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Supplemental information

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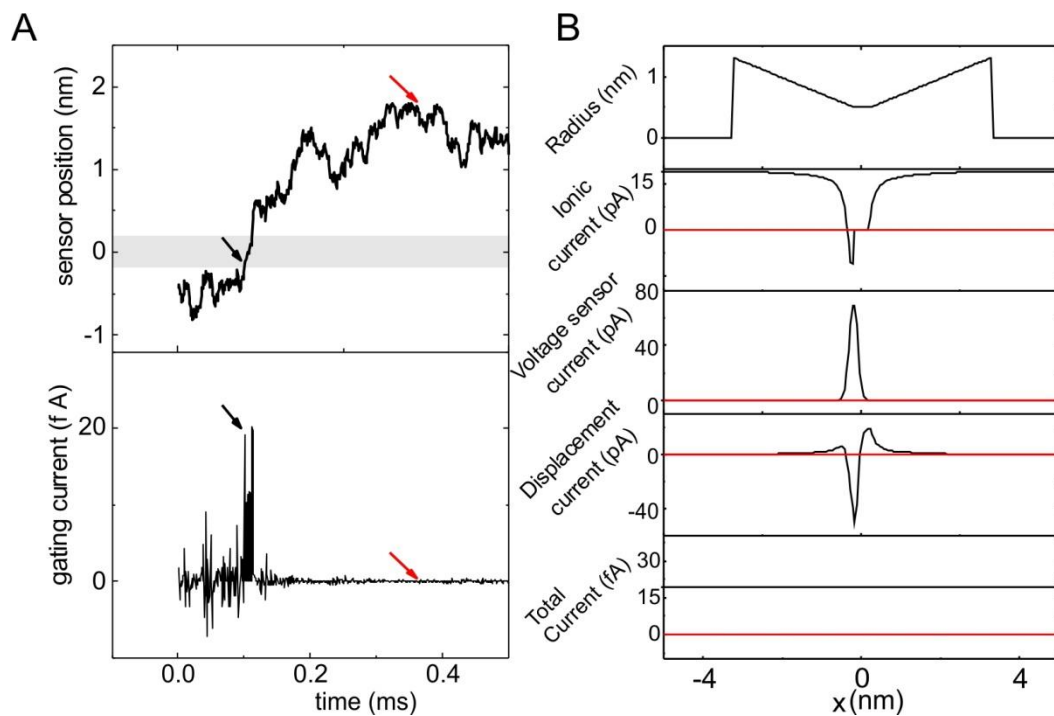
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Supplementary Data



Supplementary Figure 1. Test of the total current conservation in the Simplified model. A) Time dependent position (*top*) and unfiltered gating current (*bottom*) obtained in a simulation with the Simplified model. Friction coefficient and energy profile are the same used in Figure 4A of the main paper. Black and red arrows indicate the points in time chosen to verify the total current conservation. **B)** Spatial profile of (from top to bottom): i) radius of the voltage sensor domain; ii)

the ionic current, assessed as

$$i_{ions}(x, t) = \frac{d}{dt} \int_{x_{pl}}^{x_{pr}} A(x) F \left(\sum_{j=0}^{n_{ions}-1} c_j(x, t) z_j \right) dx = - \frac{d}{dt} \int_{x_{pr}}^x A(x) F \left(\sum_{j=0}^{n_{ions}-1} c_j(x, t) z_j \right)$$

where x_{pl} and x_{pr} are the left and right extremes of the gating pore, F is the Faraday constant,

and z_j is the valence of ion j . iii) the current carried by the voltage sensor, assessed as $i_{S4}(x, t) = \frac{d}{dt} \int_x^L e_0 z_{S4}(x, t) dx = - \frac{d}{dt} \int_0^x e_0 z_{S4}(x, t) dx$, where $z_{S4}(x, t)$ is the charge density profile of the S_4

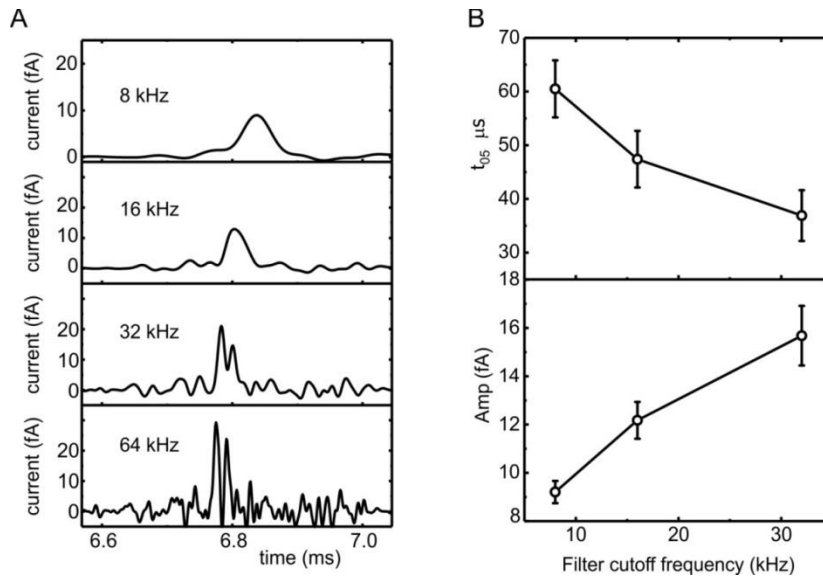
segment; iv) the displacement current, defined as $I_{displ}(x, t) = A(x) \epsilon_0 \epsilon(x) \frac{dE(x, x_4, t)}{dt}$, where

$E(x, x_4, t)$ is the electric field, for which we have explicitly indicated the dependence on the

spatial dimension, time, and position of the voltage sensor x_{S4} , $A(x)$ is the area at position x , ϵ_0 is

the permittivity of free space and $\epsilon(x)$ is the position-dependent dielectric constant; v) total

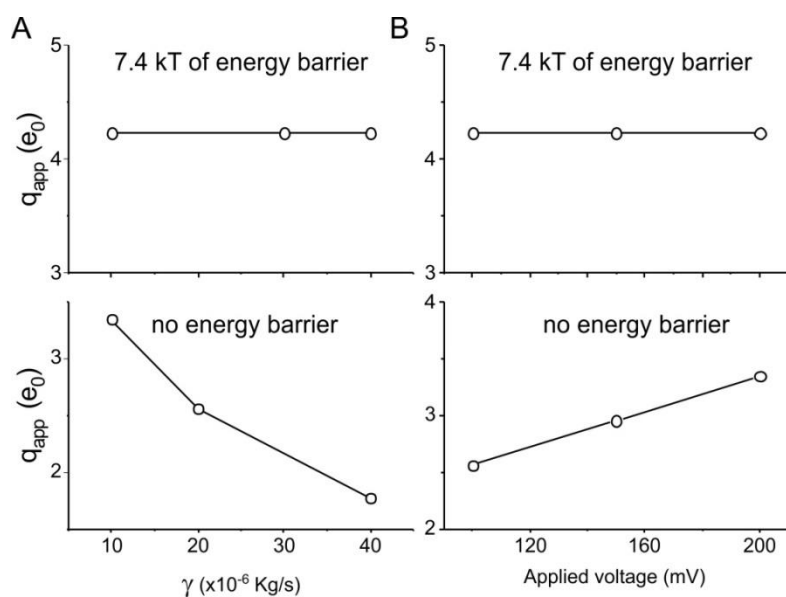
current, defined as $i_{tot}(x, t) = i_{ions}(x, t) + i_{S4}(x, t) + i_{displ}(x, t)$. Red and black lines refer to the profiles assessed at the two time points indicated with the arrows of same colors in panel A. For a more extensive treatment and derivation of the current conservation and of the mathematical forms of the various current see Supplementary material in Catacuzzeno et al., (2019).



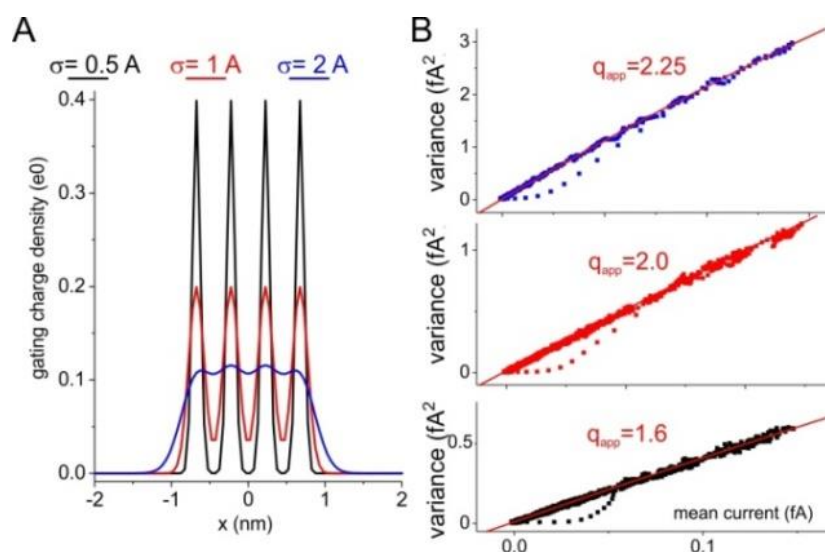
Supplementary Figure 2. Effects of filter cut-off frequency on the shape of the current shot. A)

Current shot simulated with the simplified model, no energy barrier (same parameters of Figure 2C of the main paper), filtered with an 8-pole Bessel filter at varying cut-off frequency (indicated).

B) Plot of the amplitude (Amp) and duration of the current shots at half amplitude ($t_{0.5}$), estimated at different filter frequencies.



Supplementary Figure 3. Differential dependence of the apparent charge on the friction coefficient and applied voltage. Plots of the apparent charge estimated from the Simplified model with (7.4kT, upper plots) and without (lower plots) an energy barrier, at varying friction coefficient (A) and applied potentials (B). The plots clearly show that the apparent charge depends on the two parameters in the no-barrier case, but not in the high barrier case.



Supplementary Figure 4. Dependence of the apparent charge on the spreading of the gating charges. Panel B shows variance-mean current plots obtained from the Simplified model, including four gating charges at an inter-charge distance of 5 Å. In the three simulations the standard deviation of the normal distribution used to distribute the gating charges was varied, as indicated in panel A.

Numerical solution of the PNP system

Discretization of the flux conservative equation

Ions in the baths and vestibules were subjected to electro-diffusion governed by the following flux conservative equation:

$$\frac{dC_j(x,t)}{dt} = -\nabla F_j(x,t) \quad (1)$$

that for our mono-dimensional model may be discretized following Figure S6, obtaining the following eqn.

$$\frac{c_{j,i}^{n+1} - c_{j,i}^n}{\Delta t} = \frac{F_{j,i}^n - F_{j,i+1}^n}{Vol_i} \quad \text{eqn. A1}$$

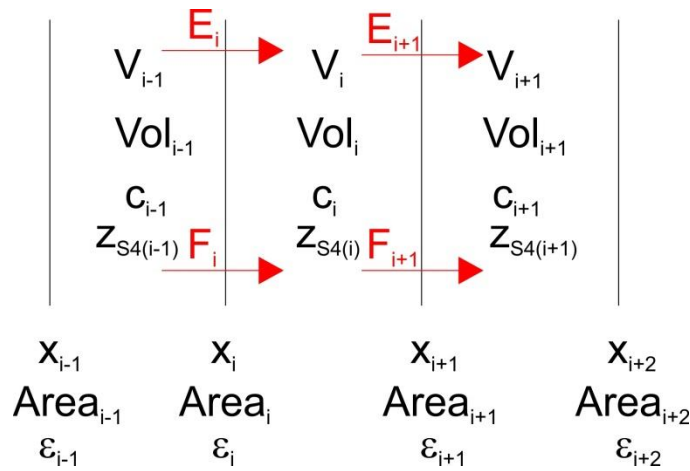
where $c_{j,i}^n$ represent the concentration of ion j in the i^{th} volume element at time n Δt , Δt is the time-step, $F_{j,i}^n$ is the flux (moles per unit time) of ion j from volume element i-1 to volume element i, and Vol_i is the volume of volume element i. The ion flux follows the Nernst –Plank equation:

$$F_j(x,t) = -Area(x)D_j(x) \left[\nabla C_j(x,t) + \frac{z_j F}{RT} \nabla V(x,t) \right] \quad (2)$$

That in our case may be discretized in the following way:

$$F_{j,i}^n = -Area_i D_{j,i} \left[\frac{c_{j,i}^{n+1} - c_{j,i-1}^{n+1}}{(x_{i+1} + x_{i-1})/2} + \frac{z_j F}{RT} \left(\frac{V_i^n - V_{i-1}^{n+1}}{(x_{i+1} + x_{i-1})/2} \right) \right] \quad \text{eqn. A2}$$

Where $Area_i$ is the surface of the left border of the i^{th} volume element, $D_{j,i}$ is the diffusion coefficient of ion j inside the i^{th} volume element, x_i is the position of the left border of volume element i^{th} , z_j is the valence of ion j, F is the Faraday constant, R is the universal gas constant, T is the absolute temperature and V_i^n is the electric potential profile in the i^{th} volume element at time n Δt .



Supplementary Figure 5. Discretization of the spatial domain in our model

Equations A1 and A2 may be combined to give the following equation

$$A_{j,i} c_{j,i-1}^{n+1} + B_{j,i} c_{j,i}^{n+1} + C_{j,i} c_{j,i+1}^{n+1} = R_{j,i} \quad \text{eqn. A3}$$

Where

$$A_{j,i} = A_{i,j}^1 + A_{i,j}^2 (V_i^n - V_{i-1}^n), \text{ with } A_{i,j}^1 = \frac{2 D_{j,i} Area_i \Delta t}{(x_{i+1}-x_{i-1}) Vol_i} \text{ and } A_{i,j}^2 = \frac{z_j F D_{j,i} Area_i \Delta t}{RT (x_{i+1}-x_{i-1}) Vol_i}$$

$$C_{j,i} = C_{i,j}^1 + C_{i,j}^2 (V_{i+1}^n - V_i^n), \text{ with } C_{i,j}^1 = \frac{2 D_{j,i+1} Area_{i+1} \Delta t}{(x_{i+2}-x_i) Vol_i} \text{ and } C_{i,j}^2 = \frac{z_j F D_{j,i+1} Area_{i+1} \Delta t}{RT (x_{i+2}-x_i) Vol_i}$$

$$B_{j,i} = -A_{i,j}^1 + A_{i,j}^2 (V_i^n - V_{i-1}^n) - C_{i,j}^1 + C_{i,j}^2 (V_{i+1}^n - V_i^n) - 1$$

$$\text{and } R_{j,i} = -c_{j,i}^n$$

Equations A3 form a linear system of N-2 equations, with $i=1, \dots, N-1$. They can be coupled with the boundary conditions imposing a constant ion concentration at the left and right boundaries

$$c_{j,0}^{n+1} = C_{j,L} \text{ and } c_{j,N-1}^{n+1} = C_{j,R}$$

to obtain a set of N linear equation for the N unknown $c_{j,0}^{n+1} \dots c_{j,N-1}^{n+1}$ that may be solved with an algorithm for tridiagonal systems as given in Press et al., 1992, thus recovering the ion concentration profiles at each timestep Δt .

Discretization of the Gauss law (Poisson equation)

Gauss law of electrostatics (that represent the integrated form of the Poisson's equation) relates the flux of the electric field out of a closed surface to the net charge existing inside

$$\oint E(x) ds = \frac{q}{\varepsilon(x) \varepsilon_0} \quad \text{eqn. A4}$$

Where \oint is the integration over a closed surface, $E(x)$ is the electric field, q is the charge contained inside the closed surface, ε_0 is the permittivity of free space and $\varepsilon(x)$ is the relative dielectric constant. Applying gauss law to the i^{th} volume element we obtain:

$$\varepsilon_{i+1} Area_{i+1} E_{i+1}^{n+1} - \varepsilon_i Area_i E_i^{n+1} = \frac{q_i^{net}}{\varepsilon_0}$$

Where ε_i is the relative dielectric constant across the left boundary of the volume element, and q_i^{net} is the net charge inside the i^{th} volume element, given by

$$q_i^{net} = F \sum_j c_{j,i} z_j Vol_i + e_0 z_{S4,i}$$

Where e_0 is the elementary charge and $z_{S4,i}$ is the amount of gating charge inside the i^{th} volume element. Considering that

$$E_i^{n+1} = -\frac{V_i^{n+1} - V_{i-1}^{n+1}}{(x_{i+1} + x_{i-1})/2}$$

We obtain the following linear system of equations:

$$A_i V_{i-1}^{n+1} + B_i V_i^{n+1} + C_i V_{i+1}^{n+1} = R_i \quad \text{eqn. A5}$$

Where

$$A_i = -\frac{2 \varepsilon_0 \varepsilon_i \text{Area}_i}{(x_{i+1} - x_{i-1}) \text{Vol}_i}, C_i = -\frac{2 \varepsilon_0 \varepsilon_{i+1} \text{Area}_{i+1}}{(x_{i+2} - x_i) \text{Vol}_i}, B_i = -(A_i + C_i), \text{ and } R_i = \frac{q_i^{net}}{\text{Vol}_i}$$

Equations A5 form a linear system of N-2 equations, with $i=1, \dots, N-1$. They can be coupled with the boundary conditions imposing a known applied potential at the left and right boundaries

$$V_0^{n+1} = V_m \text{ and } V_{N-1}^{n+1} = 0$$

to obtain a set of N linear equation for the N unknown $V_0^{n+1}, \dots, V_{N-1}^{n+1}$ that may be solved with an algorithm for tridiagonal systems as given in Press et al., 199,2 thus recovering the electrostatic potential profile at each timestep Δt .

Steady state solution of the PNP system

In our model we assume that ions relaxes much faster that the voltage sensor. This means that for each given position of the voltage sensor the ion concentration and electrostatic potential profiles assume instantaneously their equilibrium values. In our computations these equilibrium profiles were found by iteratively solving eqn A3 and A5 using a timestep of 0.2 ns, until finding equilibrium, that was defined as the situation in which the maximum relative change in the electrostatic potential within the all spatial profile obtained in the iteration was lower than 10^{-8} .