TNNP unit fixes

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This informal document describes changes to the units in the CellML models for the 2004 model by ten Tusscher et al. [1] and its 2006 update [2], and shows how the equations for the calcium concentrations are derived from those in the paper and published source code.

In the 2004 model, the paper [1] shows the correct units, but the code [3] (and CellML file as of Oct 2020 [4]) had some scaling issues. In addition, there is added precision in R and F with incorrect digits. Finally, the unit of C_m is wrong, leading to the unnecessary use of unit-scaling factors in the original CellML code (e.g. multiplication by 1 with a dimensionless unit like 1pA/mA). Note that all the numerical values worked out the same, since the errors 'cancelled out' (as shown below), but these changes will now give us correct numbers for volumes and charges in certain spaces.

Parameter	Original[4]	Updated[5]	Scaling
F	96485(.3415) C/mmol	96.485 C/mmol	10^{-3}
R	8314(.472) J/mol/K	8.314 J/mol/K	10^{-3}
C_m	0.185 μF	185 pF	10^{3}
g_{CaL}	0.000175 L/F/s	0.175 L/F/s	10^{3}
V_c	0.016404 μm^3	16404 μm^3	10^{6}
V_{sr}	0.001094 μm^3	1094 μm^3	10^{6}

Table 1: TNNP 2004 updates

The parameters always appear in a limited number of expressions, here we show these happen to be unchanged numerically because the scalings applied to each parameter in Table 1 simplify to a value of one for the scaling of each expression:

$$\frac{F}{RT} \propto \frac{10^{-3}}{10^{-3}} = 1 \tag{1}$$

$$g_{\mathrm{CaL}}\frac{F^2}{RT} \propto 10^{3}\frac{10^{-6}}{10^{-3}} = 1 \tag{2}$$

$$\frac{C_m}{V_c F} \propto \frac{10^{10^3}}{10^{6}\cdot 10^{-3}} = 1 \tag{3}$$

$$\frac{V_c}{V_{\mathrm{sr}}} \propto \frac{10^{6}}{10^{6}} = 1 \tag{4}$$

In the 2006 model (paper [2], code [6]) there is an extra term, and the value of g_{CaL} has changed:

Parameter	Original[7]	Updated[8]	Scaling
g_{CaL}	0.0000398 L/F/s	0.0398 L/F/s	10^{3}
V_{ss}	0.00005468 μm^3	54.68 μm^3	10^{6}

Table 2: Additional TNNP 2006 updates

New terms are scaled according to:

$$\frac{C_m}{V_{\mathrm{ss}} F} \propto \frac{10^{3}}{10^{6}\cdot 10^{-3}} = 1 \tag{5}$$

$$\frac{V_{\mathrm{sr}}}{V_{\mathrm{ss}}} \propto \frac{10^{6}}{10^{6}} = 1 \tag{6}$$

$$\frac{V_{\mathrm{sr}}}{V_{\mathrm{c}}} \propto \frac{10^{6}}{10^{6}} = 1 \tag{7}$$

Errata in the source code

Notes from the 2004 source code[3]:

```
/* ERRATA:
   We found a typo in the parameter values in the ms describing this model.
   Below we list the value the parameter should have and which is used
   in this implementation but that is wrong in the ms:
   GpCa=0.825nS/pF
 */
```

This is correct in the old and new CellML.

2006 model

Notes from the 2006 source code[6]:

```
/* We discovered some typo's in parameter values in the publication:
   Vrel=40.8; should be 0.102
   k4=0.000015; should be 0.005
   Vc=16.404; should be 16404
   Vsr=1.094; should be 1094
   Vss=0.05468; should be 54.68
```

The changes for 'Vrel' and 'k4' are already applied in the old CellML. The changes to volume only affect the publication (which shows units, unlike the code). But note that in the updated CellML file the new values are used.

Concentration updates

The equations that are used to update the calcium concentrations differ substantially between the CellML code and publication. The informal text below shows how manuscript, original source code, and CellML relate; and that they are all equivalent.

The example shown here is for the 'Cai' variable in the 2006 model update, but the same reasoning applies to 'Cai' and 'Cai_sr' in the 2004 model, and 'Cai', 'Cai_sr', and 'Cai_ss' in the 2006 update.

Manuscript

The following equations are given to calculate the internal calcium concentration:

$$\mathrm{Ca_{i,bufc}} = \frac{\mathrm{Ca}_i \cdot \mathrm{Bufc}}{\mathrm{Ca}_i + K_{\mathrm{bufc}}} \tag{8}$$

$$\frac{d}{dt}\mathrm{Ca_{i,total}} = -\frac{I_{\mathrm{bCa}} + I_{\mathrm{pCA}} - 2I_{\mathrm{NaCa}}}{2V_c F} + \frac{V_{\mathrm{sr}}}{V_c}(I_{\mathrm{leak}} - I_{\mathrm{up}}) + I_{\mathrm{xfer}} \tag{9}$$

where $\mathrm{Ca_{i,total}}$ is the "total (free + buffered) cytoplasmic Ca^{2+} concentration" and Ca_i is the "free cytoplasmic Ca^{2+} concentration".

Original source code

$$\mathrm{Ca_{buf}} = \frac{\mathrm{Ca}_i \cdot \mathrm{Bufc}}{\mathrm{Ca}_i + K_{\mathrm{bufc}}} \tag{10}$$

$$\mathrm{dCa_i} = \left[\frac{C_m}{2V_c F}\left(-(I_{\mathrm{bCa}} + I_{\mathrm{pCA}} - 2I_{\mathrm{NaCa}})\right) - \frac{V_{\mathrm{sr}}}{V_c}(I_{\mathrm{up}} - I_{\mathrm{leak}}) + I_{\mathrm{xfer}}\right] \cdot \mathrm{dt} \tag{11}$$

So far the equations match the text, except for a C_m omitted in the manuscript. (The three currents in the first term are normalised by capacitance, so we do need to multiply by C_m if we want to use them to update a concentration: the code is correct.) The update of the variable 'Cai' now happens as:

$$\mathrm{bc} = \mathrm{Bufc} - \mathrm{Ca_{Buf}} - \mathrm{dCai} - \mathrm{Cai} + K_{\mathrm{bufc}} \tag{12}$$

$$\mathrm{cc} = K_{\mathrm{bufc}}(\mathrm{Ca_{Buf}} + \mathrm{dCai} + \mathrm{Cai}) \tag{13}$$

$$\mathrm{Ca}_i = \frac{1}{2}\left(\sqrt{\mathrm{bc}^2 + 4 \cdot \mathrm{cc}} - \mathrm{bc}\right) \tag{14}$$

Note that, according to the manuscript, $\mathrm{dCa_i}$ in the first equation gives the update for the *total* calcium (and so should maybe be called $\mathrm{dCa_{i,total}}$). By comparing other equations in the model code (i.e. "Ileak=Vleak*(CaSR-Cai);") to the manuscript we can see that "Cai" in the code refers to the *free calcium*.

Cleaning up a bit, we get:

$$\mathrm{Ca_{i,buf}}[t_i] = \frac{\mathrm{Ca_{i,free}}[t_i] \cdot \mathrm{Bufc}}{\mathrm{Ca_{i,free}}[t_i] + K_{\mathrm{bufc}}} \tag{15}$$

$$\Delta\mathrm{Ca_{i,total}}[t_i] = \left[-\frac{C_m}{2V_c F}(I_{\mathrm{bCa}} + I_{\mathrm{pCA}} - 2I_{\mathrm{NaCa}}) + \frac{V_{\mathrm{sr}}}{V_c}(I_{\mathrm{leak}} - I_{\mathrm{up}}) + I_{\mathrm{xfer}}\right] \cdot \Delta t \tag{16}$$

To understand the update code, we can write out what an Euler update to total calcium would look like:

$$\mathrm{Ca_{i,total}}[t_i] = \mathrm{Ca_{i,free}}[t_i] + \mathrm{Ca_{i,buf}}[t_i] \tag{17}$$

$$\mathrm{Ca_{i,total}}[t_{i+1}] \approx \mathrm{Ca_{i,free}}[t_i] + \mathrm{Ca_{i,buf}}[t_i] + \Delta\mathrm{Ca_{i,total}}[t_i] \tag{18}$$

In addition, since "total = free + buffered" calcium we can express buffered calcium in terms of free calcium, to find the relationship between free and total. Using a slightly simpler notation:

$$\mathrm{Ca}_t = \mathrm{Ca}_f + \mathrm{Ca}_b = \mathrm{Ca}_f + \frac{\mathrm{Ca}_f B}{\mathrm{Ca}_f + K} \tag{19}$$

which we can rewrite as

$$\mathrm{Ca}_t(\mathrm{Ca}_f + K) = \mathrm{Ca}_f(\mathrm{Ca}_f + K) + \mathrm{Ca}_f B \tag{20}$$

$$0 = \mathrm{Ca}_f^2 + \mathrm{Ca}_f(K + B - \mathrm{Ca}_t) - K\mathrm{Ca}_t \tag{21}$$

with solutions

$$\mathrm{Ca}_f = \frac{-(K + B - \mathrm{Ca}_t) \pm \sqrt{(K + B - \mathrm{Ca}_t)^2 + 4K\mathrm{Ca}_t}}{2} \tag{22}$$

Looking at the rest of the update in the code, we can now see that it's a solution to this quadratic formula for $\mathrm{Ca}_{\mathrm{i,free}}[t_{i+1}]$, as a function of $\mathrm{Ca}_{\mathrm{i,total}}[t_{i+1}]$ — so that the Euler update is done implicitly in the intermediary variables bc and cc:

$$\begin{aligned} \mathrm{bc}[t_{i+1}] &= \mathrm{Bufc} - \mathrm{Ca}_{\mathrm{i,buf}}[t_i] - \mathrm{dCa}_{\mathrm{i,total}}[t_i] - \mathrm{Ca}_{\mathrm{i,free}}[t_i] + K_{\mathrm{bufc}} && (23)\\ &= \mathrm{Bufc} + K_{\mathrm{bufc}} - \mathrm{Ca}_{\mathrm{i,total}}[t_{i+1}] && (24) \end{aligned}$$

$$\begin{aligned} \mathrm{cc}[t_{i+1}] &= K_{\mathrm{bufc}}(\mathrm{Ca}_{\mathrm{i,buf}}[t_i] + \mathrm{dCai}_{\mathrm{i,total}}[t_i] + \mathrm{Ca}_{\mathrm{i,free}}[t_i]) && (25)\\ &= K_{\mathrm{bufc}}\mathrm{Ca}_{\mathrm{i,total}}[t_{i+1}] && (26) \end{aligned}$$

$$\mathrm{Ca}_{\mathrm{i,free}}[t_{i+1}] = \frac{-\mathrm{bc}[t_{i+1}] + \sqrt{\mathrm{bc}[t_{i+1}]^2 - 4 \cdot 1 \cdot (-\mathrm{cc}[t_{i+1}])}}{2 \cdot 1} \tag{27}$$

So it's correct if you're using forward-Euler. However, you can't use this form if you want to write out the pure equations, or if you want to allow for different ODE solving methods. One option would be to make a state variable for total calcium instead of one for free calcium, and go from there. But it doesn't look like that's what the CellML code has done.

CellML (old and new, unit scaling factors omitted)

The CellML code starts off with a bold statement

$$\mathrm{Ca}_{\mathrm{i,bufc}} = \left[1 + \frac{\mathrm{Bufc} \cdot K_{\mathrm{bufc}}}{(\mathrm{Ca}_{\mathrm{i}} + K_{\mathrm{bufc}})^2}\right]^{-1} \tag{28}$$

The parameters Bufc and K_{bufc} have the same values in the CellML code as in the C source code and the manuscript. As before, we can look for other uses of Ca_{i} to see that it represents the *free* calcium concentration. But the name $\mathrm{Ca}_{\mathrm{i,bufc}}$ is clearly used to mean something different here. The CellML code tells us the above equation is for a dimensionless quantity. We can check that this is true: Bufc, K_{bufc} and Ca_i are all in mM. So this is not a concentration, but maybe a fraction? Let's call it x.

Next, the CellML code gives an equation for the derivative of the free calcium variable:

$$\begin{aligned} \frac{d}{dt}\mathrm{Ca}_{\mathrm{i,free}} &= \mathrm{Ca}_{\mathrm{i,bufc}}\left[-(I_{\mathrm{bCa}} + I_{\mathrm{pCa}} - 2I_{\mathrm{NaCa}})\frac{C_m}{2V_cF} + (I_{\mathrm{leak}} - I_{\mathrm{up}})\frac{V_{\mathrm{sr}}}{V_c} + i_{\mathrm{xfer}}\right] && (29)\\ &= x \cdot \frac{d}{dt}\mathrm{Ca}_{\mathrm{i,total}} && (30) \end{aligned}$$

There are several ways to work out what x should be, in this equation, but here's one (again using simplified notation):

$$\begin{aligned} \mathrm{Ca}_f &= \mathrm{Ca}_t - \mathrm{Ca}_b = \mathrm{Ca}_t - \frac{\mathrm{Ca}_f B}{\mathrm{Ca}_f + K} && (31)\\ \dot{\mathrm{Ca}}_f &= \dot{\mathrm{Ca}}_t - \frac{d}{dt}\frac{\mathrm{Ca}_f B}{\mathrm{Ca}_f + K} && (32)\\ &= \dot{\mathrm{Ca}}_t - \frac{(\mathrm{Ca}_f + K)B - \mathrm{Ca}_f B}{(\mathrm{Ca}_f + K)^2}\dot{\mathrm{Ca}}_f && (33)\\ &= \dot{\mathrm{Ca}}_t - \frac{KB}{(\mathrm{Ca}_f + K)^2}\dot{\mathrm{Ca}}_f && (34)\\ \dot{\mathrm{Ca}}_f &= \dot{\mathrm{Ca}}_t\left[1 + \frac{KB}{(\mathrm{Ca}_f + K)^2}\right]^{-1} && (35) \end{aligned}$$

so this gives us the expression for what we've called x but what the CellML files unfortunately call "Ca_i_bufc". Note that we didn't need to solve a quadratic equation to get to this result!

Similar equations are used for "Ca_ss" and "Ca_sr", and in the CellML equations in the 2004 models.

References

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[2] Kirsten HWJ ten Tusscher and Alexander V Panfilov. Alternans and spiral breakup in a human ventricular tissue model. *American Journal of Physiology. Heart and Circulatory Physiology*, 291(3):H1088–H1100, 2006.

[3] Kirsten HWJ ten Tusscher, Denis Noble, Penelope J Noble, and Alexander V Panfilov. Original code for: "A model for human ventricular tissue". http://www-binf.bio.uu.nl/khwjtuss/SourceCodes/HVM/. [Online; accessed October 14th, 2020].

[4] Penny Noble, James Lawson, Hanne, Catherine Lloyd, Geoff Nunns, and nhen534. Current CellML for: "A model for human ventricular tissue". https://models.physiomeproject.org/exposure/c7f7ced1e002d9f0af1b56b15a873736. [Online; accessed October 14th, 2020].

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[6] Kirsten HWJ ten Tusscher and Alexander V Panfilov. Original code for: "Alternans and spiral breakup in a human ventricular tissue model". http://www-binf.bio.uu.nl/khwjtuss/SourceCodes/HVM2/. [Online; accessed October 14th, 2020].

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[8] Penny Noble, Dougal Cowan, James Lawson, Geoff Nunns, Catherine Lloyd, Hanne, and Michael Clerx. Updated CellML for: "Alternans and spiral breakup in a human ventricular tissue model". http://models.cellml.org/workspace/604. [Online; accessed October 14th, 2020].