SI Appendix — Pump it up: bioelectric stimulation controls tissue hydrostatic pressure and water transport via electro-inflation

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Continuum one-dimensional (1D) model. Here we derive a minimal 1D continuum model to recapitulate our experimental observations of cyst inflation. In particular, we consider that inflation stems from hydrostatic and osmotic pressure differences across the cyst's epithelium. As a first approximation, we consider that the medium in which the cyst is embedded is a 1:1 electrolyte solution, with cations of valence $z_+ = |z| > 0$ and anions of valence $z_- = -|z| < 0$ (e.g., NaCl), and further assume that the variations of the electric potential with respect to an externally applied far-field electric potential ϕ_{sys} are small, i.e. $\phi \ll \phi_{\text{sys}}$.

A relevant quantity in electrokinetic phenomena is the Debye–Hückel (DH) length, which measures the thickness of a surface charge layer and a screening cloud of ions at such surface immersed in an electrolyte solution, usually referred to as diffuse double layer (DDL) or electrical double layer (EDL). The first layer corresponds to the surface charge, either positive or negative, and the second layer corresponds to ions attracted to the surface via Coulomb force, which electrically screen the first layer. Considering the estimates of parameter values in **Table S1**, we find that the DH length is $\ell_{\text{DH}} = \sqrt{\varepsilon\phi_{\text{c}}/(c_{\text{c}}|z|e)} \sim 10 - 20$ nm, where e is the elementary charge, ε is the permittivity of the medium, and c_{c} and ϕ_{c} are a characteristic ion concentration and electrostatic potential, respectively, which we take to be the background ion concentration of the electrolyte, $c_{\text{c}} = c^0_{\text{out}}$, and the applied voltage $\phi_{\text{c}} = \phi_{\text{sys}}$. Thus, such length is significantly smaller than the average radius of cysts in our experiments, $\ell_{\text{DH}} \ll R_{\text{init}}$, implying that a very thin double diffusive layer of positive and negative ions is formed at the basal surface of the cyst. We further assume that this layer is at quasi equilibrium, which allows us to obtain the electric potential from Poisson's equation and consider that the concentration of ions is Boltzmann distributed, i.e., $c_{\text{i,out}} = c^0_{\text{out}} \exp[-z_{\text{i}} e(\phi - \phi_{\text{sys}})/(k_{\text{B}}T)]$. Here the subscript $\text{i} = (\pm, -)$ denotes positive or negative ions. We have also considered that the background concentration of the electrolyte c^0_{out} is constant and is the same for all ion species at $\boldsymbol{r} \gg \ell_{\text{DH}}$, where we assume that the medium is neutral ($\boldsymbol{r}$ denotes the positional vector). Assuming that the fluid inside the cyst is incompressible and $\phi \ll \phi_{\text{sys}}$, mass conservation equation and the linearized Poisson-Boltzmann equations read:

Lumen volume conservation:

$$\boldsymbol{\nabla}\cdot(\boldsymbol{v} - j_{\text{flux}}) = 0, \quad \text{at } 0 \le r \le R$$
$$\text{with: } j_{\text{flux}} = \lambda_{\text{w}}(\Delta\Pi - \Delta p), \quad \text{at } r = R, \tag{S1a}$$

$$\text{Cell volume conservation: } \partial_t \left(h \int_S \mathrm{d}SR \right) = 0, \tag{S1b}$$

Poisson-Boltzmann eq. in the DDL:

$$\ell^2_{\text{DH}} \boldsymbol{\nabla}^2(\phi - \phi_{\text{sys}}) = \phi - \phi_{\text{sys}}, \quad \text{at } R \le r \le \ell_{\text{DH}}, \tag{S1c}$$

Ion conservation in the lumen:

$$\int_V \mathrm{d}V\, \partial_t c_{\text{i,in}} = -\int_S \mathrm{d}S j_{\text{flux}} c_{\text{i,in}} + \int_S \mathrm{d}S j_{\text{active}}$$
$$- \int_S \mathrm{d}S \lambda_{\text{ion}} \Big[c_{\text{i,in}} - c_{\text{i,out}}|_{r=R(t)} +$$
$$\frac{z_{\text{i}} e^2 R (c_{\text{i,in}} + c_{\text{i,out}})}{12 k_{\text{B}} T C} \sum_{\text{i}} z_{\text{i}} \left(c_{\text{i,in}} - c_{\text{i,out}}|_{r=R(t)} \right) \Big], \tag{S1d}$$

where $R(\theta, \phi, t)$ and $h(\theta, \phi, t)$ denote the average radius and thickness of the cyst, respectively, $\boldsymbol{v} = (v_r, v_\theta, v_\phi)$ is the fluid velocity inside the cyst, ϕ is the electric potential in the medium where the cyst is embedded, and $\Delta\Pi$ and Δp are the osmotic and hydrostatic pressure differences across the epithelium, respectively. Here, λ_{w} and λ_{ion} are the water and ion permeability coefficients across the epithelium (assumed to be the same for cations and anions), respectively, and C is the capacitance of the epithelium. Moreover, R_{f} denotes a far-field system radius where a constant electric potential ϕ_{sys} is imposed. Equation (S1b) assumes that the displacement along the thickness of the epithelium is uniform, and that cell proliferation is negligible during cyst swelling.

Equation (S1a) has to be complemented with the momentum conservation equation at the bulk and cyst surface to determine the pressure p and velocity $\boldsymbol{v}$ inside the lumen, and with a kinematic condition relating the local velocity in the lumen with the cyst surface, i.e. $(\partial_t \boldsymbol{r}_{\text{surf}} - \boldsymbol{v}_{\text{surf}}) \cdot \boldsymbol{n} = 0$, where $\boldsymbol{n}$ is the unit normal vector to the surface, $\boldsymbol{r}_{\text{surf}}$ its parametrization, and $\boldsymbol{v}_{\text{surf}}$ its velocity.

The osmotic pressure difference is given by the total ion concentration difference between the basal and apical surface, and the hydrostatic pressure difference is determined by the

Physical parameters	Definition	Range of values
λ_{w}	Water permeability constant	$10^{-9} - 10^{-7}$ μm Pa^{-1} s^{-1} [1–3]
λ_{ion}	Ion permeability constant	$10^{-4} - 1.7 \times 10^{-1}$ μm s^{-1} [2–4]
j_{active}	Active flux density	10^{5}-10^{6} μm^{-2} s^{-1} [2, 5, 6]
q	Basal surface charge density	$1.1 \times 10^{-2} - 1.4 \times 10^{-2}$ C m^{-2} [7, 8]
C	Capacitance of the Epithelium	10^{-2} pF μm^{-2} [9]
E_{cyst}	Epithelial Young's modulus	$5 - 30$ kPa [10, 11]
μ_{cyst}	Epithelial viscosity	$10^{5} - 10^{6}$ Pa s [12, 13]
R_{init}	Initial radius of the cyst	$25 - 50$ μm
h_{init}	Initial thickness of the cyst	$5 - 10$ μm
Δp_{init}	Initial hydrostatic pressure	$20 - 300$ Pa [2, 3, 14, 15]
z	Valence	$\pm$ 1 (NaCl)
E_{gel}	Young's Modulus of Geltrex	30 ± 2 kPa
$c^0_{\mathrm{i,out}}$	Outer background ion concentration	100 mM
$c^0_{\mathrm{i,in}}$	Lumen initial ion concentration	100 mM
ϕ_{sys}	Far-field electric potential	1.1, 4.5, 6.5 V
ε	Permittivity of the outer medium	7×10^{-10} F m^{-1} $= 74.5\epsilon_0$
r_{sys}	System size	3 cm
ℓ_{DH}	Debye-Hückel length (external field)	9, 18, 21.7 nm
$\ell^{\mathrm{control}}_{\mathrm{DH}}$	Debye-Hückel length (control)	1 nm
Characteristic scales		
$l_{\mathrm{c}} = R_{\mathrm{init}}$	Length	$25 - 50$ μm
$t_{\mathrm{c}} = \dfrac{R_{\mathrm{init}}}{\lambda_{\mathrm{w}} k_{\mathrm{B}} T c^0_{\mathrm{i,out}}}$	Time	$0.3 - 56$ h
$c_{\mathrm{c}} = c^0_{\mathrm{out}}$	Ion concentration	100 mM
$\phi_{\mathrm{c}} = \phi_{\mathrm{sys}}$	Electric potential	1.1, 4.5, 6.5 V
Dimensionless parameters		
$\tilde{R}_{\mathrm{init}} = \dfrac{R_{\mathrm{init}}}{\ell_{\mathrm{DH}}}$	$\dfrac{\text{Initial size of the cyst}}{\text{Debye-Hückel length}}$	$10^{3} - 5.5 \times 10^{3}$
$Q_{\mathrm{i}} = \dfrac{q \ell_{\mathrm{DH}} z_{\mathrm{i}} e}{\varepsilon k_{\mathrm{B}} T}$	$\dfrac{\text{Electric potential across the DB layer}}{\text{Thermal energy}}$	5.5, 11, 13.3
$\alpha = \dfrac{c^0_{\mathrm{in}}}{c^0_{\mathrm{out}}}$	$\dfrac{\text{Initial ion concentration in the cyst}}{\text{Outer background concentration}}$	1
$\Lambda = \dfrac{\lambda_{\mathrm{ion}}}{\lambda_{\mathrm{w}} k_{\mathrm{B}} T c^0_{\mathrm{in}}}$	$\dfrac{\text{Ion permeability}}{\text{Water permeability}}$	$4 \times 10^{-5} - 69$
$\beta = \dfrac{e^2 R_{\mathrm{init}} c^0_{\mathrm{out}}}{k_{\mathrm{B}} T C}$	Transepithelial potential strength	10^{6}
$\mathcal{E}_{\mathrm{gel}} = \dfrac{E_{\mathrm{gel}}}{\Delta p_{\mathrm{init}}}$	$\dfrac{\text{Gel stiffness}}{\text{Hydrostatic pressure}}$	$15 - 300$
$\mathcal{E}_{\mathrm{cyst}} = \dfrac{h_{\mathrm{init}} E_{\mathrm{cyst}}}{R_{\mathrm{init}} \Delta p_{\mathrm{init}}}$	$\dfrac{\text{Epithelium stiffness}}{\text{Hydrostatic pressure}}$	0.25-480
$\tilde{\tau} = \dfrac{\tau}{\lambda_{\mathrm{w}} k_{\mathrm{B}} T c^0_{\mathrm{out}}}$	$\dfrac{\text{Viscous relaxation time scale}}{\text{Chracteristic osmotic time scale}}$	$1.7 \times 10^{-4} - 1.9$
$\mathcal{P} = \dfrac{\Delta p_{\mathrm{init}}}{k_{\mathrm{B}} T c^0_{\mathrm{out}}}$	$\dfrac{\text{Hydrostatic pressure}}{\text{Osmotic pressure}}$	$10^{-4} - 10^{-2}$
$\tilde{j}_{\mathrm{active}} = \dfrac{j_{\mathrm{active}}}{\lambda_{\mathrm{w}} k_{\mathrm{B}} T c^0_{\mathrm{out}} c^0_{\mathrm{in}}}$	$\dfrac{\text{Active ion flux}}{\text{Osmotic water flux}}$	$6.7 \times 10^{-2} - 6.7$

Table S1. Estimates and experimental measurements of the physical and dimensionless parameters of MDCK cysts used in the 1D model.

normal stress balance at the epithelium:

Osmotic pressure difference:

$$\Delta\Pi = k_{\mathrm{B}} T \sum_i \left(c_{\mathrm{i,in}} - c_{\mathrm{i,out}}\right), \quad \text{at } r = R, \tag{S2a}$$

Hydrostatic pressure difference:

$$-\Delta p\, \boldsymbol{n} + \boldsymbol{\tau} \cdot \boldsymbol{n} = -\sigma h (\boldsymbol{\nabla} \cdot \boldsymbol{n}) \boldsymbol{n} \quad \text{at } r = R, \tag{S2b}$$

where $\boldsymbol{\tau}$ is the viscous stress tensor of the fluid in the lumen, and σ denotes the wall stress of the epithelium, which we consider to be spatially uniform. Since swelling inflation is a slow process and the electrolyte is small, we assume viscous stresses are small, i.e., $\boldsymbol{\tau} \ll 1$ and disregard them [2]. We build upon previous work [14, 16, 17] and first assume that the cyst wall stress satisfies a purely elastic constitutive equation:

$$\partial_t \sigma = \frac{E_{\mathrm{cyst}}}{R} \partial_t R, \tag{S3}$$

where E_{cyst} is the Young's modulus of the epithelium.

Regarding boundary conditions for the electric potential ϕ, we impose:

$$-\boldsymbol{n}\cdot\boldsymbol{\nabla}\phi = \frac{q}{\varepsilon}, \quad \text{at } r = R, \tag{S4a}$$

$$\boldsymbol{e}_r\cdot\boldsymbol{\nabla}\phi = 0, \quad \text{at } \boldsymbol{r} \gg \ell_{\text{DH}}, \tag{S4b}$$

where q is the charge surface density at the basal domain, assumed to be spatially uniform. Finally, as initial condition we impose that the cyst is perfectly spherical, i.e. $R(\theta,\phi,t=0) = R_{\text{init}}$.

To reduce the number of parameters of our model, we non-dimensionalize the system of equations by scaling all variables with the following choice of characteristic scales:

$$\begin{aligned}
&\tilde{\boldsymbol{r}} = \frac{\boldsymbol{r}}{R_{\text{init}}}, \quad \tilde{\boldsymbol{v}} = \frac{\boldsymbol{v}}{\lambda_{\text{w}} k_{\text{B}} T c^0_{\text{out}}},\\
&\tilde{t} = \frac{t}{R_{\text{init}}/(\lambda_{\text{w}} k_{\text{B}} T c^0_{\text{out}})}, \quad \tilde{c}_{\text{i,in}} = \frac{c_{\text{i,in}}}{c^0_{\text{in}}},\\
&\tilde{c}_{\text{i,out}} = \frac{c_{\text{i,out}}}{c^0_{\text{out}}}, \quad \tilde{\phi} = \frac{\phi}{k_{\text{B}}T/(|z|e)},\\
&\Delta\tilde{p} = \frac{\Delta p}{\Delta p_{\text{init}}}, \quad \tilde{h} = \frac{h}{h_{\text{init}}}.
\end{aligned} \tag{S5}$$

where tildes denote dimensionless variables, and c^0_{in} is the initial concentration of ions in the lumen, considered to be the same for cations and anions.

To elucidate the mechanisms underlying cyst inflation, we consider that the cyst maintains a perfectly spherical shape over time, i.e. $\tilde{r} = \tilde{R}(\tilde{t})$, and thus $\tilde{\boldsymbol{v}} = \tilde{v}_r(\tilde{r})\boldsymbol{e}_r$, where $\boldsymbol{e}_r$ is the radial unitary vector, $\tilde{\phi} = \tilde{\phi}(\tilde{r})$, and $\tilde{c}_{\text{i,out}} = \tilde{c}_{\text{i,out}}(\tilde{r})$. We first solve the 1D dimensionless version of the electric potential [Eq. (S1c)], with boundary conditions Eq. (S4), which yields

$$\tilde{\phi}_{\text{out}}(\tilde{r}) = \tilde{\phi}_{\text{sys}} + \frac{Q_{\text{i}}\tilde{R}^2\tilde{R}_{\text{init}}\exp\left[(\tilde{R}-\tilde{r})\tilde{R}_{\text{init}}\right]}{\tilde{r}(1+\tilde{R}\tilde{R}_{\text{init}})}, \tag{S6}$$

where:

$$\begin{aligned}
&\tilde{R}_{\text{init}} \equiv \frac{R_{\text{init}}}{\ell_{\text{DH}}} : \frac{\text{Initial cyst radius}}{\text{Debye-Hückel length}},\\
&\tilde{\phi}_{\text{sys}} \equiv \frac{\phi_{\text{sys}}|z|e}{k_{\text{B}}T} : \frac{\text{Applied electric potential}}{\text{Thermal energy}},\\
&Q_{\text{i}} \equiv \frac{q\ell_{\text{DH}}z_{\text{i}}e}{\varepsilon k_{\text{B}}T} : \frac{\text{Electric potential across the DB layer}}{\text{Thermal energy}}.
\end{aligned} \tag{S7}$$

We can then obtain the dimensionless concentrations of ions outside the cyst as $\tilde{c}_{\text{i,out}} = \exp\left[-(\tilde{\phi}_{\text{out}} - \tilde{\phi}_{\text{sys}})\right]$. In particular, the concentration of ions at the cyst surface reads:

$$\tilde{c}_{\text{i,out}}(\tilde{r}=\tilde{R}) = \exp\left[-\frac{Q_{\text{i}}\tilde{R}\tilde{R}_{\text{init}}}{1+\tilde{R}\tilde{R}_{\text{init}}}\right]. \tag{S8}$$

Solving Eq. (S1) and employing the boundary conditions Eq. (S9d) yields the following dimensionless system of equations:

$$\text{Cell volume conservation}: \frac{\mathrm{d}\tilde{h}}{\mathrm{d}\tilde{t}} = -\frac{2\tilde{h}}{\tilde{R}}\frac{\mathrm{d}\tilde{R}}{\mathrm{d}\tilde{t}}, \tag{S9a}$$

Lumen volume conservation :

$$\frac{\mathrm{d}\tilde{R}}{\mathrm{d}\tilde{t}} = \tilde{j}_{\text{flux}} = \left[\sum_{\text{i}}\left(\alpha\tilde{c}_{\text{i,in}} - \tilde{c}_{\text{i,out}}|_{\tilde{r}=\tilde{R}}\right) - \mathcal{P}\Delta\tilde{p}\right], \tag{S9b}$$

Ion species conservation :

$$\begin{aligned}
\frac{\tilde{R}}{3}\frac{\mathrm{d}\tilde{c}_{\text{i,in}}}{\mathrm{d}\tilde{t}} = &-\tilde{j}_{\text{flux}}\tilde{c}_{\text{i,in}} + \tilde{j}_{\text{active}} - \Lambda\left[\alpha\tilde{c}_{\text{i,in}} - \tilde{c}_{\text{i,out}} + \right.\\
&\left.\beta\frac{\tilde{R}(\alpha\tilde{c}_{\text{i,in}} + \tilde{c}_{\text{i,out}})}{12}\sum_{\text{i}}\left(\tilde{c}_{\text{i,in}} - \tilde{c}_{\text{i,out}}|_{\tilde{r}=\tilde{R}}\right)\right],
\end{aligned} \tag{S9c}$$

Epithelium elastic constitutive equation :

$$\frac{\mathrm{d}\Delta\tilde{p}}{\mathrm{d}\tilde{t}} = \frac{1}{\tilde{R}}\frac{\mathrm{d}\tilde{R}}{\mathrm{d}\tilde{t}}\left(\mathcal{E}_{\text{cyst}}\frac{2\tilde{h}}{\tilde{R}} - 3\Delta\tilde{p} + \mathcal{E}_{\text{gel}}\right), \tag{S9d}$$

with $\tilde{R}(\tilde{t}=0) = \tilde{c}_{\text{i,in}}(0) = \Delta\tilde{p}(0) = \tilde{h}(0) = 1$ as initial conditions, where:

$$\begin{aligned}
&\alpha \equiv \frac{c^0_{\text{in}}}{c^0_{\text{out}}} : \frac{\text{Initial lumen ion concentration}}{\text{Initial outer ion concentration}}\\
&\mathcal{P} \equiv \frac{\Delta P_{\text{init}}}{k_{\text{B}}Tc^0_{\text{out}}} : \frac{\text{Hydrostatic pressure}}{\text{Osmotic pressure}},\\
&\Lambda \equiv \frac{\lambda_{\text{ion}}}{\lambda_{\text{w}}k_{\text{B}}Tc^0_{\text{in}}} : \frac{\text{Ion permeability}}{\text{Water permeability}},\\
&\beta \equiv \frac{e^2R_{\text{init}}c^0_{\text{out}}}{k_{\text{B}}TC} : \text{Transepithelial potential strength},\\
&\mathcal{E}_{\text{cyst}} \equiv \frac{h_{\text{init}}E_{\text{cyst}}}{R_{\text{init}}\Delta p_{\text{init}}} : \frac{\text{Epithelium elasticity}}{\text{Initial hydrostatic pressure}},\\
&\mathcal{E}_{\text{gel}} \equiv \frac{E_{\text{gel}}}{\Delta p_{\text{init}}} : \frac{\text{Gel stiffness}}{\text{Hydrostatic pressure}},\\
&\tilde{j}_{\text{active}} \equiv \frac{j_{\text{active}}}{\lambda_{\text{w}}k_{\text{B}}Tc^0_{\text{out}}c^0_{\text{in}}} : \frac{\text{Active ion flux}}{\text{Osmotic water flux}}.
\end{aligned} \tag{S10}$$

The system of nonlinear first-order ordinary differential equations [Eqs. (S9a)-(S9d)] does not admit an analytical solution, thus we solve it numerically by standard methods.

Viscoelastic model. To test whether cyst material properties play a significant role on inflation dynamics, we modify the purely elastic constitutive equation [Eq. (S3)], and consider two of the simplest viscoelastic models, i.e.,

$$\text{Maxwell model}: \partial_t\sigma + \frac{\sigma}{\tau} = \frac{E_{\text{cyst}}}{R}\partial_t R, \tag{S11}$$

where τ is a viscous relaxation time scale stemming from $\tau = \mu_{\text{cyst}}/E_{\text{cyst}}$, where μ_{cyst} is the viscosity of the epithelium [12, 13], and

$$\text{Kelvin-Voigt model}: \sigma = E_{\text{cyst}}\left(\frac{R}{R_{\text{init}}} + \frac{\tau}{R}\partial_t R\right). \tag{S12}$$

The following rheological stress-strain relationships introduce an additional dimensionless parameter, $\tilde{\tau} = \tau/[R_{\text{init}}/(\lambda_{\text{w}} k_{\text{B}} T c^0_{\text{out}})]$, i.e., the ratio between the viscous relaxation time and the osmotic characteristic time scale (see **Table S1**).

Values of the dimensionless parameters used in the 1D simulations. To compare the experimental inflation curves with our theoretical model in Fig. 3 of the Main Text, we use the following values of the dimensionless parameters: $\tilde{R}_{\text{init}} = 10^3$ (and $\tilde{R}_{\text{init}} = 10^4$ for the control case), $Q_{\text{i}} = 4.3$, 4.75 ($Q_{\text{i}} = 0.5$ for the control case), $\alpha = 1$, $\Lambda = 0.4$, $\tilde{R}_{\text{in}} = 10^3$, $\mathcal{P} = 10^{-4}$, $\mathcal{E}_{\text{gel}} = 300$, $\mathcal{E}_{\text{cyst}} = 80$, $\beta = 10^6$, $\tilde{j}_{\text{active}} = 1.5$. These values of the dimensionless parameters correspond to the following values of the dimensional parameters: $\lambda_{\text{w}} = 10^{-9}$ μm Pa^{-1} s^{-1}, $\lambda_{\text{ion}} = 10^{-4}$ μm s^{-1}, $q = 1.1 \times 10^{-2}$ C m^{-2}, $C = 10^{-2}$ pF μm^{-2}, $E_{\text{cyst}} = 20$ kPa, $R_{\text{init}} = 50$ μm, $h_{\text{init}} = 5$ μm, $\Delta p_{\text{init}} = 25$ Pa, $E_{\text{gel}} = 30$ kPa, $c^0_{\text{i,in}} = c^0_{\text{i,out}} = 100$ mM, $\phi_{\text{sys}} = 1.1 - 6.5$ V, and $\epsilon = 7 \times 10^{-10}$ F m^{-1}. In particular, we use the active flux of ions to match the control inflation curve, which yields $j_{\text{active}} = 2.2 \times 10^4$ μm^{-2} s^{-1}. This values is one order of magnitude below the range of estimates and measurements in **Table S1**, while the remaining parameters agree well with the range of values. Using these values of the parameters, the characteristic scales are: $t_{\text{c}} = 56$ h, $l_{\text{c}} = 50$ μm, $c_{\text{c}} = 100$ mM, and $\phi_{\text{c}} = 1.1 - 6.5$ V.

To match the experimental curves when ion transport is inhibited (Fig. 3d of the Main Text), we use $\Lambda = 0.15$, which yields $\lambda_{\text{ion}} = 3.7 \times 10^{-5}$ μm s^{-1}.

Moreover, if a Maxwell material is considered, we always use $\tilde{\tau} = 2$, which is the upper limit value reported in **Table S1**, and $\Delta p_{\text{init}} = 50$ Pa. Finally, to capture the longer time relaxation dynamics of cysts, for simplicity we do not consider the coupling with electrokinetcs to capture inflation. Instead, we impose a constant osmotic pressure difference $\Delta\Pi$ over time (see Fig. 3 of the Main Text). Consequently, the agreement between experiments and theory during inflation is worse. Nonetheless, this choice simplifies the numerical calculation to test whether cysts relax in an elastic or a viscoelastic fashion. In particular, at the same time when stimulation is turned off in experiments, we decrease the osmotic pressure drastically, which could be a consequence of ion rearrangement or fluid leakage. Even though the osmotic pressure is still positive, it cannot overcome the high value of the normal stress induced by hydrostatic pressure. Inflation induces a large wall stress, thus imparting a large normal stress that drives cyst shrinkage.

Strengths and limitations of our theoretical 1D model. Given the inherent complexities of experiments and the simplifications made in our 1D theoretical model, can we still make quantitative predictions of cyst swelling? Our 1D model couples the mechanics of a thin elastic membrane (the epithelium), that is permeable to ions and water, with electrokinetics arising from an externally applied electric field. The model is able to capture the inflation dynamics exhibited by cysts in experiments, using reasonable values of the model parameters. Moreover, it also captures the inflation trends observed when ion transport an cytoskeletal inhibitors are used in experiments.

Nevertheless, our 1D model has limitations and cannot capture all experimental findings. For example, we find that, to match the experimental inflation curves, we have to impose a smaller value of the dimensionless parameter that quantifies the field strength, i.e., Q, than our estimate in **Table S1**. Similarly, to match the inflation dynamics of the control experiment, the value of the ion active flux j_{active} is smaller than our estimates in **Table S1**. Also, our 1D model cannot capture well the inflation curves of the experiment with cytoskeletal inhibitor by decreasing the Young's modulus.

Where do these discrepancies come from? Even though our model takes into account many of the complexities present in experiments, it disregards many others. For example, we neglect variations along the surface of the cyst. This approximation precludes us to predict any kind of asymmetry, as found in experiments. We also approximate the epithelium as a thin permeable purely elastic layer, and consider that the elastic modulus is uniform and decoupled from the osmotic fluxes and active ion fluxes. In particular, such simplifications may explain the discrepancies between theory and experiments found with cytoskeletal inhibitors.

Estimation of shear forces induced by electro-osmotic flow. To test whether the asymmetric deformation exhibited by MDCK acini is caused by shear forces induce by electro-osmotic flow, we first obtain the electro-osmotic slip velocity around a sphere. To this end, we consider volume and momentum conservation of the electro-osmotic flow assuming that inertia is negligible

$$\boldsymbol{\nabla} \cdot \boldsymbol{u} = 0, \tag{S13a}$$

$$\mu \boldsymbol{\nabla} \boldsymbol{u}^2 - \boldsymbol{\nabla} p = e(c_+ - c_-) \boldsymbol{\nabla} \phi, \tag{S13b}$$

where μ is the shear viscosity of the electrolyte, and $\boldsymbol{u}$ is the fluid velocity field. From Eq. (S13b) we can estimate the electro-osmotic velocity, i.e. $u_{\text{c}} \sim e c_0 \phi_{\text{sys}} R_{\text{init}}/\mu$, or equivalently, $u_{\text{c}} \sim \varepsilon E_0^2 R_{\text{init}}/\mu$. Considering $E_0 \sim 200$ V m^{-1}, $u_{\text{c}} \sim 1.7$ μm s^{-1}. Such velocity yields a Reynolds number of $Re \sim 0.02$, so we can safely neglect inertia.

We obtain an analytical solution for the electro-osmotic slip velocity. For the case of a sphere, the radial and azimuthal components of such velocity field read:

$$u_r = \frac{9 \varepsilon E_0^2 R_{\text{init}}^3 (R_{\text{init}}^2 - r^2)(1 + 3\cos 2\theta)}{16 \mu r^4}, \tag{S14a}$$

$$u_\theta = \frac{9 R_{\text{init}}^5 \varepsilon E_0^2 \sin 2\theta}{8 \mu r^2}. \tag{S14b}$$

The tangential component of the viscous shear stress is given

Physical parameters	Definition	Range of values
ε	Permittivity of the medium	7×10^{-10} F m^{-1} $= 74.5\epsilon_0$
D	Ion diffusivity in the outer medium	10^{-11}-10^{-9} m^2 s^{-1} [18]
D_{cyt}	Ion diffusivity in the cytoplasm	10^{-11}-10^{-9} m^2 s^{-1}
λ_{basal}	Basal surface ion permeability	$10^{-4} - 10^{-1}$ s^{-1} [3]
ζ	Basal surface zeta potential	-20 mV [8]
ΔV	Applied voltage difference	1-9 V
R_{init}	Cyst radius	25-50 μm
h_{init}	Epithelium thickness	$5 - 15$ μm
Dimensionless parameters		
$\tilde{\zeta} \equiv \frac{\zeta}{\Delta V}$	$\frac{\text{Basal surface zeta potential}}{\text{Applied voltage}}$	$2 \times 10^{-3} - 2 \times 10^{-2}$
$\Phi_0 \equiv \frac{\Delta V}{k_{\text{B}}T/e}$	$\frac{\text{Applied voltage}}{\text{Elementary charge voltage}}$	$39 - 350$
$\Lambda \equiv \frac{\lambda_{\text{basal}}}{D/R_{\text{init}}^2}$	$\frac{\text{Basal surface ion permeability}}{\text{Ion diffusivity}}$	3×10^{-3}
$\mathcal{D} \equiv \frac{D_{\text{cyt}}}{D}$	$\frac{\text{Cytoplasm ion diffusivity}}{\text{Outer medium ion diffusivity}}$	0.01-100

Table S2. Estimates and experimental measurements of the physical and dimensionless parameters used in the 2D model.

by

$$\boldsymbol{e}_\theta \cdot \boldsymbol{\tau} \cdot \boldsymbol{e}_r = \tau_{r\theta} = \mu\left(\partial_r v_\theta - \frac{v_\theta}{r} + \frac{1}{r}\partial_\theta v_r\right) = \frac{9\varepsilon E_0^2 R_{\text{init}}^3 (3r^2 - 8R_{\text{init}}^2)\sin 2\theta}{8r^5}. \tag{S15}$$

Hence, the shear stress associated with the flow right above the DDL is

$$\tau_{r\theta}|_{r=R_{\text{init}}} = \frac{45\varepsilon E_0^2}{8}\sin 2\theta. \tag{S16}$$

Using the estimate of the far-field electric field, i.e., $E_0 \sim 200$ V m^{-1}, yields a maximum shear stress of $\max(\tau_{r\theta}|_{r=R_{\text{init}}}) \sim 2 \times 10^{-4}$ Pa, or 2×10^{-3} dynes cm^{-2}. Such shear stress is too small to induce any significant deformation to the epithelium and significantly lower than shear forces reported to affect MDCK epithelial tissues [19]. Nonetheless, this shear stress needs to be corrected to account for the shear stress exerted by the electro-osmotic flow at the basal surface in the DDL. At the basal surface, the velocity is zero due to the no-slip condition, thus the velocity increases from $u = 0$ to $u_{\text{c}} \sim ec_0\phi_{\text{sys}}R_{\text{init}}/\mu$ outside the DDL. Although the increase in velocity is small, the thickness of the DDL is just a few nanometers, yielding a shear stress of $\tau_{\text{DDL}} \sim \mu u_{\text{c}}/\ell_{\text{DH}} \sim 0.1 - 1$ Pa, corresponding to $\ell_{\text{DH}} \sim 1 - 10$ nm, which is also too small to cause any deformation to the epithelium.

Continuum Two-dimensional (2D) Model for Electrolyte Transport. To describe the dynamics of an electrolyte solution surrounding a spherical cyst subject to an external electric field, we consider a two-dimensional axisymmetric continuum model that takes into account: the electrostatic field outside the cyst, $\phi(\boldsymbol{r}, t)$, which obeys the Poisson's equation, and the conservation of positive, $c_+(\boldsymbol{r}, t)$, and negative, $c_-(\boldsymbol{r}, t)$, ion species.

$$\text{Electric potential}: \ \boldsymbol{\nabla}^2\phi = -\frac{(c_+ - c_-)e}{\varepsilon}, \tag{S17a}$$

$$\text{Ion species conservation}: \ \partial_t c_\pm + \boldsymbol{\nabla}\cdot(c_\pm \boldsymbol{v}_\pm) = 0, \tag{S17b}$$

where $\boldsymbol{r}$ and t denote the positional vector field and time, respectively, and $\boldsymbol{v}_\pm$ is the velocity of the ion species, i.e. $\boldsymbol{v}_\pm = \mp be\boldsymbol{\nabla}\phi - k_{\text{B}}Tb\boldsymbol{\nabla}\ln c_\pm$. The first term accounts for electrostatic forcing of ions, and the second term represents diffusion of ions, where $b = D/(k_{\text{B}}T)$ is the mobility of ions and D the diffusivity in the outer medium. Regarding the boundary conditions for the electrostatic potential and the local density of species, we impose no-flux conditions at every solid boundary for the ion densities, and $\phi = \phi_{\text{sys}}$ at $z = 0$, $\phi = 0$ at $z = z_{\text{sys}}$, $\boldsymbol{e}_r \cdot \boldsymbol{\nabla}\phi = 0$ at $r = 0$, r_{end}, and $\phi = \zeta$ at the cyst basal surface, where ζ is the zeta potential.

To account for transport of ions across the basal surface, we impose the following boundary condition

$$(\pm be\boldsymbol{\nabla}\phi - D\boldsymbol{\nabla}c_\pm)\cdot\boldsymbol{n} = -\lambda_\pm^{\text{basal}}(c_\pm - c_\pm^{\text{cyt}}), \tag{S18}$$

at the basal domain, where $\lambda_\pm^{\text{basal}}$ is the ion permeability constant of the basal surface and $c_\pm^{\text{cyt}}(\boldsymbol{r}, t)$ denotes the local density of ions within the epithelial cells, which satisfies a standard diffusion equation,

$$\partial_t c_\pm^{\text{cyt}} = D_{\text{cyt}}\boldsymbol{\nabla}^2 c_\pm^{\text{cyt}}, \tag{S19}$$

where D_{cyt} is the diffusivity of ions in the cells' cytoplasm. At the basal surface, we impose flux continuity:

$$-D_{\text{cyt}}\boldsymbol{\nabla}c_\pm^{\text{cyt}}\cdot\boldsymbol{n} = \lambda_\pm^{\text{basal}}(c_\pm - c_\pm^{\text{cyt}}). \tag{S20}$$

To perform full time-dependent numerical simulations, we non-dimensionalize Eqs. (S21)-(S20) by choosing $\ell_c = R_{\text{init}}$, $t_c = k_B T R_{\text{init}}^2/(De\Delta V)$, $\phi_c = \Delta V$, $c_c = c_{\text{init}}$ as characteristic length, time, electric potential, and ion concentration scales, respectively. The dimensionless version of Eqs. (S21)-(S20) read,

$$\text{Electric potential}: \boldsymbol{\nabla}^2\tilde{\phi} = -\tilde{R}_{\text{init}}^2(\tilde{c}_+ - \tilde{c}_-) \tag{S21a}$$

$$\text{Ion species conservation}:$$

$$\partial_{\tilde{t}}\tilde{c}_\pm = \Phi_0^{-1}\boldsymbol{\nabla}^2\tilde{c}_\pm + \boldsymbol{\nabla}\cdot(\tilde{c}_\pm\boldsymbol{\nabla}\tilde{\phi}), \tag{S21b}$$

$$\text{Cytoplasm ion diffusion}: \partial_{\tilde{t}}\tilde{c}_\pm^{\text{cyt}} = \mathcal{D}\boldsymbol{\nabla}^2\tilde{c}_\pm^{\text{cyt}}, \tag{S21c}$$

with the following boundary conditions for the dimensionless electric potential $\tilde{\phi}$ and ion concentration $\tilde{c}_\pm$ at the basal surface:

$$\text{Basal zeta potential}: \tilde{\phi} = \tilde{\zeta}, \tag{S22a}$$

$$\text{Basal ion permeation}: -\boldsymbol{\nabla}\tilde{c}_\pm^{\text{cyt}}\cdot\boldsymbol{n} = \Lambda(\tilde{c}_\pm - \tilde{c}_\pm^{\text{cyt}}). \tag{S22b}$$

The dimensionless parameters that emerge in Eqs. (S21)-(S20) are:

$$\begin{aligned}
\tilde{\zeta} &\equiv \frac{\zeta}{\Delta V} : \frac{\text{Basal surface zeta potential}}{\text{Applied voltage}},\\
\Phi_0 &\equiv \frac{\Delta V}{k_B T/e} : \frac{\text{Applied voltage}}{\text{Elementary charge voltage}},\\
\Lambda &\equiv \frac{\lambda_{\text{basal}}}{D/R_{\text{init}}^2} : \frac{\text{Basal surface ion permeability}}{\text{Ion diffusivity}},\\
\mathcal{D} &\equiv \frac{D_{\text{cyt}}}{D} : \frac{\text{Cytoplasm ion diffusivity}}{\text{Outer medium ion diffusivity}}.
\end{aligned} \tag{S23}$$

2D numerical simulations. We perform full time-dependent numerical simulations using the finite-element method, which involves writing the equations in weak form by means of the integral scalar product using test functions $\tilde{\varphi}_\phi$ and $\tilde{\varphi}_c$ for the electric potential $\phi(\tilde{\boldsymbol{r}},\tilde{t})$ and ion concentration $\tilde{c}_\pm(\tilde{\boldsymbol{r}},\tilde{t})$ fields, respectively. Using Green identities, we obtain an integral bilinear system of equations for the variables and their test functions:

$$\begin{aligned}
&-\int_{\mathcal{V}} \mathrm{d}\mathcal{V}\,\boldsymbol{\nabla}\tilde{\phi}\cdot\boldsymbol{\nabla}\tilde{\varphi}_\phi + \int_{\mathcal{V}} \mathrm{d}\mathcal{V}\,\tilde{R}_{\text{init}}^2(\tilde{c}_+ - \tilde{c}_-)\,\tilde{\varphi}_\phi\\
&- \mathrm{d}\mathcal{C}\,\boldsymbol{\nabla}\tilde{\phi}\cdot\boldsymbol{n}\,\tilde{\varphi}_c = 0,
\end{aligned} \tag{S24a}$$

$$\begin{aligned}
&\int_{\mathcal{V}} \mathrm{d}\mathcal{V}\,\partial_{\tilde{t}}\tilde{c}_\pm\,\tilde{\varphi}_c + \int_{\mathcal{V}} \mathrm{d}\mathcal{V}\,(\Phi_0^{-1}\boldsymbol{\nabla}\tilde{c}_\pm + \tilde{c}_\pm\boldsymbol{\nabla}\tilde{\phi})\cdot\boldsymbol{\nabla}\tilde{\varphi}_c\\
&- \int_{\mathcal{C}} \mathrm{d}\mathcal{C}(\Phi_0^{-1}\boldsymbol{\nabla}\tilde{c}_\pm + \tilde{c}_\pm\boldsymbol{\nabla}\tilde{\phi})\cdot\boldsymbol{n}\,\tilde{\varphi}_c = 0.
\end{aligned} \tag{S24b}$$

$$\begin{aligned}
&\int_{\mathcal{V}} \mathrm{d}\mathcal{V}\,\partial_{\tilde{t}}\tilde{c}_\pm^{\text{cyt}}\,\tilde{\varphi}_c + \int_{\mathcal{V}} \mathrm{d}\mathcal{V}\,\mathcal{D}\boldsymbol{\nabla}\tilde{c}_\pm^{\text{cyt}}\cdot\boldsymbol{\nabla}\tilde{\varphi}_c\\
&- \int_{\mathcal{C}} \mathrm{d}\mathcal{C}\mathcal{D}\boldsymbol{\nabla}\tilde{c}_\pm^{\text{cyt}}\cdot\boldsymbol{n}\,\tilde{\varphi}_c = 0.
\end{aligned} \tag{S24c}$$

Here, $\boldsymbol{n}$ is the outer unit normal of the boundaries $\mathcal{C}$ of the 2D domain $\mathcal{V}$, and $\mathrm{d}\mathcal{V}$ and $\mathrm{d}\mathcal{C}$ are the surface and line elements, respectively. To ensure numerical stability, the equations are discretized in space using second-order Lagrange polynomials and triangular elements for the fields, and evolved in time through a 4th-order variable-step backward differentiation formula method. The relative tolerance of the nonlinear method is always set below 10^{-6}.

Values of the dimensionless parameters used in the 2D simulations. To obtain Fig. 4c of the Main Text, we used the following values of the dimensionless parameters: $\tilde{\zeta} = 4.4\times10^{-3}$, $\Phi_0 = 174$, $\Lambda = 3\times10^{-3}$, and $\mathcal{D} = 1$, which correspond to $R_{\text{init}} = 38$ μm, $h_{\text{init}} = 15$ μm, $\Delta V = 4.5$ V, $\zeta = -20$ mV, and $D = D_{\text{cyt}} = 10^{-10}$ m^2 s^{-1}. Such values are within the ranges of parameter estimates reported in **Table S2**.

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