Supplementary Material

Description of the human atrial action potential derived from a single, congruent data source: Novel computational models for integrated experimental-numerical study of atrial arrhythmia mechanisms

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1 Novel current formulations

1.1 Time independent potassium current, \( I_{K1} \)

Due to the importance of the form of the current in the voltage range \(-80\text{mV} - -40 \text{mV}\), where the current may be very small, polynomials were used to achieve a precise fit to the complex voltage dependence of the current:

\[
I_{K1}^{\text{isolated}} = 4(0.096 + 7.12 \times 10^{-3} V_m + 8.95 \times 10^{-3} V_m^2 - 7.13 \times 10^{-4} V_m^3 - 1.35 \times 10^{-9} V_m^4) \quad (1)
\]

\[
I_{K1}^{\text{intact}} = 4(0.0029 + 1.29 \times 10^{-3} V_m + 3.51 \times 10^{-4} V_m^2 - 9.76 \times 10^{-5} V_m^3 - 1.35 \times 10^{-9} V_m^4) \quad (2)
\]

1.2 Rapid potassium currents, \( I_{to} \) and \( I_{sus} \)

\[
I_{to} = g_{to} \cdot v_{a_{to}} \cdot \left( (1 - F_s) v_{i_{to\_1}} + F_s v_{i_{to\_2}} \right) (V_m - E_K) \quad (3)
\]

\[
I_{sus} = g_{sus} \cdot v_{a_{sus}} \cdot v_{i_{sus}} (V_m - E_K) \quad (4)
\]

Where the dynamics of the gating variables (\( v_{a_{ito/sus}} \), \( v_{i_{ito/sus}} \)) are described by the general differential equation:

\[
\frac{dx}{dt} = (x_{ss} - x) / \tau \quad (5)
\]

With steady-states:

\[
v_{a_{ito\_ss}} = 1 / \left( 1 + e^{-(V_m-15)/7} \right) \quad (6)
\]

\[
v_{i_{ito\_1\_ss}} = 1 / \left( 1 + e^{(V_m-(-23)/5.3} \right) \quad (7)
\]

\[
v_{i_{ito\_2\_ss}} = v_{i_{ito\_1\_ss}} \quad (8)
\]

\[
v_{a_{itus\_ss}} = 1 / \left( 1 + e^{(V_m-(-4.25)/5.61)} \right) \cdot 4.15 \cdot e^{0.183 \cdot V_m - 0.9849} \quad (9)
\]

\[
v_{i_{itus\_ss}} = 1 / \left( 1 + e^{(V_m-(-7.5)/10)} \right) \quad (10)
\]

And time constants:

\[
v_{a_{ito\_\tau}} = 0.4 + 18e^{(V_m+40/45)} \quad (11)
\]

\[
v_{i_{ito\_1\_\tau}} = 8.6 + 62e^{(V_m+32/27)} \quad (12)
\]

\[
v_{i_{ito\_2\_\tau}} = 15 + 29.73 / \left( 1 + e^{0.0696(V_m-2.72)} \right) \quad (13)
\]
\[ v_{I_{\text{fas}}} = 0.5 + 0.9 \left( 1 + e^{(V_m+5)/12} \right) \]  
\[ v_{\bar{I}_{\text{fas}}} = 3000 + 590 \left( 1 + e^{(V_m+60)/10} \right) \]  

And proportion of fast/slow channels given by:

\[ F_s = 0.2 \left( 1 + e^{-(V_m-35)/5} \right) \]  

### 1.3 L-type calcium current, \( I_{CaL} \)

The novel formulation presented has the following form:

\[ I_{CaL} = p_{CaL} \cdot v_{I_{CaL}} \cdot (0.8 v_{I_{CaL,1}} + 0.2 v_{I_{CaL,2}}) \cdot c_i \cdot \bar{I}_{CaL, Ca} \]  

Voltage-dependent gates:

\[ v_{I_{CaL,ss}} = 1 \left( 1 + e^{-(V_m-0.5)/5.967} \right) \]  
\[ v_{I_{CaL,1ss}} = 1 \left( 1 + e^{-(V_m+18)/3.8} \right) \]  
\[ v_{I_{CaL,2ss}} = v_{I_{CaL,1ss}} \]  
\[ v_{I_{CaL,b}} = 7.02 - 2.37 e^{-(V_m-14.45)/52.33} \]  
\[ v_{I_{CaL,1b}} = 16.48 - 10.72 e^{-(V_m-2.22)/22.64} \]  
\[ v_{I_{CaL,2b}} = 12424 - 12027 e^{-(V_m-13)/83} \]  

Where \( I_{CaL,Ca_{\text{bar}}} \) was modelled as presented in Grandi et al. 2011. Calcium inactivation was modelled as in the baseline Ca\(^{2+}\)-handling system, with the following modifications for the WL models (not the modified models, which retain calcium-inactivation as originally presented):

\[ c_i = 50.0 \] \( \{ CRN \} \)  
\[ c_i = 5.1 \] \( \{ GB \} \)  
\[ c_i = 8.33 \times 10^{-3} \] \( \{ \} \)

### 1.4 Fast-sodium current, \( I_{Na} \)

\[ I_{Na} = g_{Na} \cdot v_{I_{Na}} \cdot v_{I_{Na,1}} \cdot v_{I_{Na,2}} \cdot (V_m - E_{Na}) \]  
\[ v_{I_{Na,ss}} = 0.32 \left( V_m + 39.13 \right) \left( 1 + e^{-0.09(V_m+39.13)} \right) \]  
\[ v_{I_{Na,b}} = 0.08 e^{-(V_m-8)/11.0} \]
If $V_m < -40 \text{ mV}$:

$$v_{i_{Na,1,\alpha}} = 0.135 e^{-\frac{(V_m+85)}{6.8}} \quad (29)$$

$$v_{i_{Na,1,\beta}} = 3.285 e^{0.079(V_m+5)} + 31000 e^{0.35(V_m+5)} \quad (30)$$

$$v_{i_{Na,2,\alpha}} = (-127140 e^{0.24444(V_m+5)} - 3.474 \times 10^{-5} e^{-0.0439(V_m+5)}) \left( \frac{V_m + 42.78}{1 + e^{0.3111(V_m+84.23)}} \right) \quad (31)$$

$$v_{i_{Na,2,\beta}} = 0.10908 e^{-0.01052(V_m+5)} / \left(1 + e^{-0.1378(V_m+45.14)}\right) \quad (32)$$

Else:

$$v_{i_{Na,1,\alpha}} = 0 \quad (33)$$

$$v_{i_{Na,1,\beta}} = 1 / \left(0.13 \left(1 + e^{(V_m+15.86)/11.1}\right)\right) \quad (34)$$

$$v_{i_{Na,2,\alpha}} = 0 \quad (35)$$

$$v_{i_{Na,2,\beta}} = 0.3 e^{2.535 \times 10^{-7}(V_m+5)} / \left(1 + e^{-0.3(V_m+37)}\right) \quad (36)$$

And the steady state and time constant for each gate defined by:

$$v_{ss} = v_{ss} / \left(v_{ss} + v_{ss}\right) \quad (37)$$

$$v_{t} = 1 / \left(v_{ss} + v_{ss}\right) \quad (38)$$
2 Implementation with cell models

2.1 The minimal, Workman-lab models

The WL model integrated with the CRN[1] (WL\textsubscript{CRN}) retained the additional components ($I_{NaCa}$, $I_{NaK}$, $I_{CaP}$, $I_{Cab}$) and background currents ($I_{Nab}$) as presented in the original study without modification. Implementation with the Grandi et al. 2011 model [2] (WL\textsubscript{GB}) includes these components as well as the additional inclusion of $I_{Kb}$, $I_{ClCa}$, $I_{Clb}$ from the inherited model. The conductance of these additional currents was reduced in the isolated cell model ($g_{Kb} \times 0.2$, $g_{ClCa}$, $g_{Clb} \times 0.5$ – isolated cell variants only). Furthermore, integration with the Grandi calcium handling system required modifications to maintain calcium homeostasis: the maximal flux rates for the following parameters were adjusted: $J_{leak}$ and $I_{CaP} \times 0.3$; $I_{NCX} \times 0.64$. This was performed for both the novel and modified cell models, isolated- and intact- environments.

2.2 Modified cell models

The modified cell models for the CRN, Grandi and Nygren et al. [3] were created by replacing $I_{Na}$, $I_{to}$, $I_{sus}$, $I_{K1}$ with the novel formulations, and modifying the steady states of the voltage dependence of $I_{CaL}$ to fit the experimental IV relationship and current magnitude of the WL data. The modifications were as follows:

CRN model: 3 mV positive shift in voltage dependence of all functions; gradient parameter of activation gate changed from 7.45 to 7.07; increase in current conductance of 1.725.

Grandi model: 10 mV positive shift in the voltage dependence of all functions; gradient parameter of activation gate changed from 7.2 to 6.84; decrease in current conductance of 0.9.

Nygren model: 4 mV positive shift in the voltage dependence of all functions; gradient parameter of activation gate changed from 5.8 to 6.44; increase in current conductance of 1.28. To maintain calcium homeostasis, it was also necessary to increase $I_{CaP} \times 1.5$ and $I_{Kd}/I_{Ks} \times 5$ and decrease $I_{Cab} \times 0.3$ in the intact variant.
3 Parameters

| Symbol | Parameter                                      | Value |
|--------|-----------------------------------------------|-------|
| $[K^+]_o$ | External potassium concentration (mM)       | 4     |
| $[Na^+]_o$ | External sodium concentration (mM)         | 140   |
| $[Ca^{2+}]_o$ | External calcium concentration (mM)      | 1.8   |
| $g_{Na}$ | Maximal conductance $I_{Na}$ (nS/pF)        | 17.55 |
| $g_{Io}$ | Maximal conductance $I_{Io}$ (nS/pF)        | 0.1028|
| $g_{sus}$ | Maximal conductance $I_{sus}$ (nS/pF)       | 0.0676|
| $p_{CaL}$ | Maximal flux rate $I_{CaL}$ (cm/s) – hAM_WL_CRN | $5.3 \times 10^{-4}$ |
| $p_{CaL}$ | Maximal flux rate $I_{CaL}$ (cm/s) – hAM_WL_GB | $6.4 \times 10^{-4}$ |

C/C++ code available from [https://github.com/michaelcolman/hAM_WL_model](https://github.com/michaelcolman/hAM_WL_model) and [http://physicsoftheheart.com/](http://physicsoftheheart.com/).

4 References

1. Courtemanche M, Ramirez RJ, Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. Am J Physiol. 1998 Jul;275(1 Pt 2):H301-321.

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3. Nygren A, Fiset C, Firek L, Clark JW, Lindblad DS, Clark RB, et al. Mathematical Model of an Adult Human Atrial Cell: The Role of K+ Currents in Repolarization. Circ Res. 1998 Jan 23;82(1):63–81.