Notes on astrocytic compartmental modeling

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1 Notation

- ℓ: compartment length;
- R: compartment radius; r: ER radius;
- S: cylinder/compartment surface; e.g. $S_\phi = 2\pi R\ell$: compartment lateral surface; $S_z = \pi R^2$: compartment sectional area; $S_\cap = \pi(R^2 - r^2)$: compartment cytoplasmic sectional area;
- Λ: cylinder/compartment volume; e.g. $\Lambda = \Lambda_{\rm cyt} + \Lambda_{\rm ER}$ is the total compartment volume (otherwise somewhat ambiguously defined as 'intracellular' volume);
- ς: (read: 'varsigma') compartment's surface-to-volume ratio: i.e. S/Λ;
- ρ: ratio between ER volume and the total compartment volume, i.e. $\rho = \Lambda_{\rm ER}/\Lambda$;
- ρ_A: ratio between ER volume and cytosolic volume, i.e. $\rho_A = \Lambda_{\rm ER}/\Lambda_{\rm cyt}$;
- ξ_i: Surface ratio of two connected compartments: i.e. $\xi_i = S_{\cap_i}/S_{\cap_{i-1}}$;
- C, h, I: calcium, deinactivating IP_3R gating, IP_3;

2 Outline of derivation of compartment equations

We consider the cylindrical tube of extension z, $z + \Delta z$ in cylindrical coordinates (z, ϕ). Take the concentration (in molars) of a generic species in the tube as $c(z, t)$. Then this concentration is subjected to the law of conservation of mass [see also Fall et al., p. 175], i.e.:

$$\frac{\rm d}{{\rm d}t}\int_z^{z+\Delta z} c(z,t){\rm d}z = J(z,t) - J(z+\Delta z,t) + \int_z^{z+\Delta z} f(z,t,c){\rm d}z \tag{1}$$

where $J(z, t)$ is the diffusion flux and $f(z, t, c)$ represents the rate of *net* increase of the species meant as (production – degradation). By simple analytical arguments (given the arbitrariness of the interval), it follows that:

$$\partial_t c(z,t) = \partial_z J(z,t) + f(z,t,c)$$

$$= \underbrace{D\partial_z^2 c(z,t)}_{=J_{\text{diff}}} + f(z,t,c) \tag{2}$$

where the last equation was obtained by means of Fick's second law of diffusion. Note that ∂_z^2 is the Laplacian in cylindrical coordinates along z which coincides with the 1-d Laplacian in Cartesian coordinates (by simple definition of this latter, we can actually obtain current equations 2.19 and 2.20 on p. 20). Note that the production term remains, in this derivation, for how we defined it and the diffusion term can be developed independently (accordingly, equations 2.19 and 2.20 should refer only to J_{diff} term in the above equation, or be corrected otherwise as you carry on the $f(z,t,c)$ term). Depending on what species we allow for diffusion, we have either one equation for C or two equations for C and I (right now it is not clear from Evan's manuscript whether both C and I are allowed to diffuse or only one of the two).

3 Expression of ρ vs. ς

There are some issues with $\rho(\varsigma)$ orginally suggested by Oschmann et al. (2017, see Figure 3 and equation 1), and also re-proposed on p. 342 of their book chapter (Mergenthaler et al., 2019). The main issue is that their formula would predict $\rho > 0$ as $\varsigma \to 0$, which is clearly a physical absurdity. If we reconsider the original data by Patrushev et al. (2013, Figure 4A) and do a basic fitting by a classic α-function (see `jupyter` notebook file), we obtain:

$$\rho(\varsigma) = \bar{\rho}\frac{\varsigma}{\sigma}\exp\left(1 - \varsigma/\sigma\right) \tag{3}$$

where $\bar{\rho} = 0.14$; $\sigma = 4.355\,\mu\text{m}^{-1}$.

4 Constraints in the choice of compartment size parameters R, r and ℓ

Equation 3 set some important constraints in the choice of compartment size parameters. This is because both ς and ρ are functions of R, ℓ, i.e.

$$\varsigma = \frac{S}{\Lambda} = \frac{S_\phi + 2S_z}{\Lambda} = \frac{2\pi R\ell + 2\pi R^2}{\pi R^2 \ell} = \frac{2(R+\ell)}{R\ell} \tag{4}$$

$$\rho = \frac{\Lambda_{\text{ER}}}{\Lambda} = \frac{\pi r^2 \ell}{\pi R^2 \ell} = \left(\frac{r}{R}\right)^2 \tag{5}$$

Solving equation 3 for ς provides

$$\rho = \bar{\rho}\frac{\varsigma}{\sigma}\exp\left(1 - \varsigma/\sigma\right)$$
$$\frac{\rho}{\bar{\rho}} = \frac{\varsigma}{\sigma}\exp\left(1 - \varsigma/\sigma\right)$$

$$\ln\frac{\rho}{\bar{\rho}} = \ln\frac{\varsigma}{\sigma} + \ln\left(\exp\left(1-\varsigma/\sigma\right)\right) = \ln\frac{\varsigma}{\sigma} + 1 - \frac{\varsigma}{\sigma}$$

$$\ln\frac{\rho}{\bar{\rho}} - 1 = \ln\frac{\varsigma}{\sigma} - \frac{\varsigma}{\sigma}$$

$$\exp\left(\ln\frac{\rho}{\bar{\rho}} - 1\right) = \exp\left(\ln\frac{\varsigma}{\sigma} - \frac{\varsigma}{\sigma}\right) = \frac{\varsigma}{\sigma}\exp\left(-\frac{\varsigma}{\sigma}\right)$$

$$-\exp\left(\ln\frac{\rho}{\bar{\rho}} - 1\right) = -\frac{\varsigma}{\sigma}\exp\left(-\frac{\varsigma}{\sigma}\right) = x\exp(x)|_{x\equiv-\frac{\varsigma}{\sigma}}$$

$$x = \mathcal{W}\left(-\exp\left(\ln\frac{\rho}{\bar{\rho}} - 1\right)\right) = \mathcal{W}\left(-\frac{\rho}{e\,\bar{\rho}}\right)$$

$$\Rightarrow \varsigma = -\sigma\mathcal{W}\left(-\frac{\rho}{e\,\bar{\rho}}\right) \tag{6}$$

where $\mathcal{W}$ is the Lambert function. For convenience of notation let us just rewrite the r.h.s. of equation 6 as $w(\rho) = -\mathcal{W}\left(-\frac{\rho}{e\,\bar{\rho}}\right)$ where we put in relief the fact that the argument of the Lambert $\mathcal{W}$ function depends on ρ. Accordingly, replacing ς in the l.f.s. of equation 6 by equation 4 we get:

$$2R + 2\ell - \sigma w(\rho) R\ell = 0 \tag{7}$$

Equation 7 is the starting point for our choice of compartment parameters. In particular in our simulations we take ρ as a free parameter. This is tantamount of setting either r or R as free parameters once we respectively fix R or r. We then have two scenarios:

1. We fix ℓ instead, then by equation 7 R is given by:

$$R = \frac{2\ell}{2 + \sigma w(\rho)\ell} \tag{8}$$

   and accordingly $r = \sqrt{\rho}R$.

2. We fix r instead then $R = r/\sqrt{\rho}$ (or vice versa) must also satisfy equation 7 which has solutions that are parametrized by ℓ, and accordingly ℓ must also be taken to vary with the compartment, being

$$\ell = -\frac{2R}{2 - \sigma w(\rho) R} \tag{9}$$

   As we will see in the next section the latter case is the one that we need to follow once we set the branching structure.

5 Branching and interface section areas

5.1 Convention

Let us denote by '0' the somatic compartment, and use the positional index notation $0n_1n_2\ldots$ to quickly describe branching structures of n_1 tier-1 compartments (i.e. primary branches) stemming

out from the soma, with n_2 tier-2 compartments (i.e. secondary processes) originating from each tier-1 branch, and so on. Alternatively, we use the notation $\ldots n_2 n_1 0 k_1 k_2 \ldots$ to denote the branching structure that starting from left side of the somatic cylinder branches into $n_1 n_2 \ldots$ processes, while on the right side develops into $k_1 k_2 \ldots$ processes. Note that these two classes of branching structures are a direct consequence of the choice of compartment geometry, as in the case $0 n_1 \ldots$ we only assume branching stemming from one of the sides of the somatic cylinder, whereas in the case $\ldots n_1 0 k_1 \ldots$ we allow branching from both sides.

$0 n_1 \ldots$ **configuration**. In this case $S_{\cap_i} = S_{\cap_{i-1}}/n_i$ so that

$$\xi_i = \frac{S_{\cap_i}}{S_{\cap_{i-1}}} = \frac{1}{n_i} \tag{10}$$

$\ldots n_1 0 k_1 \ldots$ **configuration**. This case allows to have different branching structures on the left vs. right of the somatic compartment. Both structures develops as $0 j_1 \ldots$ structures independently so that

$$ {}_i\xi = \frac{1}{n_i} \qquad \text{left-side branching} \tag{11}$$

$$\xi_i = \frac{1}{k_i} \qquad \text{right-side branching} \tag{12}$$

Corollary. Equations 10–12 provide recurrence relationships between interface areas of consecutive compartments, and allows for expression of each compartment interface area as a fraction of the somatic compartment, being:

$$S_{\cap_i} = \xi_i S_{\cap_{i-1}} = \xi_i \cdot \xi_{i-1} S_{\cap_{i-2}} = \xi_i \cdots \xi_1 \cdot S_{\cap_0} \tag{13}$$

Accordingly, we can write for each compartment:

$$S_{\cap_i} = \tilde{\xi}_i S_{\cap_0} \qquad \text{with:} \quad \tilde{\xi}_i = \prod_{j=1}^{i} \xi_j \tag{14}$$

or, equivalently, in the case of left and right branching:

$$ {}_iS_{\cap} = {}_i\tilde{\xi} S_{\cap_0} \qquad \text{with:} \quad {}_i\tilde{\xi} = \prod_{j=1}^{i} {}_j\xi \qquad \text{(left)} \tag{15}$$

$$S_{\cap_i} = \tilde{\xi}_i S_{\cap_0} \qquad \text{with:} \quad \tilde{\xi}_i = \prod_{j=1}^{i} \xi_j \qquad \text{(right)} \tag{16}$$

5.2 Solution of geometrical constraints introduced by branching

A generic simulation consists of:

1. Setting somatic parameters R_0, r_0, $\ell_0 \Rightarrow$ automatically compute ρ_0, ρ_{A_0};
2. Choosing the configuration and set ρ_i (for $i > 0$) for each tier/compartment (see equation 17). This will also automatically set ρ_{A_i} (see equation 19).
3. Computing the $(n-1)$-tuple of $(\tilde{\xi}_1, \tilde{\xi}_i, \ldots)$ by equation 14;
4. Computing the n-tuple of compartment radii $(R_0, R_1, \ldots)$ (see equation 20);
5. Computing the n-tuple of compartment ER radii $(r_0, r_1, \ldots)$ by equation 5 so that $r_i = \sqrt{\rho_i} R_i$;
6. Computing ℓ_i for each tier (compartment) based on equation 9. This will guarantee that the relation 3 between ρ_i and ς_i is matched at the level of individual compartments (see equations 22 and 23).

Choice of ρ_i. For each compartment, ρ_i must be chosen so as to have $\varsigma \in \mathbb{R}$. This requires that the argument of the Lambert function in equation 6 is such that

$$\mathcal{W}\left(-\frac{\rho_i}{e\,\bar{\rho}}\right) \in \mathbb{R} \Leftrightarrow -\frac{\rho_i}{e\,\bar{\rho}} \geq -\frac{1}{e} \Leftrightarrow \rho_i \leq \bar{\rho} \tag{17}$$

Computation of ρ_{A_i} **by** ρ_i. It follows by the definitions of ρ_i and ρ_{A_i} that

$$\Lambda_{\mathrm{ER}_i} = \rho_i \Lambda_i \tag{18}$$

$$\rho_{A_i} = \frac{\Lambda_{\mathrm{ER}_i}}{\Lambda_{\mathrm{cyt}_i}} = \frac{\Lambda_{\mathrm{ER}_i}}{\Lambda - \Lambda_{\mathrm{ER}_i}}$$

$$\Rightarrow \rho_{A_i} = \frac{\rho_i}{1-\rho_i} \tag{19}$$

Computation of R_i. Once we choose the branching configuration, the n-tuple of interface areas $(S_{\cap_0}, S_{\cap_1}, \ldots)$ is simply given by equation 14, which translates to:

$$\begin{aligned} S_{\cap_i} &= \tilde{\xi}_i S_{\cap_0} \\ \pi(R_i^2 - r_i^2) &= \tilde{\xi}_i \pi(R_0^2 - r_0^2) \\ R_i^2(1-\rho_i) &= \tilde{\xi}_i R_0^2 (1-\rho_0) \\ \Rightarrow R_i &= \sqrt{\frac{\tilde{\xi}_i}{1-\rho_i}}\sqrt{(1-\rho_0)} R_0 \end{aligned} \tag{20}$$

Computation of ℓ_i. Since $\ell_i > 0$, then, by equation 9 it must be $w(\rho_i) R_i > 2$, that is

$$\mathcal{W}\left(-\frac{\rho_i}{e\,\bar{\rho}}\right) < -\frac{2}{\sigma R_i} \tag{21}$$

Note that the above condition eventually sets a limit on the acceptable values of R_i (or ρ_i), as it must be $R_i > 2/w(\rho_i)$ (or alternatively, $w(\rho_i) > 2/R_i$) for ℓ_i to be found. Supposing that this constraint is verified, then, depending on the value of the product σR_i, we know what branch of $\mathcal{W}$ to consider to set ℓ_i. That is, if $\sigma R_i > 2$, then $-1 < \mathcal{W}\left(-\frac{\rho_i}{e\,\bar{\rho}}\right) < 0$ so that

$$\ell_i = -\frac{2R_i}{2 - \sigma \mathcal{W}_0\left(-\frac{\rho_i}{e\,\bar{\rho}}\right) R_i} \qquad \text{if } \sigma R_i > 2 \tag{22}$$

Vice verse, if $\sigma R_i < 2$, then $-\infty < \mathcal{W}\left(-\frac{\rho_i}{e\,\bar{\rho}}\right) < -1$ so that

$$\ell_i = -\frac{2R_i}{2 - \sigma \mathcal{W}_{-1}\left(-\frac{\rho_i}{e\,\bar{\rho}}\right) R_i} \qquad \text{if } \sigma R_i < 2 \tag{23}$$

5.3 Fundamental branching configurations

To understand the effect of branching on statistics, we consider the following cases:

i. 01 ii. 101 iii. 011;

iv. 021 v. 11011 vi. 12021;

vii. 022 viii. 21012 ix. 22022

The code must allow however for asymmetric branching. The general rule for branching must indeed be $S_{z_{i-1}} \geq \sum_{j=1}^{n_i} S_{z_j}$. This will be used in the later stage where we will assess how such asymmetries in sectional areas among compartments of the same tier could influence the ISI statistics.

6 Model equations

6.1 Proper scaling of IP_3 rates

The equation for IP_3 dynamics in the version of the G-ChI model adopted by Matrosov et al. (2019), and which we use in the simulations, must be modified to account for the fact that IP_3 concentration changes with the compartment's cytosol volume (Λ_{cyt}). The rates of IP_3 production and degradation O_β, O_δ, $O_{3\mathrm{K}}$, $O_{5\mathrm{P}}$ indeed depend on Λ_{cyt}. It is easy to think of these rates as given by the generic formula:

$$O = \frac{\text{\# molecules } IP_3 \text{ produced/degraded in the unit time}}{N_A \Lambda_{\mathrm{cyt}}} \tag{24}$$

where the numerator is in $\mathrm{molecules/s}$, and N_A is the Avogadro constant. On the other hand,

$$\Lambda_{\mathrm{cyt}_i} = \Lambda_i - \Lambda_{\mathrm{ER}_i} = \Lambda_i - \rho_i \Lambda_i = (1 - \rho_i)\Lambda_i \tag{25}$$

Moreover, the number of IP_3 molecules divided by N_A provide the mol of IP_3 produced (degraded) so that we can define the rate of IP_3 production or degradation in $\mathrm{mol/s}$ by

$$\bar{O} = \frac{\text{\# molecules } IP_3 \text{ produced/degraded in the unit time}}{N_A} = IP_3 \text{ production/degradation in } \mathrm{mol/s} \tag{26}$$

Accordingly,

$$O = \frac{\bar{O}}{\Lambda(1 - \rho)} \tag{27}$$

Because we want O to be in $\mu\mathrm{M/s}$ it is worth to understand what units we should best use to express $\bar{O}$ and Λ. Consider for this task, the case of a somatic compartment, for which $\Lambda_0 = 2100 \pm 300 \mu\mathrm{m}^3$ (Chvátal et al., 2007) and $\rho_0 = 0.185$ (De Pittà et al., 2009) so that $\bar{\Lambda}_0 = \Lambda_0(1 - \rho_0) \approx 1800\,\mu\mathrm{m}^3$, then for a generic $O = 1\,\mu\mathrm{M/s}$ it must be:

$$\begin{aligned} \bar{O} &= 1\,\mu\mathrm{M/s} \cdot 1800\,\mu\mathrm{m}^3 = \frac{1\,\mu\mathrm{mol}}{\mathrm{dm}^3 \cdot \mathrm{s}} \cdot 1800 \times 10^{-15}\,\mathrm{dm}^3 = \frac{1 \times 10^{-6}\,\mathrm{mol}}{\mathrm{s}} \cdot 1800 \times 10^{-15} \\ &= 1800 \times 10^{-21}\,\mathrm{mol/s} = 1800\,\mathrm{zmol/s} \end{aligned} \tag{28}$$

In other words the rates $\bar{O}$ must be provided in $\mathrm{zmol/s}$ and the volume in $\mu\mathrm{m}^3$ in order to obtain rates O in the needed units of $\mu\mathrm{M/s}$.

6.2 Compartment equations

Recall that $\rho_A = \rho/(1-\rho)$. We want to have ρ instead of ρ_A in the equations, since we directly work with ρ_i in setting our parameter constraints.

$$\dot{C}_i = J_{\mathrm{r}} + J_{\mathrm{l}} - J_{\mathrm{p}} - J^C_{\mathrm{diff}} \tag{29}$$

$$\dot{C}_{\mathrm{ER}_i} = -\frac{1-\rho_i}{\rho_i}\left(J_{\mathrm{r}} + J_{\mathrm{l}} - J_{\mathrm{p}}\right) \tag{30}$$

$$\dot{h}_i = \Omega_h\left(h_\infty - h\right) \tag{31}$$

$$\dot{I}_i = \frac{1}{\Lambda_i(1-\rho_i)}\left(J_\beta + J_\delta - J_{3\mathrm{K}} - J_{5\mathrm{P}} + J^I_{\mathrm{diff}}\right) \tag{32}$$

$$\tag{33}$$

where:

$$J_{\mathrm{r}} = \Omega_C\, m_\infty^3 n_\infty^3 h^3\left(C_{\mathrm{ER}_i} - C_i\right) \tag{34}$$

$$J_{\mathrm{l}} = \Omega_L\left(C_{\mathrm{ER}_i} - C_i\right) \tag{35}$$

$$J_{\mathrm{p}} = O_P \mathcal{H}_2\left(C_i, K_P\right) \tag{36}$$

$$m_\infty = \mathcal{H}_1\left(I_i, d_1\right) \tag{37}$$

$$m_\infty = \mathcal{H}_1\left(I_i, d_1\right) \tag{38}$$

$$h_\infty = d_2\frac{I_i + d_1}{d_2(I + d_1) + (I_i + d_3)C_i} \tag{39}$$

$$\Omega_h = \frac{\Omega_2(I_i + d_1) + O_2(I_i + d_3)C_i}{I_i + d_3} \tag{40}$$

$$J_\beta = \bar{O}_\beta\, \mathcal{U}_\beta(0, 1|t_k)\sum_k \delta(t - t_k) \tag{41}$$

$$J_\delta = \bar{O}_\delta\left(1 - \mathcal{H}_1\left(I_i, \kappa_\delta\right)\right)\mathcal{H}_2\left(C_i, K_\delta\right) \tag{42}$$

$$J_{3\mathrm{K}} = \bar{O}_{3\mathrm{K}}\, \mathcal{H}_4\left(C_i, K_D\right)\mathcal{H}_1\left(I_i, K_3\right) \tag{43}$$

$$J_{5\mathrm{P}} = \bar{O}_{5\mathrm{P}}\mathcal{H}_1\left(I_i, K_{5\mathrm{P}}\right) \tag{44}$$

and diffusion fluxes are defined by:

$$J^C_{\mathrm{diff}} = 2D_C\left(\frac{\xi_{i+1}C_{i+1} - C_i}{\ell_{i+1} + \ell_i} - \frac{C_i - \xi_{i-1}^{-1}C_{i-1}}{\ell_i + \ell_{i-1}}\right) \tag{45}$$

$$J^I_{\mathrm{diff}} = 2D_I\left(\frac{\xi_{i+1}I_{i+1} - I_i}{\ell_{i+1} + \ell_i} - \frac{I_i - \xi_{i-1}^{-1}I_{i-1}}{\ell_i + \ell_{i-1}}\right) \tag{46}$$

Note that $\Lambda_i = \pi R_i^2 \ell_i$ and it is thus automatically estimated by the formulas derived in the previous sections.

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