Supplemental Materials to "Flow-driven cell motility under an external direct electric field"

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PARAMETERS

In Tab.I we provide parameters for the electromotility model (Figs. 2 and 3 in the main text).

PERTURBATION

The predicted cell re-orientation seen in Fig. 2 in the main text can be explained by a perturbative expansion that can be performed for a large class of ion transport models. The calculation below will, however, be performed without the NKCC in favor of algebraic simplicity. Let ϕ be a generic expression for any quantity under consideration, which can be $c_{c,n}$, V_c, or other variables. We can write

$$\phi(x) = \phi^{(0)} + \phi^{(1)}(x)\,, \tag{1}$$

where $\phi^{(0)}$ represents the unpolarized, resting state quantities when $\Delta V = 0$. $\phi^{(0)}$ are the steady state solutions when $v_0 = 0$ and are constant in space. The perturbed part is small: $|\phi^{(1)}| \ll |\phi^{(0)}|$. As an approximation, we assume that the flux from the Na^+/K^+ pump remains the same when the external voltage drop ΔV is applied, i.e., $J^{\mathrm{b/f(1)}}_{\mathrm{Na/K}} = 0$. At the resting state $J^{\mathrm{b/f(0)}}_n = 0$ so that

$$J^{\mathrm{b/f}}_n = J^{\mathrm{b/f(0)}}_n + J^{\mathrm{b/f(1)}}_n = J^{\mathrm{b/f(1)}}_{n,p}\,. \tag{2}$$

We also assume that the passive channels are not tension gated. Hence, the first order Taylor expansion of the fluxes gives

$$J^{\mathrm{b}}_n = -g_n RT c^{\mathrm{b(1)}}_{c,n}/c^{(0)}_{c,n} - g_n z_n F(V^{\mathrm{b(1)}}_c - \Delta V)\,, \tag{3}$$

$$J^{\mathrm{f}}_n = -g_n RT c^{\mathrm{f(1)}}_{c,n}/c^{(0)}_{c,n} - g_n z_n F V^{\mathrm{f(1)}}_c \tag{4}$$

where $g_n = g^{\mathrm{b}}_n = g^{\mathrm{f}}_n$ for an unpolarized cell. From the electroneutrality condition we know that $V^{(1)}_c$, and thus $c^{(1)}_{c,n}$, are linear in x. Therefore, the leading order of the intracellular flux (Eq. 4) becomes

$$\begin{aligned} J_n = &-D_n\big(c^{\mathrm{f(1)}}_{c,n} - c^{\mathrm{b(1)}}_{c,n}\big)/L \\ &- D_n z_n F c^{(0)}_{c,n}\big(V^{\mathrm{f(1)}}_c - V^{\mathrm{b(1)}}_c\big)/RTL - v_0 c^{(0)}_{c,n}\,. \end{aligned} \tag{5}$$

TABLE I. Membrane channel related parameters in the model used in the electromotility model.

Parameters	Description	values
L (μm)	Cell length	35
b (μm)	Cell width	3
w (μm)	Cell depth	10
η (Pa s)	Fluid dynamic viscosity	1×10^{-3}
ξ_w (Pa s/m)	Coefficient of friction of the channel wall	8×10^{8}
D_{Na} (m^2/s)	Diffusion constant of Na^+	1.33×10^{-9}
D_{K} (m^2/s)	Diffusion constant of K^+	1.96×10^{-9}
D_{Cl} (m^2/s)	Diffusion constant of Cl^-	2.03×10^{-9}
D_{A} (m^2/s)	Diffusion constant of A^-	5.0×10^{-10}
N^- (mol)	Total number of the intracellular A^-	1.5×10^{-13}
$c_{0,\mathrm{Na}}$ (mol/m^3)	Extracellular Na^+ concentration	145
$c_{0,\mathrm{K}}$ (mol/m^3)	Extracellular K^+ concentration	5
$c_{0,\mathrm{Cl}}$ (mol/m^3)	Extracellular Cl^- concentration	110
$c_{0,\mathrm{A}}$ (mol/m^3)	Extracellular A^- concentration	40
$\alpha^{\mathrm{b/f}}$ (m/s/Pa)	Water permeability constant	3.0×10^{-11}
$G^{\mathrm{b/f}}_{0,\mathrm{Na}}$ (mol^2/Kg/m^3)	Passive Na channel constant	7.5×10^{-9}
$G^{\mathrm{b/f}}_{0,\mathrm{K}}$ (mol^2/Kg/m^3)	Passive K channel constant	2.5×10^{-7}
$G^{\mathrm{b/f}}_{0,\mathrm{Cl}}$ (mol^2/Kg/m^3)	Passive Cl channel constant	1.25×10^{-7}
$c^{\mathrm{b/f}}_{\mathrm{ATP}}$ (mol/m^3)	ATP concentration in $J_{\mathrm{Na/K}}$	1
$\alpha^{\mathrm{b/f}}_{\mathrm{ATP}}$ (m/s)	Coefficient in $J_{\mathrm{Na/K}}$	1
$\alpha^{\mathrm{b/f}}_{\mathrm{Na/K,Na}}$	Calibration constant in $J_{\mathrm{Na/K}}$	1
$\alpha^{\mathrm{b/f}}_{\mathrm{Na/K,K}}$	Calibration constant in $J_{\mathrm{Na/K}}$	0.1
$\alpha^{\mathrm{b/f}}_{\mathrm{NKCC}}$ ($\mathrm{mol/m}^2$/s)	Coefficient in J_{NKCC}	$5. \times 10^{-9}$
$\beta^{\mathrm{b/f}}_1$	Constant in T_m	1
$\beta^{\mathrm{b/f}}_2$ (N/m)	Constant in T_m	3.0×10^{-4}
$\beta^{\mathrm{b/f}}_3$	Constant in G_V	13
$\beta^{\mathrm{b/f}}_4$ (mV)	Constant in G_V	-150

We then use the relation $J_n|_{x=0} + J_n|_{x=L} = J_n^{\rm b} - J_n^{\rm f}$ and sum over n. Note that $\sum_n z_n c_{c,n}^{(1)} = 0$ and $v_0 = \sum_n \left(c_{c,n}^{{\rm f}(1)} - c_{c,n}^{{\rm b}(1)} \right) / \gamma$. The cell velocity can then be expressed as

$$v_0 = -\frac{F \sum_n (H_n^{-1} g_n z_n)}{\gamma + 2 \sum_n H_n^{-1} c_{c,n}^{(0)}} \Delta V \,, \tag{6}$$

where $H_n = 2D_n/L + g_n RT/c_{c,n}^{(0)}$. The denominator of Eq. 6 is always positive so that the sign of v_0, which is the direction of cell migration, depends on the sign of ΔV and $\sum_n (H_n^{-1} g_n z_n)$. The latter is

$$\sum_n (H_n^{-1} g_n z_n) = \sum_n \frac{L c_{c,n}^{(0)} g_n z_n}{2 D_n c_{c,n}^{(0)} + g_n RTL} \,. \tag{7}$$

Although not expressed explicitly, Eq. 7 depends on the active pump through its role in setting the stationary concentrations $c_{c,n}^{(0)}$. To gain a physical understanding of Eq. 7, we may consider a cell with membrane impermeable to anions. In this case, Eq. 7 can only be positive and the cell moves in the direction of higher voltage. Indeed, impermeability to anions makes the cell an enclosure of negative ions being pulled toward locations of higher voltage. We also see from Eq. 7 that the velocity decreases with greater diffusion coefficient because a high diffusion coefficient leads to nearly equal concentrations on the two ends, reducing the discrepancy in osmotic pressure at the two ends of the cell.

In a typical cell, $c_{c,{\rm K}}$ and $G_{0,{\rm K}}^{\rm b/f}$ are much higher than those of other ions. Thus, Eq. 7 is dominated by the K^+ contribution so that v_0 is negative for a positive ΔV, indicating a backward cell migration [Fig. 2(a-d)]. If $G_{0,{\rm Cl}}^{\rm b/f}$ increases to a sufficiently high value, however, Eq. 7 will become negative since $z_{\rm Cl}$ is negative. This explains the reversal cell migration predicted in Fig. 2(e-h).

Figure 1 compares the analytical solution (Eq. 6 in the Supplemental Materials) with the numerical solution in the main text. The cell velocity v_0 is plotted against the unpolarized channel constant of Cl^-, $G_{0,{\rm Cl}}$. To obtain the unperturbed solution $c_{c,n}^{(0)}$, the numerical solution is sought when $\Delta V = 0$. As shown in the figure, the two solutions agree well, both showing the reversed direction of cell migration as $G_{0,{\rm Cl}}$ increases.

POLARIZATION

Here we examine a simple model of how cells can develop polarized membrane channels/pumps in a 1-D cell. These proteins can diffuse in the membrane due to concentration

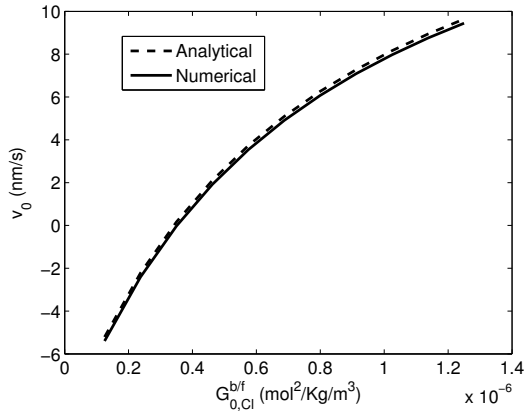

FIG. 1. Comparison of the analytical solution (Eq. 6 in the Supplemental Materials) with the numerical solution in the main text. The cell velocity v_0 is plotted against the unpolarized channel constant of Cl^-. $\Delta V = 2$ mV. To make a fair comparison, tension gating of passive channels and the NKCC are removed in the numerical solution. The transport rate of the Na/K pump is also reduced by a factor of 500.

gradients. The fluidity of the lipid membrane contributes protein transport in the membrane (convection). At the same time there is vesicle trafficking in the cytoplasm (mainly from microtubule motors). Therefore membrane proteins can be transported from the back to the front (see Fig. 2 for an illustration). Denote $\varrho_p(x)$ as the 2D density of proteins in the cell membrane. We assume that $\varrho_p(x)$ is continuous and smooth. The dynamics of membrane proteins can be described as

$$\frac{\partial \varrho_p}{\partial t} = \frac{\partial}{\partial x}\left(D_p \frac{\partial \varrho_p}{\partial x} - v_{\rm lip}\varrho_p \right) , \tag{8}$$

where D_p is the diffusion constant of the proteins in the membrane and $v_{\rm lip}$ is the velocity of the membrane lipid (assumed constant). For steady-state solution, the flux

$$J = -D_p \frac{d\varrho_p}{dx} + v_{\rm lip}\varrho_p \tag{9}$$

must be a constant in x. Here we have used the same notation J for flux of the proteins. This is different from the flux of ions in the main text. The fluxes of the proteins at the two end of the cell through the vesicles are (see Fig. 2)

$$J^{\rm b} = v_p^{\rm b}\varrho_p^{\rm f} - v_p^{\rm f}\varrho_p^{\rm b} , \tag{10}$$

$$J^{\rm f} = v_p^{\rm f}\varrho_p^{\rm b} - v_p^{\rm b}\varrho_p^{\rm f}\,, \tag{11}$$

where $v_p^{\rm b/f}$ is the backward/forward transport velocity of the vesicles that carry proteins. These fluxes determine the boundary condition of Eq. 9, i.e., $J = J^{\rm b} = -J^{\rm f}$. Since J is a constant, the membrane protein density, ϱ_p, can be solved from Eq. 9 as

$$\varrho_p = c_1 e^{v_{\rm lip}x/D_p} + \frac{J}{v_{\rm lip}}\,, \tag{12}$$

where c_1 is a constant to be determined. Define $\varrho_p^{\rm b} = \varrho_p|_{x=0}$ and $\varrho_p^{\rm f} = \varrho_p|_{x=L}$, from Eq. 12 we then have

$$\varrho_p^{\rm f} - \varrho_p^{\rm b} = c_1\left(e^{v_{\rm lip}L/D_p} - 1\right)\,. \tag{13}$$

This equation solves c_1 as $c_1 = \theta_1(\varrho_p^{\rm f} - \varrho_p^{\rm b})$, where $\theta_1 = 1/(e^{v_{\rm lip}L/D_p} - 1)$. By substituting the expression of c_1 and using $J = J^{\rm b}$, Eq. 12 yields

$$\varrho_p^{\rm b} = \theta_1(\varrho_p^{\rm f} - \varrho_p^{\rm b}) + \frac{v_p^{\rm b}\varrho_p^{\rm f} - v_p^{\rm f}\varrho_p^{\rm b}}{v_{\rm lip}}\,. \tag{14}$$

Rearrangement of Eq. 14 gives the ratio of polarization of the proteins at the two ends of the cell:

$$\frac{\varrho_p^{\rm f}}{\varrho_p^{\rm b}} = \theta_2 = \frac{1 + \theta_1 + v_p^{\rm f}/v_{\rm lip}}{\theta_1 + v_p^{\rm b}/v_{\rm lip}}\,. \tag{15}$$

A polarized channel/pump distribution ($\varrho_p^{\rm f}/\varrho_p^{\rm b} \neq 1$) requires $v_{\rm lip} + v_p^{\rm f} \neq v_p^{\rm b}$. The values of $\varrho_p^{\rm b/f}$ can be solved from the known total number of a specific protein, N_p, in the membrane,

$$C\int_0^L \varrho_p(x)dx = N_p\,, \tag{16}$$

where $C = 2(b + w)$ is the circumference of the cross section. It is easy to find

$$\varrho_p^{\rm b} = \frac{N_p v_{\rm lip}}{C}\left[D_p(\theta_2 - 1) + \left(v_p^{\rm b}\theta_2 - v_p^{\rm f}\right)L\right]^{-1}\,. \tag{17}$$

We can perform some simple numerical estimates of parameters. Membrane protein diffusion constant is on the order of $D_p \sim$ 1-10 μm^2/s, and $L = 20 - 100$ μm. Microtubule motors, on the other hand, transports vesicles with velocity of ~ 1 μm/s. The rate of arrival of lipid vesicle is around 1/s. Therefore, for a vesicle of 2μm in diameter and a cell cross sectional size of 6μm$\times$6μm, $v_{\rm lip} \sim 0.2\mu$m/s. Each vesicle also contains potentially many proteins, therefore $v_p^{\rm f} \gg v_{\rm lip}$ and $v_p^{\rm b} \sim 0$. Therefore, depending on the values of $v_p^{\rm f,b}$, nearly any polarization ratio is possible.

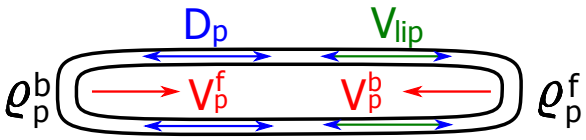

FIG. 2. (Color online) Schematics of the dynamics of membrane proteins. $\varrho_p^{\mathrm{b/f}}$ is the areal density of membrane proteins at the back/front end of the cell. These proteins diffuses in the membrane (with diffusion coefficient D_p), are carried between the two ends of the cell within the cytoplasm through vesicles (with the backward/forward transport velocity $v_p^{\mathrm{b/f}}$), and are transported within the plasma membrane due to the fluidity of the lipid membrane (with the lipid velocity v_{lip}).

OSMOTIC CONDITIONS

The current model also predicts the cell migration under different osmotic conditions, as a model with electro-neutral ion does [1]. Figure 3 compares the model prediction with the experimental data by Stroka *et al.* (Fig. 3 in Ref. [1]). As the properties of ion channels vary with cell types, a different set of parameters were used in this case (see Tab. II). The flux through each channel in this case is in the order of 10^{-14} mol/μm^2/s. The relatively higher ion fluxes compared to the electromotility model is due to the higher extracellular osmotic pressure difference across the cell, which imposes higher chemical potential difference across the membrane.

[1] K. M. Stroka, H. Jiang, S.-H. Chen, Z. Tong, D. Wirtz, S. X. Sun, and K. Konstantopoulos. *Cell*, 157:611–623, 2014.

TABLE II. Membrane channel related parameters used in the osmotic shock model.

Parameters	Description	values
N^- (mol)	Total number of the intracellular A^-	1.3×10^{-13}
$c_{0,\mathrm{Na}}$ (mol/m^3)	Extracellular Na^+ concentration	155
$c_{0,\mathrm{K}}$ (mol/m^3)	Extracellular K^+ concentration	5
$c_{0,\mathrm{Cl}}$ (mol/m^3)	Extracellular Cl^- concentration	120
$c_{0,\mathrm{A}}$ (mol/m^3)	Extracellular A^- concentration	60
$\alpha^{\mathrm{b/f}}$ (m/s/Pa)	Water permeability constant	3.0×10^{-13}
$G^{\mathrm{b/f}}_{0,\mathrm{Na}}$ (mol^2/Kg/m^3)	Passive Na channel constant	1.5×10^{-7}
$G^{\mathrm{b/f}}_{0,\mathrm{K}}$ (mol^2/Kg/m^3)	Passive K channel constant	5.0×10^{-6}
$G^{\mathrm{b/f}}_{0,\mathrm{Cl}}$ (mol^2/Kg/m^3)	Passive Cl channel constant	5.0×10^{-5}
$c^{\mathrm{b/f}}_{\mathrm{ATP}}$ (mol/m^3)	ATP concentration in $J_{\mathrm{Na/K}}$	1
$\alpha^{\mathrm{b/f}}_{\mathrm{ATP}}$ (m/s)	Coefficient in $J_{\mathrm{Na/K}}$	1
$\alpha^{\mathrm{b/f}}_{\mathrm{Na/K,Na}}$	Calibration constant in $J_{\mathrm{Na/K}}$	1
$\alpha^{\mathrm{b/f}}_{\mathrm{Na/K,K}}$	Calibration constant in $J_{\mathrm{Na/K}}$	0.1
$\alpha^{\mathrm{b/f}}_{\mathrm{NKCC}}$ (mol/m^2/s)	Coefficient in J_{NKCC}	$5. \times 10^{-4}$
$\beta^{\mathrm{b/f}}_1$	Constant in T_m	10
$\beta^{\mathrm{b/f}}_2$ (N/m)	Constant in T_m	3.0×10^{-4}
$\beta^{\mathrm{b/f}}_3$	Constant in G_V	13
$\beta^{\mathrm{b/f}}_4$ (mV)	Constant in G_V	-150

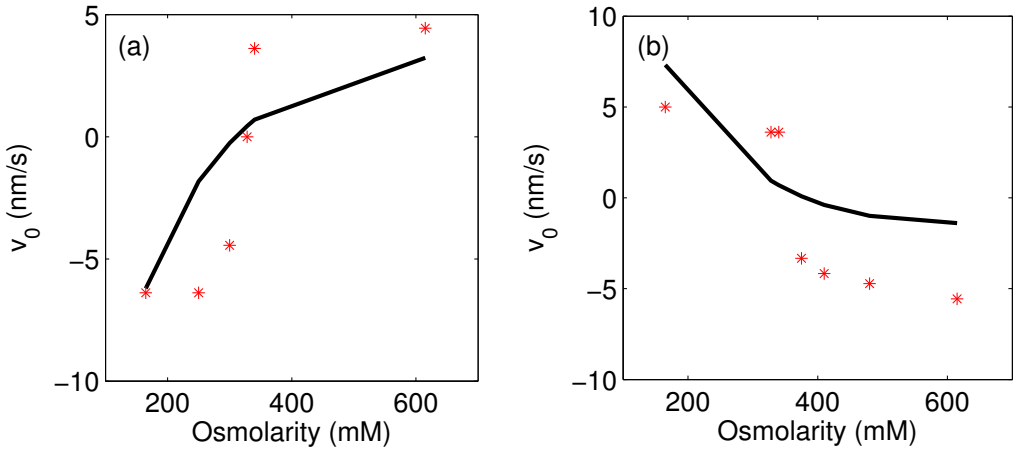

FIG. 3. (Color online).Comparison between the theoretical model (solid lines) and the experimental data (red stars, Fig. 3 in Ref. [1]). (a) Cell velocity under osmotic shocks at the front end. (b) Cell velocity under osmotic shocks at the back end.