

Electrodiffusion model of synaptic potentials in dendritic spines

Supplementary Information

Thibault Lagache,^{1,2,3} Krishna Jayant,^{1,2,3,4} and Rafael Yuste^{1,2,3}

¹*Department of Biological Sciences, Columbia University, New York, 10027*

²*Neurotechnology Center, Columbia University, New York, 10027*

³*Kavli institute of Brain Science, Columbia University, New York, 10027*

⁴*Department of Electrical Engineering, Columbia University, New York, 10027*

This document contains:

I Two supplementary figures that describe: **Supplementary Figure 1:** the charging time constant of the head capacitor as function of dendritic spine geometry, and **Supplementary Figure 2:** the steady-state synaptic current, head voltage and ion concentration for increased synaptic conductance.

II Details of computations leading to main equations of the manuscript.

I. SUPPLEMENTARY FIGURES

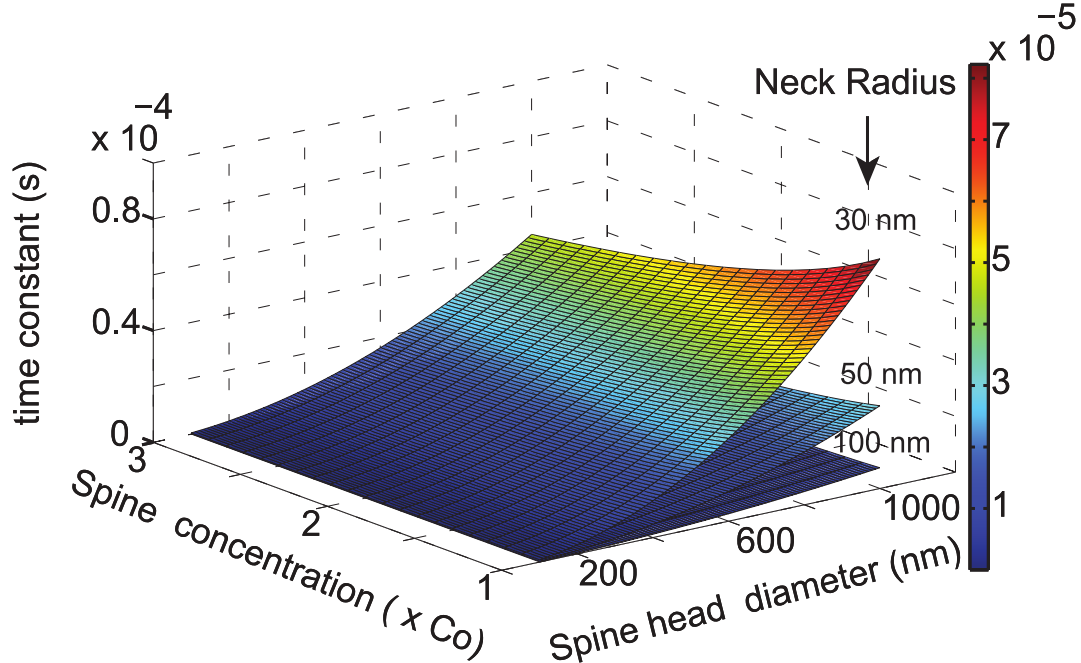


FIG. S1: **Charge kinetics of spine head capacitor** The charging time constant of head capacitor is plotted as function of spine head size and ion concentration for constant neck length $L = 1 \mu\text{m}$ and different neck radii (small (30 nm), medium (50 nm) and large (100 nm)).

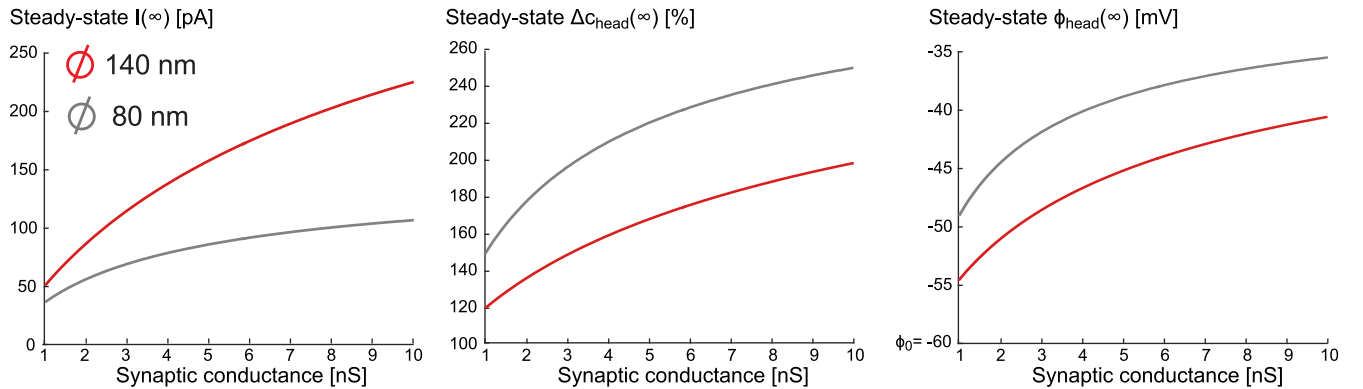


FIG. S2: **Steady-state analysis for sustained synaptic current.** For increasing synaptic conductance and different neck geometries (constant length $L = 1 \mu\text{m}$, thin (80 nm, grey) or large (140 nm, red) diameter), we computed the steady state synaptic current, head concentration and potential when a sustained current of positive ions is injected inside the spine head, *i.e.* when the conductance does not change over time (see detailed analysis in section II-C-2).

II. SUPPLEMENTARY METHODS: DETAILS OF MATHEMATICAL DERIVATIONS

A. Electrostatics within the spine head

We modeled the geometry of the spine head with a ball of radius R (see Fig. 1a in main text), and considered that the cell membrane is homogeneous and thin bilayer with a thickness equal to $d \ll R$ and a relative permittivity ϵ_m that is much smaller than cytoplasmic permittivity $\epsilon_m \ll \epsilon_c$ (see **Table 1** in main text). Inside the cytoplasm, *i.e.* apart of the membrane bilayer, Poisson equation reads

$$\Delta_r \Phi(r, t) = \frac{e}{\epsilon_0 \epsilon_c} (c^-(r, t) - c^+(r, t)) \quad (1)$$

with Δ_r the Laplacian operator with respect to the radial coordinate $r \geq 0$, Φ the electrical potential and c^+, c^- the concentrations of positive and negative charges. e , the elementary charge, ϵ_0 the vacuum permittivity and ϵ_c , the relative permittivity of the cytoplasm, are constants (see **Table 1** in main text). Origin $r = 0$ corresponds to the center of the spine head ball, $r = R$ to the interior membrane and $r = R + d$ to the exterior membrane of spine head. Nernst-Planck equations reads

$$\frac{\partial c^v(r, t)}{\partial t} = D \nabla_r \cdot \left(\nabla_r c^v(r, t) + \frac{ve}{k_B T} c^v(r, t) \nabla_r \Phi(r, t) \right) \quad (2)$$

where $v = \pm 1$ is the ion valence, ∇_r the gradient operator, k_B the Boltzmann constant and T the temperature. We assumed that the diffusion coefficient D is the same for positive and negative ions (see **Table 1** in the main text).

To derive asymptotical expressions for the electrical potential and ion concentration inside the spine head, we developed singular perturbation analysis of PNP equations (1 and 2) which consists of three main steps (for a detailed overview of singular perturbation methods in electro-diffusion problems, see Part 3 *A primer on Singular Perturbation Theory* in [1]):

1. Rewrite PNP equations in dimensionless variables and make appear a very small pre-factor on one hand of equations allowing their asymptotical analysis
2. Compute an approximate solution far from the domain boundaries called *outer solution* by letting the small parameter tend to 0. Usually, *Outer solution* does not satisfy the boundary conditions.
3. Compute the local *inner solution* inside the boundary layer that satisfies boundary conditions and match *inner* and *outer* solutions at some intermediate distance from the boundary layer.

Step 1: Rewriting the PNP system of equations in a dimensionless system of variables.

Let denote

$$u = \frac{r}{R}, \phi(u, t) = \frac{e}{k_B T} \Phi(r, t) = \gamma \Phi(r, t), p(u, t) = \frac{c^+(r, t)}{c_0}, n(u, t) = \frac{c^-(r, t)}{c_0}, \quad (3)$$

and Poisson equation then reduced to

$$\delta_1 \Delta_u \phi(u, t) = n(u, t) - p(u, t), \quad (4)$$

where Δ_u is the Laplace operator in dimensionless variable u and

$$\delta_1 = \frac{\epsilon_0 \epsilon_c}{e \gamma c_0 R^2} = 2 \left(\frac{\lambda_D}{R} \right)^2 \ll 1, \quad (5)$$

where $\lambda_D = \sqrt{\frac{\epsilon_0 \epsilon_c}{2e \gamma c_0}}$ is the Debye length.

Step 2: Asymptotic computation of *outer* solution inside the bulk (*i.e.* except for the thin boundary layer near the membrane and the neck junction)

As $\delta_1 \ll 1$, singular perturbation analysis allowed the expansion of potential and concentrations as

$$\begin{aligned} \phi(u, t) &= \phi_0(u, t) + \delta_1 \phi_1(u, t) + o(\delta_1^2), \quad p(u, t) = p_0(u, t) + \delta_1 p_1(u, t) + o(\delta_1^2) \\ \text{and } n(u, t) &= n_0(u, t) + \delta_1 n_1(u, t) + o(\delta_1^2). \end{aligned}$$

Letting δ_1 tend to 0 in reduced Poisson equation (4), we obtained that the bulk inside spine head, except for the boundary layer near the membrane, was electro-neutral

$$p_0(u, t) = n_0(u, t), \quad (6)$$

On the other hand, reduced Nernst-Planck equations read

$$\begin{aligned}\frac{\partial p(u, t)}{\partial t} &= \frac{D}{R^2} \nabla_u (\nabla_u p(u, t) + p(u, t) \nabla_u \phi(u, t)), \\ \frac{\partial n(u, t)}{\partial t} &= \frac{D}{R^2} \nabla_u (\nabla_u n(u, t) - n(u, t) \nabla_u \phi(u, t)),\end{aligned}\quad (7)$$

Addition of reduced NP equations, together with asymptotic electro-neutrality condition (6), led to

$$\frac{\partial p_0(u, t)}{\partial t} = \frac{D}{R^2} \Delta_u p_0(u, t). \quad (8)$$

As $\frac{D}{R^2} = O(10^5 \text{ Hz})$, ion concentration rapidly equilibrates and singular perturbation theory yields

$$\Delta_u p_0(u, t) = O\left(\frac{R^2}{D} \left\| \frac{\partial p_0(u, t)}{\partial t} \right\|_{\infty}\right) = o(1) \quad (9)$$

where $\|\cdot\|_{\infty}$ is the infinity norm (*i.e.* maximum of the time derivative) which is bounded. Because the spine neck diameter is small compared to the size the spine head $\epsilon = \frac{a(0)}{R} \ll 1$, Narrow escape theory ensured that we could approximate $p_0(u, t)$ with the constant solution $p_0(t)$ of the harmonic equation (9) within a ball with no neck junction [2, 3].

On the other hand, subtraction of reduced Nernst-Planck equations (7) with constant bulk concentration led to

$$\frac{D p_0(t)}{R^2} \Delta_u \phi_0(u, t) = O\left(\delta_1 \left\| \frac{\partial p_1(u, t)}{\partial t} \right\|_{\infty}\right). \quad (10)$$

Thus,

$$\Delta_u \phi_0(u, t) = O\left(\frac{\lambda_D^2}{D} p_0^{-1}(t) \left\| \frac{\partial p_1(u, t)}{\partial t} \right\|_{\infty}\right) = o(1) \quad (11)$$

meaning that potential is nearly harmonic inside the spine head. For $\epsilon = \frac{a(0)}{R} \ll 1$, we neglected the effects of neck junction at the center of the spine head, and assumed the symmetric condition $\left[\frac{\partial \phi_0(u, t)}{\partial u}\right]_{u=0} = 0$. The solution of equation (11) is then constant within the bulk

$$\phi_0(u, t) = \phi_0(t) (1 + o(1)). \quad (12)$$

To obtain the full solutions for the potential and the ions' concentrations, we then computed the *inner* solutions within the boundary layers near the membrane that match the boundary conditions, that are the no-flux condition for ions and the continuity of the electrical field for the potential.

Step3: Computation of *inner solutions* of PNP equations near the membrane (*i.e.* within the boundary layer)

Denoting \mathbf{n} the membrane outward normal vector, continuity of the electrical field at both sides of the spine membrane imposes that

$$\frac{\partial \Phi}{\partial \mathbf{n}}(r = R) = \frac{\partial \Phi}{\partial \mathbf{n}}(r = R + d). \quad (13)$$

Considering that the cell membrane is homogeneous and thin, we approximated the variation of the electric field across the membrane with a linear function [4]

$$\epsilon_c \frac{\partial \Phi}{\partial \mathbf{n}}(r = R) = \epsilon_m \frac{\Phi(r = R + d) - \Phi(r = R)}{d}, \quad (14)$$

where $\epsilon_m \ll \epsilon_c$ is the relative permittivity of the membrane bilayer (see **Table 1** in main text). The electro-neutrality of the bulk inside and outside the spine head derives from the singular expansion of the potential solution (6), and imposes that

$$\frac{\partial \Phi}{\partial \mathbf{n}}(r \rightarrow \infty) = 0. \quad (15)$$

Finally, we set the external potential far from the membrane to 0 (*i.e.* $\Phi(r \rightarrow \infty) = 0$).

Charging time of the Debye-Hückle boundary layer is of the order of $\frac{R \lambda_D}{D} \approx 10^{-6}$ seconds. We thus assumed that ion concentrations are quasi-static inside the boundary layer (*i.e.* equilibrate fast compared to the other time scales of electro-diffusion processes), and are governed by Boltzmann equilibrium distribution inside the spine head

$$c^+(r, t) = c_{head}(t) \exp\left(\frac{e}{k_B T} (\Phi(r, t) - \Phi_{head}(t))\right) \text{ and } c^-(r, t) = c_{head}(t) \exp\left(\frac{-e}{k_B T} (\Phi(r, t) - \Phi_{head}(t))\right) \quad (16)$$

with $c_{head}(t)$ and $\Phi_{head}(t)$ the bulk concentration and potential inside the spine head, and outside the spine head

$$c^+(r, t) = c_0 \exp\left(\frac{e}{k_B T} (\Phi(r, t))\right) \text{ and } c^-(r, t) = c_0 \exp\left(\frac{-e}{k_B T} (\Phi(r, t))\right) \quad (17)$$

with c_0 the bulk ion concentration in the extracellular medium, that we assumed to be equal to the resting ion concentration inside the dendritic spine (see Table 1 in main manuscript). Inside the boundary layer, we approximate the Laplacian operator $\Delta_r \approx \frac{\partial}{\partial r^2}$, and re-introducing Boltzmann profiles of ion concentrations in the Poisson equation (1), we found that potential is solution of the one-dimensional Poisson-Boltzmann equation

$$\frac{\partial \Phi(r, t)}{\partial r^2} = \frac{e c_{head}(t)}{\epsilon_0 \epsilon_c} \left(\exp\left(\frac{-e}{k_B T} (\Phi(r, t) - \Phi_{head}(t))\right) - \exp\left(\frac{e}{k_B T} (\Phi(r, t) - \Phi_{head}(t))\right) \right) \quad (18)$$

inside the spine head, and

$$\frac{\partial \Phi(r, t)}{\partial r^2} = \frac{e c_0}{\epsilon_0 \epsilon_c} \left(\exp\left(\frac{-e}{k_B T} (\Phi(r, t))\right) - \exp\left(\frac{e}{k_B T} (\Phi(r, t))\right) \right) \quad (19)$$

outside the spine head. Given that the relative permittivity of membrane bilayer is much smaller than the relative permittivity of the cytoplasm $\epsilon_m \ll \epsilon_c$, most of the voltage drop occurs through the membrane rather than inside the Debye-Hückel boundary layer, meaning that $\Phi(r, t) = \Phi_{head}(t) + o(\Phi_{head}(t))$ for all $0 \leq r \leq R$ inside the spine head, and $\Phi(r, t) \approx 0$ mV for $r \geq R + d$ outside the spine head. We thus linearized previous Poisson-Boltzmann equation and obtained the well-established exponential profile of potential

$$\Phi(r, t) = \Phi_{head}(t) + (\Phi(R, t) - \Phi_{head}(t)) \exp\left(-\frac{R-r}{\lambda_D} \sqrt{\frac{c_0}{c_{head}(t)}}\right), \quad (20)$$

inside the spine head, and

$$\Phi(r, t) = \Phi(R + d, t) \exp\left(-\frac{r - R - d}{\lambda_D}\right), \quad (21)$$

outside the spine head.

Finally, we computed the value of the potential at membrane boundary, $\Phi(R, t)$ and $\Phi(R + d, t)$, by using the continuity of the electric field at the membrane (Eq. 13)

$$\Phi(R, t) + \sqrt{\frac{c_{head}(t)}{c_0}} \Phi(R + d, t) = \Phi_{head}(t). \quad (22)$$

and linear approximation (14) together with exponential profile (20)

$$(\Phi(R, t) - \Phi_{head}(t)) = \sqrt{\frac{c_{head}(t)}{c_0}} \frac{\lambda_d \epsilon_m}{d \epsilon_c} (\Phi(R + d) - \Phi(R)). \quad (23)$$

Solving previous linear system of equations, and using Taylor expansions of solutions for $\frac{\lambda_d \epsilon_m}{d \epsilon_c} \ll 1$ led to

$$\Phi(R, t) = \left(1 - \sqrt{\frac{c_{head}(t)}{c_0}} \frac{\epsilon_m \lambda_D}{\epsilon_c d}\right) \Phi_{head}(t), \quad (24)$$

and

$$\Phi(R + d, t) = \frac{\epsilon_m \lambda_D}{\epsilon_c d} \Phi_{head}(t). \quad (25)$$

Finally, by summing *inner* (*i.e.* inside the Debye-Hückel boundary layer near the membrane) and *outer* solutions (*i.e.* inside the bulk cytoplasm), we obtained that potential inside the spine head is given by

$$\Phi(r, t) \approx \Phi_{head}(t) \left(1 - \sqrt{\frac{c_{head}(t)}{c_0}} \frac{\epsilon_m \lambda_D}{\epsilon_c d} \exp\left(-\frac{R-r}{\lambda_D} \sqrt{\frac{c_0}{c_{head}(t)}}\right)\right) \text{ for } 0 \leq r \leq R \quad (26)$$

and outside the spine head, we computed that

$$\Phi(r, t) \approx \frac{\epsilon_m \lambda_D}{\epsilon_c d} \Phi_{head}(t) \exp\left(-\frac{r - R - d}{\lambda_D}\right) \text{ for } r \geq R + d. \quad (27)$$

Finally, to relate the potential $\Phi_{head}(t)$ to the total number of charges inside the spine head, we integrated the Poisson equation over the spine interior volume, and used Green's first identity

$$s_h \frac{\partial \Phi(R, t)}{\partial r} = -\frac{e}{\epsilon_0 \epsilon_c} (n^+(t) - n^-(t)), \quad (28)$$

where $n^+(t)$ and $n^-(t)$ are the total number of charges inside the spine head at time t and $s_h = 4\pi R^2$ the surface of the spine head membrane. Using equation (26) for the interior solution of potential, we computed that

$$\frac{\partial \Phi(R, t)}{\partial r} = -\Phi_{head}(t) \frac{\epsilon_m}{\epsilon_c d}, \quad (29)$$

and we obtained that

$$\Phi_{head}(t) = \frac{ed}{\epsilon_0 \epsilon_m s_h} (n^+(t) - n^-(t)) = \frac{e(n^+(t) - n^-(t))}{c_m s_h}, \quad (30)$$

where $c_m = \frac{\epsilon_0 \epsilon_m}{d} = O(10^{-2} \text{F.m}^{-2})$ is membrane capacitance per unit of surface. Eq. (30) indicates that spine head behaves like an ideal capacitor with capacitance $C_{head} = c_m s_h$.

Overall, our results indicate that (i) Bulk is electro-neutral, (ii) Electrical potential is constant except for the boundary layer near the membrane where it increases (iii) Main potential drop occurs across the membrane bilayer due to its low permittivity $\epsilon_m \ll \epsilon_c$, and (iv) Potential within the spine head is proportional to the absolute number of excess negative charges in excess. The spine head behaves like a pure capacitor with capacitance $C_{head} = c_m s_h$.

B. Asymptotic analysis of ions' fluxes (current and diffusion) inside the spine neck

In this section, we reduced the PNP equations inside the neck to one-dimensional equations along neck's principal axis. Then, we computed the asymptotic current and diffusion flux between the spine head and the parent dendrite.

1. One-dimension reduction of PNP equations inside the spine neck

The bulk concentration of ions yields a Debye length of $\lambda_D \approx 1 \text{nm}$, which is much smaller than neck radius in most spines [5]. Moreover, spine length is typically an order of magnitude bigger than neck radius [5]. These two results justify well the one-dimensional approximation of PNP equations where each cross section $S(l)$ is approximated as an iso-potential and iso-concentration surface [1]. Following the methodology used in [6, 7], we derived hereafter the one-dimensional approximation of PNP equations in spine neck.

The 1D approximation relies on applying the divergence theorem on small cylindrical volumes around the position $0 \leq l \leq L$ inside the spine neck, delimited longitudinally by cross-sections $S(l - dl)$ and $S(l + dl)$ and laterally by the membrane $m(l)$. In a first approximation, we considered that each cross-section is a disc of radius $a(l)$ (*i.e.* $S(l) = \pi a^2(l)$), and that ion concentrations $c^+(l, t)$ and $c^-(l, t)$ are constant within the disc. We neglected here the effects of negative surface charge at neck membrane. Effect of negative surface charge on I-V relation, known as current rectification, appears when surface charge density or radius of the spine neck vary (Eq. (28) in [6]). However, in the physiological and geometrical conditions of spine electro-physiology, current rectification can be neglected. Indeed, even for an important surface charge density $\sigma = 1e \text{ nm}^{-2}$, a potential difference $\Phi_{head}(t) - \Phi_0 = 25$, and a 50 nm difference between the initial radius of the spine $a(0) = 50 \text{ nm}$ and the final radius $a(L) = 100 \text{ nm}$, the current rectification (inside the brackets of the right-hand side of equation (28) [6]) would be very close to 1 (which corresponds to no rectification): Rectification = $\left[1 - \frac{1}{12} \frac{\sigma}{\epsilon_0 F} \left(\frac{1}{a(0)} - \frac{1}{a(L)}\right) \gamma (\Phi_{head}(t) - \Phi_0)\right] \approx 0.99$. Moreover, we highlight that rectification is equal to 0 when surface charge and neck's cross-section are constant. Then, the integration of the Poisson equation over infinitesimal volume, and the first Green's identity led to

$$\left[S \frac{\partial \Phi}{\partial l} \right]_{l-dl}^{l+dl} (t) + 2\pi a(l) dl \frac{\partial \Phi}{\partial r} (a(l), t) = -dl \frac{e}{\epsilon_0 \epsilon_c} S(l) (c^+(l, t) - c^-(l, t)), \quad (31)$$

and, after dividing by dl and letting $dl \rightarrow 0$, to

$$\frac{1}{S(l)} \frac{\partial}{\partial l} \left[S \frac{\partial \Phi}{\partial l} \right] (l, t) + \frac{2}{a(l)} \frac{\partial \Phi}{\partial r} (a(l), t) = -\frac{e}{\epsilon_0 \epsilon_c} (c^+(l, t) - c^-(l, t)). \quad (32)$$

Using the gradient equation (14), and relations (26-27) inside the neck at position $0 \leq l \leq L$, we found that

$$\frac{\partial \Phi}{\partial r} (a(l), t) = \frac{\epsilon_m}{\epsilon_c d} \Phi(l, t), \quad (33)$$

and

$$\frac{1}{S(l)} \frac{\partial}{\partial l} \left[S \frac{\partial \Phi}{\partial l} \right] (l, t) + \frac{2\epsilon_m}{a(l)\epsilon_c d} \Phi(l, t) = -\frac{e}{\epsilon_0 \epsilon_c} (c^+(l, t) - c^-(l, t)). \quad (34)$$

Integration of Nernst-Planck equation and Green's identity led to (no ions flux at the membrane)

$$\frac{\partial c(l, t)}{\partial t} S(l) dl = D \left[S \left(\nabla c + \frac{ve}{kT} c \nabla \Phi \right) \right]_l^{l+dl} (t), \quad (35)$$

where $v = \pm 1$ is ion valence. That is, after dividing by dl and letting $dl \rightarrow 0$

$$\frac{\partial c(l, t)}{\partial t} = \frac{D}{S(l)} \frac{\partial}{\partial l} \left[S \left(\frac{\partial c}{\partial l} + \frac{ve}{kT} c \frac{\partial \Phi}{\partial l} \right) \right] (l, t). \quad (36)$$

2. Asymptotic analysis of PNP equations inside the neck

a. Computation of the diffusion fluxes of ions. To perform asymptotic analysis of PNP equations inside the neck, we introduced the dimensionless variables

$$u = \frac{l}{L}, \phi(u, t) = \gamma \Phi(l, t), s(u) = \frac{S(l)}{S(0)}, \tilde{a}(u) = \frac{a(l)}{a(0)}, p(u, t) = \frac{c^+(l, t)}{c_0}, n(u, t) = \frac{c^-(l, t)}{c_0}. \quad (37)$$

Reduced Poisson equation then reads

$$\delta_2 \left(s^{-1}(u) \frac{\partial}{\partial u} \left[s \frac{\partial \phi}{\partial u} \right] (u, t) + c_1 \tilde{a}^{-1}(u) \phi(u, t) \right) = n(u, t) - p(u, t) \quad (38)$$

where

$$\delta_2 = \frac{\epsilon_0 \epsilon_c}{e L^2 \gamma c_0} = 2 \left(\frac{\lambda_D}{L} \right)^2 \ll 1 \text{ and } c_1 = 2 \frac{L^2}{da(0)} \frac{\epsilon_m}{\epsilon_c} \ll \delta_2^{-1}. \quad (39)$$

On the other hand, reduced Nernst-Planck equations read

$$\frac{\partial p(u, t)}{\partial t} = -s^{-1}(u) \frac{\partial j_p(u, t)}{\partial u} \text{ and } \frac{\partial n(u, t)}{\partial t} = -s^{-1}(u) \frac{\partial j_n(u, t)}{\partial u}, \quad (40)$$

with

$$\frac{De}{L^2} \left[s \left(\frac{\partial p}{\partial u} + p \frac{\partial \phi}{\partial u} \right) \right] (u, t) = -j_p(u, t) \text{ and } \frac{De}{L^2} \left[s \left(\frac{\partial n}{\partial u} - n \frac{\partial \phi}{\partial u} \right) \right] (u, t) = -j_n(u, t). \quad (41)$$

Letting δ_2 tend to 0 in Poisson equation, we obtained the electro-neutrality condition

$$p(u, t) = n(u, t) + O(\delta_2). \quad (42)$$

The addition of reduced Nernst-Planck equations (40) leads to

$$\frac{\partial p(u, t)}{\partial t} = \frac{D}{L^2} \left[s^{-1}(u) \frac{\partial}{\partial u} \left[s \frac{\partial p}{\partial u} \right] (u, t) + O(\delta_2) \right] \quad (43)$$

As $\frac{D}{L^2} = O(10^3 \text{ Hz})$, we conclude that $\frac{\partial}{\partial u} \left[s \frac{\partial p}{\partial u} \right] (u) = o(1)$, and spatial integration with respect to u leads to

$$p(u, t) = \alpha(t) \int_0^u s^{-1}(x) dx + \beta(t) + o(1). \quad (44)$$

where $\alpha(t), \beta(t)$ are time functions that do not depend on spatial coordinate u . Denoting $c_{head}(t)$ the ionic concentration inside the spine head at time t , and assuming that the dendrite is an infinite reservoir with constant concentration c_0 , boundary conditions are then given by $p(0, t) = \frac{c_{head}(t)}{c_0}$ and $p(1, t) = 1$, leading to $\beta(t) = \frac{c_{head}(t)}{c_0}$ and $\alpha(t) = \frac{c_0 - c_{head}(t)}{c_0 \int_0^1 s^{-1}(u) du}$ leading to the concentration profile along the neck

$$p(u, t) = \frac{c_0 \int_0^u s^{-1}(x) dx + c_{head}(t) \int_u^1 s^{-1}(x) dx}{c_0 \int_0^1 s^{-1}(u) du} + o(1). \quad (45)$$

Using previous equation (45) for the concentration profile of ions through the neck, we can then compute diffusion fluxes of charges inside the neck $j_{neck}(u, t) = j_p(u, t) + j_n(u, t) = -\frac{2De}{L^2} \left[s \frac{\partial p}{\partial u} \right] (u, t)$

$$j_{neck}(u, t) = j_{neck}(t) = \frac{2De}{L^2} \frac{(c_{head}(t) - c_0)}{c_0 \int_0^1 s^{-1}(u) du}, \quad (46)$$

In original variables, the diffusive flux is equal to $J_{neck}(l, t) = -2eDS(l) \frac{\partial c(l, t)}{\partial l}$. Thus, $J_{neck}(l, t) = J_{neck}(t) = Lc_0S(0)j_{neck}(t)$, *i.e.*

$$J_{neck}(t) = \frac{2D(c_{head}(t) - c_0)e}{\int_0^L S^{-1}(l) dl}. \quad (47)$$

b. Computation of the electrical current. Electrical current is the net difference between the fluxes of negative and positive ions. Due to electro-neutrality, diffusion currents do not produce any electrical current. Net current is thus equal to

$$i_{neck}(u, t) = [j_p - j_n](u, t) = -2 \frac{De}{L^2} \left[sp \frac{\partial \phi}{\partial u} \right] (u, t). \quad (48)$$

Substraction of reduced NP equations (40) yields

$$\frac{\partial i_{neck}(u, t)}{\partial u} = \left[\frac{\partial j_p(u, t)}{\partial u} - \frac{\partial j_n(u, t)}{\partial u} \right] = \frac{\partial [n - p](u, t)}{\partial t} = O(\delta_2). \quad (49)$$

Thus, $i_{neck}(u, t) = i_{neck}(t) (1 + o(1))$ and injecting the concentration profile through the neck (45) in Eq. (48), we obtain that current is given by

$$i_{neck}(t) = -\frac{De}{L^2} \frac{2s(u)}{c_0 \int_0^1 s^{-1}(u) du} \left(c_0 \int_0^u s^{-1}(x) dx + c_{head}(t) \int_u^1 s^{-1}(x) dx \right) \frac{\partial \phi(u, t)}{\partial u}, \quad (50)$$

that reads in original variables

$$I_{neck}(t) = Lc_0S(0)i_{neck}(t) = -\frac{2\gamma eS(l)D}{\int_0^L S^{-1}(y) dy} \left(c_0 \int_0^l S^{-1}(y) dy + c_{head}(t) \int_l^L S^{-1}(y) dy \right) \frac{\partial \Phi(l, t)}{\partial l}. \quad (51)$$

Finally, the current expression (51) indicates that the neck electrical resistance per unit of length is equal to

$$R(l, c_{head}(t)) = \frac{\int_0^L S^{-1}(y) dy}{2\gamma eS(l)D \left(c_0 \int_0^l S^{-1}(y) dy + c_{head}(t) \int_l^L S^{-1}(y) dy \right)}. \quad (52)$$

The overall electrical resistance of the neck R_{neck} is obtained by integrating the resistance per unit of length over the entire neck length

$$R_{neck}(c_{head}(t)) = \int_0^L R(l, c_{head}(t)) dl. \quad (53)$$

3. Simplification of mathematical expressions for constant neck cross-section $S(l) = S = \pi a^2$, for all $0 \leq l \leq L$

For constant cross-section, the expression for the neck resistance per unit of length (52) simplifies to

$$R(l, c_{head}(t)) = \frac{L}{2\gamma eSD(c_0l + c_{head}(t)(L-l))}, \quad (54)$$

leading to total neck resistance

$$R_{neck}(c_{head}(t)) = \frac{L}{2\gamma eSD(c_{head}(t) - c_0)} \log \left(\frac{c_{head}(t)}{c_0} \right), \quad (55)$$

which tends, for constant ion concentration $c_0 \approx c_{head}(t)$ (cable theory hypothesis), to

$$R_{neck}(c_0) = \frac{L}{2\gamma eSDc_0}. \quad (56)$$

Re-injecting the expression for the neck resistance (55) in current expression (51), we obtained that

$$I_{neck}(t) = R_{neck}^{-1}(c_{head}(t)) (\Phi_{head}(t) - \Phi_0(t)).. \quad (57)$$

Here, we considered that dendritic resistance ($\approx 10 - 15 M\Omega$ [8]) was negligible compared to neck resistance, and thus, that dendritic potential was close to resting potential Φ_0 . Note that current is positive when head potential is higher than resting potential. Finally, diffusive outflux (47) reads

$$J_{neck}(t) = \frac{2DS_e}{L} (c_{head}(t) - c_0). \quad (58)$$

C. Kinetics analysis of the electrical potential and ion concentration within the spine head when ion channels open

1. Derivation of slow-fast dynamical system of equations (11-12) in the main text

To derive the coupled system of equations (11-12) in the main manuscript, we considered the dynamics of the number of positive $n^+(t)$ and negative $n^-(t)$ inside the spine head when glutamate receptors are activated and trigger an influx of positive ions inside the spine head with a rate

$$I_{synaptic}(t) = -g^+(t) (\Phi_{head}(t) - \Phi_{reversal}(t)), \quad (59)$$

where $\Phi_{reversal}(c_{head}(t))$ is the reversal potential of AMPA receptors. Considering that potassium and sodium are the main ions transiting through AMPA receptors (*i.e.* neglecting the permeability of AMPA to chloride and calcium ions), Goldman-Hodgkin-Katz equation states that $\Phi_{reversal}(t)$ is given by

$$\Phi_{reversal}(t) = \gamma^{-1} \log \left(\frac{P_K [K^+]_{out} + P_{Na} [Na^+]_{out}}{P_K [K^+]_{in} + P_{Na} [Na^+]_{in}} \right), \quad (60)$$

where P_K and P_{Na} are the receptor permeabilities to potassium and sodium, and $[.]_{out}$ and $[.]_{in}$ are the concentration of ions outside and inside the spine head. Given that AMPA receptors are almost equally permeable to sodium and potassium ions, *i.e.* $P_{Na} \approx P_K$, equation (60) simplifies to

$$\Phi_{reversal}(t) = \gamma^{-1} \log \left(\frac{[K^+]_{out} + [Na^+]_{out}}{[K^+]_{in} + [Na^+]_{in}} \right), \quad (61)$$

that is, as $c_0 = [K^+]_{out} + [Na^+]_{out}$ and $c_{head}(t) = [K^+]_{in} + [Na^+]_{in}$,

$$\Phi_{reversal}(c_{head}(t)) = \gamma^{-1} \log \left(\frac{c_0}{c_{head}(t)} \right) \leq 0. \quad (62)$$

Influx of positive ions through AMPA receptors is counterbalanced by the diffusive outflow $J_{neck}(t)$ (47) through the neck, and half of the neck current $\frac{1}{2}I_{neck}(t)$ (the other half of the current being due to the inward flow of negative ions from dendrite to spine head), leading to the conservation equation

$$e \frac{dn^+(t)}{dt} = I_{synaptic}(t) - \frac{1}{2} (J_{neck}(t) + I_{neck}(t)). \quad (63)$$

On the other hand, the dynamics of number $n^-(t)$ of negative ions inside the spine head results from the net difference between the inwards electrical current and the diffusive outflow towards the dendrite and reads

$$e \frac{dn^-(t)}{dt} = \frac{1}{2} (I_{neck}(t) - J_{neck}(t)). \quad (64)$$

Subtracting equations (63) and (64), and using the capacitor relation (30), we obtain that

$$c_m s_h \frac{d\Phi_{head}(t)}{dt} = I_{synaptic}(t) - I_{neck}(t). \quad (65)$$

The small capacitance of spines precludes large differences between the number of positive and negative ions inside the head $n^+(t) = n^-(t) + O(e^{-1}c_m s_h \Phi_0)$. Thus, the addition of kinetics equations (63) and (64) leads to the following equation for the ion concentration inside the spine head

$$e v_h \frac{dc_{head}(t)}{dt} = \frac{1}{2} (I_{synaptic}(t) - J_{neck}(t)). \quad (66)$$

2. *Derivation steady-state potential and concentration for sustained synaptic input $g^+(t) = g^+$ for all $t \geq 0$*

At steady state, the diffusive outflow of negative charge equilibrates inward current. This corresponds to set $\frac{dn^-(\infty)}{dt} = 0$ in Eq. (64) and leads to steady-state concentration

$$c_{head}(\infty) = c_0 + \frac{LI_{neck}(\infty)}{2SDe}, \quad (67)$$

Moreover, using steady-state concentration in neck resistance expression (55) we obtained the steady state I-V relation

$$\Phi_{head}(\infty) = \Phi_0 + \frac{1}{\gamma} \log \left(1 + \frac{LI_{neck}(\infty)}{2DSc_0e} \right). \quad (68)$$

At steady-state, neck current $I_{neck}(\infty)$ is equal to the synaptic current $I_{synaptic}(\infty) = -g^+ \left(\Phi_{head}(\infty) - \gamma^{-1} \log \left(\frac{c_0}{c_{head}(\infty)} \right) \right)$, which leads to the implicit equation for steady-state intensity

$$I_{neck}(\infty) = -g^+ \left(\Phi_0 + 2\gamma^{-1} \log \left(1 + \frac{LI_{neck}(\infty)}{2DSc_0e} \right) \right). \quad (69)$$

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- [1] D. Gillespie, *A Singular Perturbation Analysis of the Poisson-Nernst-Planck System*, Ph.D. thesis, Ph. D. thesis, Rush University (1999).
 - [2] M. J. Ward and J. B. Keller, *SIAM Journal on Applied Mathematics* **53**, 770 (1993).
 - [3] Z. Schuss, A. Singer, and D. Holman, *Proc Natl Acad Sci U S A* **104**, 16098 (2007).
 - [4] F. Ziebert, M. Z. Bazant, and D. Lacoste, *Phys Rev E Stat Nonlin Soft Matter Phys* **81**, 031912 (2010).
 - [5] J. I. Arellano, R. Benavides-Piccione, J. Defelipe, and R. Yuste, *Front Neurosci* **1**, 131 (2007).
 - [6] I. D. Kosińska, I. Goychuk, M. Kostur, G. Schmid, and P. Hänggi, *Phys Rev E Stat Nonlin Soft Matter Phys* **77**, 031131 (2008).
 - [7] U. Marini Bettolo Marconi, S. Melchionna, and I. Pagonabarraga, *J Chem Phys* **138**, 244107 (2013).
 - [8] M. T. Harnett, J. K. Makara, N. Spruston, W. L. Kath, and J. C. Magee, *Nature* **491**, 599 (2012).