvironment $A_{\mu env}^{2D} = \pi (W_{neu} + d_{nn})^2$, as seen from a top view. Larger occupations of area cause larger perturbations of the local ion concentrations in the ECF, for the same stimulation protocol. From top to bottom, rows indicate: 1) the applied stimulus V_{app} , the extracellular concentrations of 2) [K⁺] and 3) [Na⁺] in different points of the ECF, and 4) the membrane potential V.



Figure S5. Ideally-selective CP (isCP). The ionic stimulation transient of Fig. 4.a is repeated for different extents of the CP-neuron cleft $d_{\rm CPm}$ (see Fig. 3): a) 200 nm (used as reference value as in the main text), b) 60 nm, and c) 400 nm. A smaller cleft yields a more pronounced perturbation of the local ion concentrations in the ECF, for the same stimulation protocol, which induces a larger depolarization of the neural membrane. The converse applies to a larger cleft. From top to bottom, rows indicate: 1) the applied stimulus $V_{\rm app}$, the extracellular concentrations of 2) [K⁺] and 3) [Na⁺] in different points of the ECF, and 4) the membrane potential V.



Figure S6. Non-selective CP (nsCP). Examples of ionic stimulation transients are performed by keeping either fixed or variable the reversal potentials $V_{\rm K}$, $V_{\rm Na}$, $V_{\rm Cl}$. Different slopes of the applied potential are considered (with $V_{\rm app,max} = 1 \text{ V}$): a) v = 10 V/s (as in Fig. 6.b), b) v = 50 V/s, and c) v = 60 V/s (as in Fig. 6.c). This is a sanity check to confirm that the AP observed in Fig. 6 is mainly caused by the electric component of neurostimulation, rather than the change of the extracellular Na⁺ and K⁺ concentrations. From top to bottom, rows indicate: 1) the applied stimulus $V_{\rm app}$, the extracellular concentrations of 2) [K⁺] and 3) [Na⁺] in different points of the ECF, and the membrane potential V setting 4) fixed or 5) variable reversal potentials during the simulation.



Figure S7. Optimizing the ionoCP properties with simulations based on a compartmentalized CP/ECF structure (see Supplementary Note 3). The optimum is evaluated based on the maximum $[K^+]$ change achievable in the ECF for $t \to +\infty$. a-c) K^+ vs fixed charge concentrations in the CP for different total concentrations of ionophore $[L]_{tot}$ in the polymer. While larger concentrations of ionophores yield larger release of K^+ , steric considerations suggest that an upper limit of ca. 200 mM. Interestingly, in all cases the optimum association constant is $\beta_{KL} = 100 \text{ M}^{-1}$ (green curves). In this work, values as in (b) were used ([PSS⁻] $\approx 637 \text{ mM}$). Further analysis regarding the maximum voltage applied at the CP electrode, $V_{app,max}$, reveals that this parameter impacts the optimum amount of fixed charges (plot (d)). Plot (e) shows that changes of [PSS⁻] only slightly impact the ion actuation process, i.e., the change in [K⁺] in the extracellular cleft. (f) The choice of the ECF volume does not impact the optimum amount of fixed charges significantly (V_{ECF}^{nom} indicates the nominal value used in (a-e), see Supplementary Note 3).



Figure S8. Comparison between (left) the ionophores-induced selective CP (ionoCP) and (right) the non-selective CP (nsCP). Simulations of ionic release are performed in both cases with a stimulus V_{app} with slope v = 10 V/s (as in Figs. 7.b and 6.b, respectively). Different values for the maximum applied potential $V_{app,max}$ are considered. From top to bottom, rows indicate: the concentrations of 1) K⁺ and 2) Na⁺ in the cleft between neuron and CP for different $V_{app,max}$ (markers) and different delays from the end of the V_{app} ramp (colors). The CP containing ionophores achieve higher [K⁺] modulation that persists in time due to the continuing unbinding processes of ionophores until a new equilibrium is reached. The modulation of [Na⁺] decays faster in both cases since associated only to sodium drift-diffusion in the ECF (similarly to K⁺ in the nsCP case). Note that the ratio of the quantity of emitted K⁺ and Na⁺ increases with $V_{app,max}$ in the ionoCP case but not in the nsCP one. This means that the unbinding of ionophore complexes KL is promoted for larger potentials applied to the polymer.



Figure S9. Ionophores-induced selective CP (ionoCP). Examples of ionic stimulation transients are performed by keeping either fixed or variable the neuron reversal potentials $V_{\rm K}$, $V_{\rm Na}$, $V_{\rm Cl}$. Different slopes of the applied potential are considered (with $V_{\rm app,max} = 1$ V): a) v = 10 V/s (as in Fig. 7.b), b) v = 40 V/s (as in Fig. 7.c), and c) v = 50 V/s. This is a sanity check to confirm that the AP observed in Fig. 7 results from both the electric and ionic components of neurostimulation. From top to bottom, rows indicate: 1) the applied stimulus $V_{\rm app}$, the extracellular concentrations of 2) [K⁺] and 3) [Na⁺] in different points of the ECF, and the membrane potential V elicited with 4) fixed and 5) variable reversal potentials during the simulation.



Figure S10. Ionophores-induced selective CP (ionoCP). The ionic stimulation transient of Fig. 9.b is shown for different values of the diffusivity coefficient of ionophores. Namely, by reducing them with respect to the one of free K⁺ by a factor a) 100 (used as reference value as in the main text), b) 10⁶, and c) 10⁹ (fixed ionophore approximation). The results are very mildly affected by this parameter, thereby confirming that the choice of modeling ionophores as mobile rather than fixed species is not critical. From top to bottom, rows indicate: 1) the applied stimulus V_{app} , the extracellular concentrations of 2) [K⁺] and 3) [Na⁺] in different points of the ECF, and 4) the membrane potential V.



Figure S11. Calibration of the total synaptic conductance for sodium $G_{\text{Na,syn}}$ to the threshold to elicit an AP. The potassium one $G_{\text{K,syn}}$ is scaled accordingly (see footnote (d) in Table S3). Note that $G_{\text{Na,syn}}$, $G_{\text{K,syn}}$ are obtained by multiplying the synaptic conductances $g_{\text{Na,syn}}$, $g_{\text{K,syn}}$ mentioned in the main body by the neuronal surface area A_{neu} (see Table S5), and are adopted for ease of comparison with the original model of the synapse [7]. The CP, assumed ideal, is held at $V_{\text{app}} = -1$ V, hence no ionic release takes place. Three examples of synaptic events are shown for: a) a sub-threshold value $G_{\text{Na,syn}} = 2.0$ nS (no AP elicited), b) the threshold value $G_{\text{Na,syn}} = 2.22$ nS (AP elicited, used in the main body), and c) a supra-threshold value $G_{\text{Na,syn}} = 2.5$ nS (AP elicited earlier than in (b)). The threshold has been found with an accuracy of the 2.2%. From top to bottom, rows indicate: 1) the total synaptic current $I_{\text{syn}} = I_{\text{K,syn}} + I_{\text{Na,syn}}$, the extracellular concentrations of 2) [K⁺] and 3) [Na⁺] in different points of the ECF, and 4) the membrane potential V.



Figure S12. Test of electroneutrality in the CP-neuron cleft. Two transients of ionic stimulation are considered for a) the ionophores-induced selective CP (ionoCP) and b) the non-selective CP (nsCP). They are compared to the purely physiological case of synaptic-induced AP in c). We point out that the transients a)-c) correspond to those in Fig. 7.b, Fig. 6.b, and Fig. S11.b, respectively. From top to bottom, rows indicate: 1) the applied stimulus (either the potential applied to the CP, V_{app} , or the synaptic current, I_{syn}), 2) the extracellular concentration of $[K^+]$, 3) the membrane potential V, and 4) the deviation of charged ionic species from electroneutrality in the CP-neuron cleft $Q = F([K^+] + [Na^+] - [Cl^-] - [A^-])$. The charge induced in a) results up to an order of magnitude greater than that in c). The charge in b) is instead comparable to that in c), with the exception of the starting and ending phases of the V_{app} ramp. We also point out that the time scales in a)-b) are much larger than in c), with charge density perturbation lasting hundreds of ms in the former ones while just a few ms in the latter one. These results suggest that the electroneutrality assumption might not be trivially satisfied in the ionoCP case. Only more in-depth investigations and comparisons with the KNP formalism (see Discussion) can better shed light on the problem.

Supplementary Note 1: COMSOL implementation details

The model equations reported in Figs. 1, 2 of the main body were implemented using COMSOL Multiphysics v6.0 [8]. For the sake of reproducibility, we herein report the main features adopted in our models.

Rotational symmetry To enforce the symmetry around the vertical axis of the geometry (see Fig. 3), the model has been implemented as a 2D Axisymmetric Component. In such a way, the 3D geometry is defined by its 2D cross-section, and the model equations are automatically adapted to ensure rotational symmetry in the solutions.

Physical interfaces PNP models employed for the ICF, ECF and CP were obtained by combining the *Transport of Dilute Species* and *Electrostatic* physical interfaces, that belong to the electrochemistry and AC/DC packages, respectively. Given the peculiar form of the PNP model describing the CP (see Fig. 1 in the main text), we used user-defined variables to handle the coupling between Poisson and continuity equations, instead of the built-in multiphysics features. The HH model was implemented using *Boundary Ordinary Differential Equations (Boundary ODEs)* at the neuron membrane boundaries. Sample points at 6 nm distance inside and outside the cell membrane were made accessible to the HH model for computing the reversal potentials by using *linear extrusion* operators, available among non-local coupling functions. Similar functions were also employed to create a common set of variables at both sides of the membrane boundary.

Meshing Meshes were designed using the non-linear Boundary Layer mesh-generator with an initial element size of subnanometer length (set using the miminum step size allowed by COMSOL) close to charged interfaces, followed by mesh elements whose size varies exponentially until a maximum predefined size is reached. The number of mesh elements along boundaries was controlled by the *distribution* feature. In the bulk of each simulation domain, the maximum predefined size was set to 1.5 μ m in the ECF, 0.6 μ m in the ICF, and 0.15 μ m in the CP. A convergence analysis was performed to make sure that the selected mesh size provided sufficient accuracy on the results. As shown in Figure S13, a reduction of the maximum element size in the chosen mesh does not induce any change in the solution found by the model.

Studies The initial conditions for ionic actuation transients in the isCP and nsCP cases were found through stationary studies. In the ionoCP case, to help convergence, the initial conditions were found via a stationary study with the dynamics of ionophores disabled and followed by a time-dependent study (10 s) of the full model. Ionic actuation transients starting from such initial conditions were simulated through time-dependent studies with *intermediate* time step setting. The results shown in the main text were sampled at the actual time steps taken by the solver using *probes*.



Figure S13. Convergence analysis of the mesh used in the work. The transient in Fig. 4.a (here, in solid lines) is repeated after reduction of the 25% of the maximum element size in the ECF (dashed lines), ICF (dotted line), and CP (dashed-dotted line). From top to bottom, rows indicate: 1) the applied stimulus to the CP V_{app} , the extracellular concentration of 2) [K⁺] and 3) [Na⁺], and 4) the membrane potential V. The results are in perfect agreement (all curves overlap), thereby confirming the appropriate meshing of the system.

Computational burden Given the numerical complexity of the modeled problems, we used a cluster of servers to perform simulations. To this aim, we employed the *batch* command-line interface to COMSOL Multyphysics.

To provide a glimpse on the mentioned computational burden, we herein report the computational time for the parameter sweeps in Figs. 9.B and 9.D. For such simulations, two servers with the following specifications were used in parallel:

- Server 1: 2x Intel[®] Xeon[®] CPU X5690 at 3.47 GHz (12 cores), 189 GB RAM.
- Server 2: 2x Intel[®] Xeon[®] CPU Gold 6136 at 3.00 GHz (24 cores), 500 GB RAM.

Simulations in Fig. 9.B consisted of time-dependent studies lasting 300 ms with a maximum time step of 1 ms. The total solving time was 30:53:03 (hh:mm:ss), with 13:52:22 carried out by Server 1 and 17:00:41 by Server 2. Table S6 reports the times (mm:ss) of each simulation (bold text: Server 1, plain text: Server 2).

Simulations in Fig. 9.D consisted of time-dependent studies lasting 400 ms with a maximum time step of 1 ms. The total solving time was 39:03:26 (hh:mm:ss), with 19:32:55 carried out by Server 1 and 19:30:31 by Server 2. Table S7 reports the times (mm:ss) of each simulation (bold text: Server 1, plain text: Server 2).

					$V_{\rm app,m}$	$_{\rm lax}$ [V]			
		-0.75	-0.50	-0.25	0	0.25	0.50	0.75	1.00
	0.9	32:37	45:54	44:46	23:52	24:50	24:12	24:18	24:20
	0.8	32:35	35:20	45:57	23:56	23:36	23:46	23:47	24:02
'n	0.7	31:31	33:56	33:43	23:36	24:07	24:29	24:45	24:22
i, sy	0.6	33:21	34:14	34:11	18:16	24:36	24:34	24:23	24:08
\mathcal{S}	0.5	31:30	34:42	33:50	18:00	18:08	24:29	24:07	23:49
ale	0.4	32:09	34:00	33:01	18:19	17:52	18:53	23:51	24:24
$^{\rm SC}$	0.3	32:00	34:04	18:07	17:45	17:48	18:09	18:24	24:28
	0.2	31:12	33:50	17:59	17:34	18:00	18:16	18:22	18:27
	0.1	31:21	32:38	18:06	17:53	17:33	17:57	17:56	18:10

Table S6. Simulation time of the studies in Fig. 9.B.

Table S7. Simulation time of the studies in Fig. 9.D.

					-				
					$V_{\rm app,m}$	$_{\rm nax}$ [V]			
		-0.75	-0.50	-0.25	0	0.25	0.50	0.75	1.00
	0.9	41:54	44:57	55:55	28:23	28:39	29:12	29:18	29:25
i, syn	0.8	42:04	43:57	44:23	28:41	28:08	29:31	29:43	29:01
	0.7	42:08	44:33	43:27	29:30	29:15	29:53	28:56	28:52
	0.6	42:35	43:49	43:19	23:33	23:12	30:30	28:24	30:13
g_{λ}	0.5	41:37	43:47	43:28	23:25	23:04	23:56	29:45	29:11
ale	0.4	41:44	44:12	43:54	22:39	23:23	23:31	23:05	29:52
$_{\rm SC}$	0.3	41:16	43:28	43:10	23:21	22:25	23:21	23:32	23:35
	0.2	41:04	43:02	43:20	23:16	22:25	23:11	23:31	23:30
	0.1	41:29	42:04	42:19	22:52	22:48	23:03	22:37	22:54

Supplementary Note 2: model verification

Given the transient nature of the mechanisms under study, we are interested in timedependent simulations of the polymer – cellular fluids – neural membrane system (see Fig. 1 in the main text). To the extent of our knowledge, analytical solutions are not available for such scenarios. Therefore, to verify the correct implementation of our model, we considered simplified geometries and limit cases as benchmarks.

Simplified geometry: AP propagation along an unmyelinated fiber We reproduced the results of electrodiffusive model for an unmyelinated axon (1 um diameter, 10 mm length) from [9]. Therein, the system was implemented with a formalism very similar to ours (the minor differences are discussed in Sections 2.1.2 - 2.1.3) and solved with a custom software. Figure S14.a shows that our COMSOL implementation reproduces quite closely the propagation of an action potential excited by a 0.965 nA stimulus applied at t = 0 for 2 ms (namely, Fig. 2 in [9]). The propagation velocity results 0.90 ms/s instead of 0.93 m/s as in [9]. Notwithstanding, the referenced work does not provide a convergence analysis of the solution. The difference emerges from the finer mesh employed in our model, with a minimum element size of 0.07 nm along the transverse direction (instead of 0.5 nm in [9]) and 5 μ m along the longitudinal direction (instead of 100 μ m in [9]). Indeed, as shown in Fig. S14.b, we find a better agreement by simulating the system with a coarser mesh resembling that of [9]. This analysis confirms the correctness of our implementation of the coupling between the neural membrane and the cellular fluids.

Limit case: ohmic approximation for cellular fluids A verification of the entire system (including the conductive polymer) has been carried out considering the limit case of electrical stimulation. This limit case occurs when the perturbation of ionic concentrations in the extracellular fluid during the actuation phase is negligible, and the electric field increase is the main mechanism responsible for generating the action potential. In this case (referred to as *pure electrical stimulation* in the main text), the electrolyte can be effectively modeled as an ohmic conductor, thereby neglecting diffusion currents. This formalism is typically employed to model the interface between neurons and implanted electrodes, both for stimulation [10] and recording [11].

In the ohmic electrolyte approximated model, the PNP equations (Eqs. 1-3 in Fig. 1) are replaced in our COMSOL deck by

$$\nabla \cdot \left(\sigma_{\rm el} \nabla \psi_c + \varepsilon_{\rm el} \frac{\partial \nabla \psi_c}{\partial t} \right) = 0, \tag{S1}$$

where $\sigma_{\rm el}$ is the ionic conductivity, defined as

$$\sigma_{\rm el} = \frac{F^2}{RT} \left(D_{\rm K} \left[{\rm K}^+ \right]_{\rm B} + D_{\rm Na} \left[{\rm Na}^+ \right]_{\rm B} + D_{\rm Cl} \left[{\rm Cl}^- \right]_{\rm B} \right).$$
(S2)

By inserting the parameters values used in Table S3 we obtain $\sigma_{\rm el} = 1.3$ S/m for the extracellular fluid and $\sigma_{\rm el} = 2.0$ S/m for the intracellular fluid. While the description of



Figure S14. Comparison of our model to the electrodiffusive model of unmyelinated axon from [9]. The system is excited by a 0.965 nA stimulus applied at t = 0 for 2 ms. The solid lines represent the membrane potential predicted by our model, while the dashed ones are from Fig. 2 in [9]. The x refers to the longitudinal position along the axon where the membrane potential V is sampled. In a) we use a finer mesh than in [9]. In b) we use a coarser mesh resembling the one used in [9].

the neural membrane (HH model) does not change (Eqs. 6-8 in Fig. 1), the boundary conditions that couple the neural membrane and the cellular fluids (Eqs. 4-5, 9-10 in Fig. 1) need to be substituted with

$$\left. \hat{u} \cdot \nabla \psi_c \right|_{\substack{\text{intra}\\ \text{extra}}} = \mp \left(C_{\text{m}} \frac{dV}{dt} + I_{\text{K}} + I_{\text{Na}} + I_{\text{Cl}} \right), \tag{S3}$$

$$V = \psi_c \Big|_{\text{intra}} - \psi_c \Big|_{\text{extra}},$$
(S4)

where \hat{u} is the vector normal to the membrane surface. In a similar way, the conductive polymer is substituted by a flux boundary condition that injects in the extracellular fluid the same ionic current predicted by the electrodiffusive model (i.e., the PNP model in COMSOL) according to

$$\hat{u} \cdot (\sigma_{\rm el} \nabla \psi_c) \Big|_{\rm CP} = I_{\rm CP} = F \frac{d}{dt} \left(\int_{\rm CP} p \ d\Omega \right).$$
(S5)

Figure S15 reports the ionic actuation transients obtained with the non-selective CP (nsCP) following either the electrodiffusive or the ohmic formalisms. Two widths of the



Figure S15. Comparison of the predictions of the electrodiffusive and ohmic models during an actuation transient with the non-selective CP (nsCP). The title of each inset denotes the model used to solve the plotted variable. In a) a neuron-CP cleft of 1 um is considered and the two model predictions differ due to the non-negligible change of ionic concentrations. Conversely, in b) a neuron-CP cleft of 10 μ m is considered and the results of the two models are in good mutual agreement.

neuron-CP cleft (d_{CP_n}) are considered: a) 1 μ m and b) 10 μ m. The rows 1-4 of the plots are results from simulations of the electrodiffusive model, while row 5 contains the results from the ohmic model. In a), the perturbation of ionic concentrations is not negligible due to the small size of the neuron-CP cleft. Therefore, the profile of membrane potential predicted by the two models differs. In fact, in this situation, the electrodiffusive description is more general than the ohmic one. In b) the cleft is very large and ionic concentrations are mildly perturbed by the action of the ionic actuator. Therefore, the predictions of the two models are in good agreement, corroborating the correctness of the implementation of our electrodiffusive model (that naturally tends to the ohmic model in the cases where this latter is valid).

Supplementary Note 3: reduced ionoCP-ECF model

For the optimization of the ionophores-induced selective CP (ionoCP), we considered a phase-boundary model of the interaction between the ionic actuator and the ECF. Namely, we lumped the CP, CP contact, and ECF in compartments. Further, we considered only the equilibrium state of the system. The model is employed to study, 1), the precharging capacity of the ionoCP and, 2), the subsequent release step (see Section 3.3 and Fig. S7).

ionoCP precharge: This model assumes:

- (i) Electroneutrality everywhere in the domain.
- (ii) Electrodiffusion processes at thermodynamic equilibrium. Namely, concentrations follow Boltzmann distributions

$$[\mathbf{X}_i] = [\mathbf{X}_i]_{\mathbf{B}} \left(-\frac{z_{\mathbf{X}_i} F}{RT} \exp(\psi_c - \psi_{c,\mathbf{B}}) \right)$$
(S6)

$$p = p_{\rm M} \left(-\frac{F}{RT} \exp(\psi_p - \psi_{p,\rm M}) \right), \tag{S7}$$

where $X_i \in \{K^+, Na^+, Cl^-\}$. The subscript B denotes the reference point for ionic concentrations and is taken at the bulk of the ECF. The subscript M denotes the reference point for holes and is taken at the CP (metal) contact.

(iii) Chemical reactions (for ionophores) are at thermodynamic equilibrium, i.e., it holds

$$\beta_{\rm KL} = \frac{[\rm KL]}{[\rm K^+]_{\rm CP}[\rm L]} \tag{S8}$$

(iv) Mass conservation for ionophores:

$$[L] + [KL] = [L]_{tot}$$
(S9)

We point out that (ii) and (iii) hold true at equilibrium only if ionophores are regarded as fixed species, i.e., their fluxes $f_{\rm L}$, $f_{\rm KL}$ are null. As seen in the main body, this is not a critical assumption. Hereafter, we summarize the variables solved in the reduced model and those set according to assumption i) \ddagger .

Full model		Reduced model	l	Units
	CP contact	CP	ECF	
ψ_c	-	ψ_c	$\psi_{c,\mathrm{B}}$ = 0	V
$\psi_{m p}$	$\psi_{p,\mathrm{M}} = -1$	$\psi_{m p}$	-	V
$[K^+]$	-	$[\mathrm{K}^{+}]_{\mathrm{CP}}$	$[K^{+}]_{B} = 4$	mM
$\left[\mathrm{Na}^{+}\right]$	-	$\left[\mathrm{Na}^{+}\right]_{\mathrm{CP}}$	$[Na^{+}]_{B} = 144$	mM
[Cl-]	-	$\left[\text{Cl} - \right]_{\text{CP}}$	$[Cl-]_{B}^{B} = 130$	mM
[L]	-	[L]	-	mM
[KL]	-	[KL]	-	mM
p	$p_{\rm M}$ = 97.97	p	-	М

 $\ddagger~p_{\rm M}$ assumed from the concentration of free electrons in gold, i.e, $5.9\cdot10^{28}~{\rm m}^{-3}.$

In the model equations considered in this study there are 8 free variables to solve: ψ_c , ψ_p , $[K^+]_{CP}$, $[Na^+]_{CP}$, $[Cl^-]_{CP}$, [L], [KL], p. From the assumptions i), ii), iii), and iv) follow the below Eqs. S5.a-b), c-f), g), and h), respectively.

$$[K^{+}]_{CP} + [Na^{+}]_{CP} - [Cl^{-}]_{CP} + p - [PSS^{-}] + [KL] = 0$$
(S10a)

$$p - \frac{C_V}{F}(\psi_p - \psi_c) = 0$$
 (S10b)

$$[\mathbf{K}^+]_{\rm CP} - [\mathbf{K}^+]_{\rm B} \exp\left(-\frac{F\psi_c}{RT}\right) = 0 \qquad (S10c)$$

$$[\mathrm{Na}^+]_{\mathrm{CP}} - [\mathrm{Na}^+]_{\mathrm{B}} \exp\left(-\frac{F\psi_c}{RT}\right) = 0 \qquad (S10d)$$

$$[Cl^{-}]_{CP} - [Cl^{-}]_{B} \exp\left(\frac{F\psi_{c}}{RT}\right) = 0$$
 (S10e)

$$p - p_{\rm M} \exp\left(\frac{F}{RT}(V_{\rm app,0} - \psi_p)\right) = 0 \tag{S10f}$$

$$[KL] - \beta_{KL}[K^+]_{CP}[L] = 0 \qquad (S10g)$$

$$[L] + [KL] - [L]_{tot} = 0$$
 (S10h)

ionoCP release: this study analyzes the concentration change of potassium ions in the ECF at equilibrium based on the final value of the applied stimulus at the metal contact, $\psi_{p,M} = V_{app,max}$. Therefore, the model uses the solution obtained with the pre-charging study (see above) as initial conditions for concentrations of potassium ions (free and complexed indicated as $[K^+]_{CP,0}$ and $[LK]_0$ in the following) and enforces mass conservation of these ions using fixed CP and ECF volumes. This model has therefore 9 unknown variables to solve: the 8 of the previous study plus $[K^+]_{ECF}$:

$$[K^{+}]_{CP} + [Na^{+}]_{CP} - [Cl^{-}]_{CP} + p - [PSS^{-}] + [KL] = 0$$
(S11a)

$$p - \frac{C_{\rm V}}{F} (\psi_p - \psi_c) = 0 \qquad (S11b)$$

$$[\mathrm{K}^+]_{\mathrm{CP}} - [\mathrm{K}^+] \exp\left(-\frac{F\psi_c}{RT}\right) = 0 \qquad (S11c)$$

$$[\mathrm{Na}^+]_{\mathrm{CP}} - [\mathrm{Na}^+]_{\mathrm{B}} \exp\left(-\frac{F\psi_c}{RT}\right) = 0 \qquad (S11d)$$

$$[\mathrm{Cl}^{-}]_{\mathrm{CP}} - [\mathrm{Cl}^{-}]_{\mathrm{B}} \exp\left(\frac{F\psi_{c}}{RT}\right) = 0 \qquad (S11e)$$

$$p - p_{\rm M} \exp\left(\frac{F}{RT} (V_{\rm app,max} - \psi_p)\right) = 0 \qquad (S11f)$$

$$[KL] - \beta_{KL}[K^+]_{CP}[L] = 0 \qquad (S11g)$$

$$[L] + [KL] - [L]_{tot} = 0$$
 (S11h)

$$([K^+]_{CP} + [LK] - [K^+]_{CP,0} - [LK]_0)V_{CP} + ([K^+] - [K^+]_B)V_{ECF} = 0,$$
(S11i)

where $V_{\rm CP}$ and $V_{\rm ECF}$ are the volumes of the CP and the ECF, respectively.

Compartments volume: while V_{CP} is given by the adopted geometry (see Table S5), the value used for V_{ECF} must reflect the dynamics of the ionic actuator, namely the

ion diffusion space around the CP for a given time interval. In fact, this optimization tool provides an estimate on the total modulation at $t = \infty$ while the ionoCP operates in dynamic conditions. Thus, one way to exploit the results of the simplified model is to assume an effective volume that is actually modulated during the ion release, before ions disperse in the bulk of ECF. In this paper, based on the results presented in the main body, we used an interval $\Delta t = 150$ ms and considered the ECF volume as the 3D space within $\sqrt{D_K \Delta t}$ all around the CP, and subtracted the volume occupied by the neuron cell.

Solver: Solutions of Eqs. (S10) and (S11) were found developing an *ad-hoc* Newton-Raphson solver. Parameters such as β_{KL} , [PSS⁻], [L]_{tot}, $V_{\text{app,max}}$ were varied according to the optimization process as described in the main body.

References

- J. R. Cressman, G. Ullah, J. Ziburkus, S. J. Schiff, and E. Barreto, "The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: I. single neuron dynamics," *Journal of computational neuroscience*, vol. 26, no. 2, pp. 159–170, 2009. DOI: 10.1007/s10827-008-0132-4.
- [2] M. O. Bamgbopa, J. Edberg, I. Engquist, M. Berggren, and K. Tybrandt, "Understanding the characteristics of conducting polymer-redox biopolymer supercapacitors," *Journal of Materials Chemistry A*, vol. 7, no. 41, pp. 23973– 23980, 2019. DOI: 10.1039/c9ta07030c.
- [3] A. J. Bard, L. R. Faulkner, and H. S. White, *Electrochemical methods: fundamentals and applications*, 2nd ed. John Wiley & Sons Inc., 2001, ISBN: 9780471043720.
- [4] K. Tybrandt, I. V. Zozoulenko, and M. Berggren, "Chemical potential-electric double layer coupling in conjugated polymer-polyelectrolyte blends," *Science advances*, vol. 3, no. 12, eaao3659, 2017. DOI: 10.1126/sciadv.aao3659.
- [5] J. Rivnay, P. Leleux, M. Ferro, et al., "High-performance transistors for bioelectronics through tuning of channel thickness," Science Advances, vol. 1, no. 4, pp. 1–6, 2015. DOI: 10.1126/sciadv.1400251.
- [6] J. J. Jasielec, T. Sokalski, R. Filipek, and A. Lewenstam, "Neutral-Carrier Ion-Selective Electrodes Assessed by the Nernst-Planck-Poisson Model," *Analytical Chemistry*, vol. 87, no. 17, 2015. DOI: 10.1021/acs.analchem.5b00065.
- [7] M. J. Sætra, G. T. Einevoll, and G. Halnes, "An electrodiffusive neuronextracellular-glia model for exploring the genesis of slow potentials in the brain," *PLoS Computational Biology*, vol. 17, no. 7, 2021. DOI: 10.1371/journal.pcbi. 1008143.
- [8] Comsol multiphysics user manual, COMSOL Inc., Sweden, 2022.
- [9] J. Pods, J. Schönke, and P. Bastian, "Electrodiffusion models of neurons and extracellular space using the poisson-nernst-planck equations - Numerical simulation of the intra- and extracellular potential for an axon model," *Biophysical Journal*, vol. 105, no. 1, 2013. DOI: 10.1016/j.bpj.2013.05.041.
- [10] A. Fellner, A. Heshmat, P. Werginz, and F. Rattay, "A finite element method framework to model extracellular neural stimulation," *Journal of Neural Engineering*, vol. 19, no. 2, p. 022001, Apr. 2022. DOI: 10.1088/1741-2552/ AC6060.
- R. Bestel, U. Van Rienen, C. Thielemann, and R. Appali, "Influence of Neuronal Morphology on the Shape of Extracellular Recordings with Microelectrode Arrays: A Finite Element Analysis," *IEEE Transactions on Biomedical Engineering*, vol. 68, no. 4, 2021. DOI: 10.1109/TBME.2020.3026635.