Supporting Information

A Model of ${\rm Ca}^{2+}$ Dynamics in an Accurate Reconstruction of Parotid Acinar Cells

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1 Equations of the model

Here we present the secretion model applied to five acinar cells. We compute the primary fluid flow rate and their corresponding ionic concentrations. For an in-depth explanation of the results in cell 7 and 4, please refer to the two main papers Pages et al. (2018); Sigüenza et al. (2018). For information related to the construction of the individual cells from experimental data, please refer to the appendix of Pages et al. (2018).

The subscripts, e, i, and l denote, respectively, the interstitial, intracellular, and luminal compartments. S_b represents the surface area of the basolateral plasma membrane: $\partial \Omega_b$ (PM). The apical PM surface area is denoted: $\partial \Omega_a$. C_m and F are the PM capacitance and Faraday's constant, respectively. These can be found in section 2.11, along with other the parameters of the system. The PM fluxes, denoted by jand J, are represented by a mathematical sub-models.

$$\omega_l \frac{d[\mathrm{Na}^+]_l}{dt} = J_{Na}^t - J_{\mathrm{out}}^w [\mathrm{Na}^+]_l, \tag{1}$$

$$\omega_l \frac{d[\mathbf{K}^+]_l}{dt} = J_K^t - J_{\text{out}}^w [\mathbf{K}^+]_l, \tag{2}$$

$$\omega_l \frac{d[\mathrm{Cl}^-]_l}{dt} = \int_{\partial\Omega_a} j_{\mathrm{Cl}} \, dS - J^w_{\mathrm{out}}[\mathrm{Cl}^-]_l,\tag{3}$$

$$\frac{d\omega_i}{dt} = J_b^w - J_a^w,\tag{4}$$

$$\frac{d\left([\mathrm{Na}^+]_i\omega_i\right)}{dt} = S_b\left(J_{\mathrm{Nkcc1}} - 3J_{\mathrm{NaK}} + J_{\mathrm{Nhe1}} - J_{\mathrm{Ae4}}\right),\tag{5}$$

$$\frac{d\left([\mathrm{K}^{+}]_{i}\omega_{i}\right)}{dt} = S_{b}\left(J_{\mathrm{Nkcc1}} + 2J_{\mathrm{NaK}}\right) - \int_{\partial\Omega_{b}} j_{\mathrm{K}} \, dS,\tag{6}$$

$$\frac{d\left([\mathrm{Cl}^{-}]_{i}\omega_{i}\right)}{dt} = S_{b}\left(2J_{\mathrm{Nkcc1}} + J_{\mathrm{Ae4}}\right) - \int_{\partial\Omega_{a}} j_{\mathrm{Cl}} \, dS,\tag{7}$$

$$\frac{d\left([\text{HCO}_3^-]_i\omega_i\right)}{dt} = \omega_i J_{\text{Buffer}} - S_b 2 J_{\text{Ae4}},\tag{8}$$

$$\frac{d\left([\mathrm{H}^+]_i\omega_i\right)}{dt} = \omega_i J_{\mathrm{Buffer}} - S_b J_{\mathrm{Nhe1}},\tag{9}$$

$$\frac{\partial [\operatorname{Ca}^{2+}]_{i}}{\partial t} = D_{c} \nabla^{2} [\operatorname{Ca}^{2+}]_{i} \qquad \dots \qquad (10)$$

$$+ \frac{\omega_{i_{0}}}{\omega_{i_{0}}} \left(J_{\operatorname{Way}}([\operatorname{Ca}^{2+}]_{ER} - [\operatorname{Ca}^{2+}]_{i}) - J_{SERCA} \right) - \frac{d\omega_{i}}{\omega_{i_{0}}} \frac{[\operatorname{Ca}^{2+}]_{i}}{\omega_{i_{0}}}.$$

$$\frac{\partial [\operatorname{Ca}^{2+}]_{ER}}{\partial t} = D_c \nabla^2 [\operatorname{Ca}^{2+}]_{ER} \qquad \dots \qquad (11)$$

$$-\frac{1}{\gamma(\omega_i)}\Big(J_{\mathrm{Wav}}([\mathrm{Ca}^{2+}]_{ER}-[\mathrm{Ca}^{2+}]_i)-J_{SERCA}\Big),$$

$$\frac{\partial [\mathrm{IP}_3]_i}{\partial t} = D_p \nabla^2 [\mathrm{IP}_3]_i + \frac{\omega_{i_0}}{\omega_i} \left(V_{PLC} - V_{deg} \right) - \frac{d\omega_i}{dt} \frac{[\mathrm{IP}_3]_i}{\omega_i},\tag{12}$$

$$\frac{dg}{dt} = (g_{\infty} - g)/\tau, \tag{13}$$

$$\frac{\partial [\operatorname{Ca}^{2+}]_i}{\partial n} = J_{IPR}([\operatorname{Ca}^{2+}]_{ER} - [\operatorname{Ca}^{2+}]_i)$$
(14)

$$\frac{\partial [\mathrm{Ca}^{2+}]_{ER}}{\partial n} = \frac{1}{\gamma(\omega_i)} - J_{IPR}([\mathrm{Ca}^{2+}]_{ER} - [\mathrm{Ca}^{2+}]_i),$$
(15)

$$\frac{dh}{dt} = \frac{1}{\tau([\mathrm{Ca}^{2+}]_i)} (h_\infty - h),$$
(16)

$$\left(\frac{C_m}{F}\right)\frac{dV_a}{dt} = \int_{\partial\Omega_a} j_{\rm Cl} \, dS - \left(J_{\rm K}^t + J_{\rm Na}^t\right),\tag{17}$$

$$\left(\frac{C_m}{F}\right)\frac{dV_b}{dt} = -\int_{\partial\Omega_b} j_{\rm K} \, dS - S_b J_{\rm NaK} + \left(J_{\rm K}^t + J_{\rm Na}^t\right),\tag{18}$$

2 Fluxes of the Model

2.1 NaK-ATPase

$$j_{\text{NaK}} = \alpha_{\text{NaK}} \left(r \frac{[\text{K}^+]_e^2 [\text{Na}^+]_i^3}{[\text{K}^+]_e^2 + \alpha [\text{Na}^+]_i^3} \right).$$
(19)

Parameter	Description	Value	Units
$lpha_{ m NaK}$	Membrane surface density NaK-ATPase rate	1.6 0.0016	$\frac{\text{amol } / \ \mu \text{m}^2}{\text{mM}^{-3} \text{ s}^{-1}}$

2.2 Nkcc1 Cotransporter

$$j_{\rm Nkcc1} = \alpha_{\rm Nkcc1} \left(\frac{a_1 - a_2 [\rm Na^+]_i [\rm K^+]_i [\rm Cl^-]_i^2}{a_3 + a_4 [\rm Na^+]_i [\rm K^+]_i [\rm Cl^-]_i^2} \right),$$
(20)

Parameter	Description	Value	Units
$\overline{a_1}$	Nkcc1 rate	157.55	s^{-1}
a_2	Nkcc1 rate	2.009×10^{-5}	$\mathrm{mM^{-4}~s^{-2}}$
a_3	Nkcc1 rate	1.0306	s^{-1}
a_4	Nkcc1 rate	1.38×10^{-6}	$\mathrm{mM}^{-4} \mathrm{s}^{-2}$
$\alpha_{\rm Nkcc1}$	Surface density	2.15	$amol/\mu m^2$

2.3 Nhe1 Antiporter

$$j_{\rm Nhe1} = G_{\rm Nhe1} \left[\left(\frac{[{\rm H}^+]_i}{[{\rm H}^+]_i + K_{\rm H}} \right)^2 \left(\frac{[{\rm Na}^+]_e}{[{\rm Na}^+]_e + K_{\rm Na}} \right) - \left(\frac{[{\rm Na}^+]_i}{[{\rm Na}^+]_i + K_{\rm Na}} \right) \left(\frac{[{\rm H}^+]_e}{[{\rm H}^+]_e + K_{\rm H}} \right)^2 \right].$$
(21)

Parameter	Description	Value	Units
K _H	Half half maximal H ⁺ concentration	4.5×10^{-4}	mM
K_{Na}	Half half maximal Na ⁺ concentration	15	mM
$G_{\rm Nhe1}$	Surface density	0.9	$\mathrm{amol}/\mathrm{\mu m}^2$

2.4 Ae4 Exchanger

$$j_{Ae4} = G_{Ae4} \left(k_+ [\text{Cl}^-]_e [\text{HCO}_3^-]_i^2 [\text{Na}^+]_i - k_- [\text{Cl}^-]_i [\text{HCO}_3^-]_e^2 [\text{Na}^+]_e \right),$$
(22)

Parameter	Description	Value	Units
$\overline{k_+}$	Rate	1.9×10^{-2}	$\mathrm{mM}^{-4} \mathrm{s}^{-1}$
k_{-}	Rate	1.3×10^{-5}	$\mathrm{mM}^{-4}~\mathrm{s}^{-1}$
$G_{\rm Ae4}$	Surface density	1.3	$\mathrm{amol}/\mathrm{\mu m}^2$

2.5 Bicarbonate Buffer

$$J_{\text{Buffer}} = k_1 [\text{CO}_2]_i - k_{-1} [\text{H}^+]_i [\text{HCO}_3^-]_i.$$
(23)

Parameter	Description	Value	Units
$\overline{k_n}$	HCO_3^- Buffer Dissociation rate	0.132	s^{-1}
k_p	HCO_3^- Buffer Association rate	312	s^{-1}

2.6 Tight Junctional Cation Fluxes

$$J_{c}^{t} = \frac{G_{c}^{t}}{Fz^{c}} (V_{a} - V_{b} - V_{c}^{t}), \qquad (24)$$

where,

 $V_c^t = \frac{RT}{F} \ln\left(\frac{[c]_l}{[c]_e}\right).$

Here $c = Na^+$ or K^+ .

Parameter	Description	Value	Units
$\overline{G_{\mathrm{Na}}^t}$	Conductance	0.2	nS
G_{K}^{t}	Conductance	0.16	nS
z^{Na}	Na^+ valence	+1	-
z^K	${\rm K}^+$ valence	+1	-

2.7 Water Fluxes

$$J_a^w = P_a \left(\sum [c]_l + \Psi_l - \sum [c]_i - \frac{x_i}{\omega_i} \right), \tag{25}$$

$$J_b^w = P_b \left(\sum [c]_i + \frac{x_i}{\omega_i} - \sum [c]_e \right), \tag{26}$$

$$J_t^w = P_t \left(\sum [c]_l + \Psi_l - \sum [c]_e \right).$$
(27)

Where,

$$\sum [c]_e = [\mathrm{K}^+]_e + [\mathrm{Na}^+]_e + [\mathrm{Cl}^-]_e + [\mathrm{HCO}_3^-]_e + [\mathrm{H}^+]_e + [\mathrm{CO}_2]_e,$$

$$\sum [c]_i = [\mathrm{K}^+]_i + [\mathrm{Na}^+]_i + [\mathrm{Cl}^-]_i + [\mathrm{HCO}_3^-]_i + [\mathrm{H}^+]_i + [\mathrm{CO}_2]_i,$$

$$\sum [c]_l = [\mathrm{K}^+]_l + [\mathrm{Na}^+]_l + [\mathrm{Cl}^-]_l + [\mathrm{HCO}_3^-]_l + [\mathrm{H}^+]_l.$$

The parameter x_i denotes the amount of negatively charged ions with valence z = -1 permeable to the cellular PM. It's value is solved by imposing electroneutrality in the cellular compartment. As such, each compartment of the model is assumed electroneutral at all times.

Parameter	Description	Value	Units
$\overline{P_a}$	Apical PM water permeabitlity	4.43	$\mu m^3 m M^{-1} s^{-1}$
P_b	Basolateral PM waterpermeability	1.94	$\mu m^3 m M^{-1} s^{-1}$
P_t	Tight junction's water permeability	0.05	$\mu m^3 m M^{-1} s^{-1}$
Ψ_l	Luminal uncharged particles	51.74	mM

2.8 IPR dynamics

$$J_{IPR} = k_{IPR} P_0, (28)$$

where P_0 is the open probability of the channel defined as

$$P_0 = \frac{\beta}{\beta + k_\beta(\beta + \alpha)},\tag{29}$$

where

$$\alpha = A([\mathrm{IP}_3]_i)(1 - m([\mathrm{Ca}^{2+}]_i)h_{\infty}([\mathrm{Ca}^{2+}]_i)), \qquad (30)$$

$$\beta = B([\mathrm{IP}_3]_i)m([\mathrm{Ca}^{2+}]_i)h([\mathrm{Ca}^{2+}]_i), \qquad (31)$$

$$m(c) = \frac{[\mathrm{Ca}^{2+}]_i^4}{K_c^4 + [\mathrm{Ca}^{2+}]_i^4},\tag{32}$$

$$1 - A([IP_3]_i) = B([IP_3]_i) = \frac{[IP_3]_i^2}{K_p^2 + [IP_3]_i^2},$$
(33)

$$h_{\infty}([\operatorname{Ca}^{2+}]_i) = \frac{K_h^4}{K_h^4 + [\operatorname{Ca}^{2+}]_i^4},\tag{34}$$

$$\tau_h([\mathrm{Ca}^{2+}]_i)\frac{dh}{dt} = h_\infty([\mathrm{Ca}^{2+}]_i) - h,$$
(35)

and

$$\tau_h([\operatorname{Ca}^{2+}]_i) = \tau_{max} \frac{K_{\tau}^4}{K_{\tau}^4 + [\operatorname{Ca}^{2+}]_i^4}.$$
(36)

Parameter	Description	Value	Units
$\overline{k_{IPR}}$	IPR rate	45	$\mu M.m.s^{-1}$
k_{eta}	-	0.4	_
K_c	Half maximal concentration of calcium for positive feedback on IPR	0.2	μM
K_p	Half maximal concentration of $[IP_3]_i$ for feedback on the IPR	0.2	μM
$\dot{K_h}$	Half maximal concentration of calcium for negative feedback on IPR	0.08	μM
K_{τ}	Half maximal concentration of calcium for feedback on the time scaling factor	0.1	μM
$ au_{max}$	Time scaling for negative feedback of calcium on the IPR	100	\mathbf{S}

2.9 SERCA pumps

$$J_{SERCA} = V_p \frac{[\mathrm{Ca}^{2+}]_i^2 - \bar{K}[\mathrm{Ca}^{2+}]_{ER}^2}{[\mathrm{Ca}^{2+}]_i^2 + k_p^2}$$
(37)

Parameter	Description	Value	Units
$\overline{V_p}$	SERCA pump Rate	0.9	$\mu M.s^{-1}$
\bar{K}	-	0.00001957	-
k_p	-	0.2	μM

2.10 IP₃ dynamics

$$V_{\rm PLC} = \mu(x) \frac{[{\rm Ca}^{2+}]_i^2}{[{\rm Ca}^{2+}]_i^2 + K_{\rm PLC}^2},$$
(38)

$$V_{deg} = \left(V_{5K} + V_{3K} \frac{[\mathrm{Ca}^{2+}]_i^2}{[\mathrm{Ca}^{2+}]_i^2 + K_{3K}^2} \right) [\mathrm{IP}_3]_i,$$
(39)

$$\mu(x) = \begin{cases} k_{PLC} & \text{if} \quad d_b(x) < d_{PLC} \text{ and } d_a(x) > dl_{PLC}, \\ 0 & \text{else}, \end{cases}$$
(40)

Parameter	Description	Value	Units
$\overline{K_{PLC}}$	Half maximal concentration of $[IP_3]_i$ for feedback on PLC	0.07	μM
K_{3K}	Half maximal concentration of $[IP_3]_i$ for feedback on $[IP_3]_i$ 3-Kinase	0.4	μM
V_{3K}	$[IP_3]_i$ degradation rate by $[IP_3]_i$ 3-Kinase	0.05	s^{-1}
V_{5K}	$[IP_3]_i$ degradation rate by $[IP_3]_i$ 5-Kinase	0.05	s^{-1}
d_{PLC}	Critical distance from the basal membrane for the expression of PLC	0.8	$\mu { m m}$
dl_{PLC}	Minimum distance from the apical membrane for the expression of PLC	0.6	$\mu { m m}$
k_{PLC}	Maximum PLC rate	0.6	$\mu M.s^{-1}$
$d_b(x)$	Distance to the basal region of the point x	-	$\mu { m m}$
$d_a(x)$	Distance to the basal region of the point x	-	$\mu { m m}$

2.11 Wave propagation model

$$\begin{cases} J_{\text{Wav}} = V_{\text{Wav}}(x) \frac{[\text{Ca}^{2+}]_{i}^{4}}{[\text{Ca}^{2+}]_{i}^{4} + K_{\text{Wav}}^{4}} g \\ \frac{\mathrm{d}g}{\mathrm{d}t} = (g_{\infty} - g) / \tau_{\text{Wav}}, \end{cases}$$
(41)

where

$$g_{\infty} = \frac{K_{\rm hWav}^2}{K_{\rm hWav}^2 + [{\rm Ca}^{2+}]_i^2}.$$
(42)

and

$$V_{\text{Wav}}(x) = \begin{cases} V_{\text{Wav}}^{\max} \frac{d_a(x)}{d_{\text{Wav}}} & \text{if} \quad d_a(x) < d_{\text{Wav}}, \\ V_{\text{Wav}}^{\max} & \text{else.} \end{cases}$$
(43)

Parameter	Description	Value	\mathbf{Units}
$V_{\rm Wav}^{ m max}$	Wave propagation model rate	0.15	$\mu M.s^{-1}$
$K_{\rm wav1}$	Half maximal concentration of calcium for positive feedback on wave propagation	0.2	μM
d_{Wav}	Critical distance for the expression of the wave propagation	1	$\mu { m m}$
$K_{\rm hWav}$	Half maximal concentration of calcium for negative feedback on wave propagation	0.15	μM
$ au_{\mathrm{wav}}$	Time scaling for negative feedback of calcium on the wave propagation	1	S











<u>1 μ</u>m

























Parotid Acini Cluster



Calcium oscillations comparison



Parameters of the Fluid Secretion Model

Parameter	Description	Value	Units
$\overline{D_c}$	Calcium diffusion coefficient	5	$\mu m^2 . s^{-1}$
D_p	IP_3 diffusion coefficient	285	$\mu m^2 . s^{-1}$
γ	ratio of ER volume over cytosolic volume	0.185	_
K_{CaKC}	Half half maximal concentration for basal K ⁺ channels	0.3	$\mu { m M}$
η_2	Hill coefficient for basal K ⁺ channels	4.7	-
$G_{\rm K}$	Cl ⁻ channel whole cell conductance	14.6	nS
K_{CaCC}	Half half maximal concentration for apical Cl ⁻ channels	0.2	$\mu { m M}$
η_1	Hill coefficient for apical Cl^- channels	4.49	-
$G_{\rm Cl}$	Cl ⁻ channel whole cell conductance	18.2	nS
ω_l/ω_i	Lumen to cell volume ratio	0.02	-
R	Universal gas constant	8.3144621	$\rm J~mol^{-1}~K^{-1}$
Т	Temperature	310	Κ
F	Faraday's constant	96485.3365	$\rm C\ mol^{-1}$
C_m	PM capacitance	1	F
pH_e	Interstitial pH	7.41	-
pH_i	Cellular pH	6.91	-
pH_l	Luminal pH	6.81	-
$[\mathrm{Na}^+]_e$	Interstitial Na ⁺	140.2	mM
$[\mathrm{K}^+]_e$	Interstitial K^+	5.3	mM
$[\mathrm{Cl}^-]_e$	Interstitial Cl ⁻	102.6	mM
$[\mathrm{CO}_2]_e$	Interstitial CO_2	1.6	mM
$[\mathrm{HCO}_3^-]_e$	Interstitial HCO_3^-	40	mM
$[\mathrm{H}^+]_e$	Interstitial H ⁺	$1e3 \times 10^{-pH_e}$	mM
$[\mathrm{Na}^+]_i$	Intracellular Na^+ at rest	25.94	mM
$[K^+]_i$	Intracellular K^+ at rest	116.83	mM
$[\mathrm{Cl}^-]_i$	Intracellular Cl^- at rest	49.78	mM
$[\mathrm{Ca}^{2+}]_i$	Intracellular Ca^{2+} at rest	0.05	$\mu { m M}$
$[\mathrm{HCO}_3^-]_i$	Intracellular HCO_3^- at rest	10	mM
$[\mathrm{H}^+]_i$	Intracellular H^+ at rest	$1e3 \times 10^{-pH_i}$	mM
$[\mathrm{CO}_2]_i$	Intracellular CO_2	6.6	mM
$[Na^+]_l$	Luminal Na^+ at rest	123.4	mM
$[K^+]_l$	Luminal K^+ at rest	5.29	mM
$[\mathrm{Cl}^-]_l$	Luminal Cl^- at rest	128.75	mM
$[\mathrm{HCO}_3^-]_i$	Luminal HCO_3^- at rest	0.00015	mM
$[\mathrm{H}^+]_l$	Luminal H^+ at rest	$1e3 \times 10^{-pH_l}$	mM
V_a	Apical PM potential	58.9	mV
V_b	Basal PM potential	62.8	mV

3 Parameters of the homogeneous model

Parameter	Description	Value	Units
$\overline{k_{IPR}}$	IPR rate	45	s^{-1}
V_p	SERCA pump rate	0.9	-
$ au_{max}$	Time scaling for negative feedback of calcium on the IPR	100	\mathbf{S}
$V_{\rm Wav}^{\rm max}$	Wave propagation model rate	0.07	$\mu M.s^{-1}$

Table 1: Parameters of the homogeneous model

4 Parameters of the open-cell model

Parameter	Description	Value	Units
$\overline{lpha_0}$	Constant leak of Ca^{2+} from the exterior of the cell	0.0027	$\mu M.s^{-1}$
α_1	Maximum rate of the SOCC	0.07	$\mu M.s^{-1}$
α_2	Agonist-dependent influx	15	s^{-1}
δ	Permeability of the cell	1	-
$V_{\rm PM}$	Maximum Ca^{2+} flux through the PMCA	0.11	$\mu M.s^{-1}$
$K_{\rm PM}$	Half-activation of the PMCA	0.3	μM
$K_{\rm CE}$	sensitivity of the SOCC to $[Ca^{2+}]$ in the ER	8	μM

Table 2: Parameters of the open-cell model

Experimental data

Excised parotid gland lobules were loaded with 5 μ M fluo4 and mounted in a superfusion chamber on the stage of an Olympus FV1000 multiphoton microscope. The Ca²⁺ indicator was excited by a Mai Tai femtosecond pulsed laser at 880 nm and emission measured at >510 nm. The lobule was exposed to the IP3-generating agonist, Carbachol (300 nM) resulting in the oscillatory changes in fluorescence observed for the duration of the agonist exposure. Figures 6 show the fluorescence ratio before and after the exposure of the cell to Carbachol. These data have been extracted from the video in the supporting material.



Figure 6: Time series of the mean fluorescence of the Ca^{2+} , in randomly chosen cells of the movie in the supporting material, indicator Fluo-4, averaged over the whole cell. Ca^{2+} oscillations appear after the exposure of the cell to Carbachol. These data have been extracted from a movie given in the supplementary material.

References

- Pages N., Sigüenza E., Kirk V., Rugis J., Yule D., Sneyd J. (2018) A Model of Calcium Dynamics in an Accurate Reconstruction of Parotid Acinar Cells. To be submitted
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