Supplementary material: Exponential integrators for a Markov chain model of the fast sodium channel of cardiocytes

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The numeration of equations in this document continues from the main text, and the literature references are to the literature list in the main text, repeated in the end of this document for the reader's convenience.

I. Cell Model Definition

This section contains the definition of the model according to the authors' code [8]. The format of equations and subsections aims to correspond to the papers where those equations were published to facilitate a straightforward comparison. The known differences with the papers are marked by the sign: $^{\#}$. Voltages are measured in mV, time in ms and concentrations in mmol/L.The membrane currents are adjusted to the specific membrane capacitance $C = 1\,\mu\mathrm{F}/\mathrm{cm}^2$[9] and are measured in μA/μF.

Standard ionic concentrations

$$[\mathrm{Na}^+]_o = 140 \quad ^{\#} \tag{20}$$
$$[\mathrm{K}^+]_o = 4.5 \quad ^{\#} \tag{21}$$
$$[\mathrm{Ca}^{2+}]_o = 1.8 \tag{22}$$

which differs from [9] where $[\mathrm{Na}^+]_o = 150$; $[\mathrm{K}^+]_o = 5.4$.

Initial Values of Variables

$$x_{s1} = 0 \quad ^{\#} \tag{23}$$
$$x_{s2} = 0 \quad ^{\#} \tag{24}$$
$$V_m = -95 \tag{25}$$
$$[\mathrm{Ca}^{2+}]_{\mathrm{NSR}} = 1.8 \tag{26}$$
$$[\mathrm{Ca}^{2+}]_{\mathrm{JSR}} = 1.8 \tag{27}$$
$$[\mathrm{Ca}^{2+}]_i = 0.00012 \tag{28}$$
$$b = 0.00141379 \tag{29}$$
$$g = 0.98831 \tag{30}$$
$$d = 6.17507 \times 10^{-6} \tag{31}$$
$$f = 0.999357 \tag{32}$$
$$X_r = 2.14606 \times 10^{-4} \tag{33}$$
$$[\mathrm{Na}^+]_i = 7.9 \quad ^{\#} \tag{34}$$
$$[\mathrm{K}^+]_i = 147.23 \quad ^{\#} \tag{35}$$

which differs from [9] where $[\mathrm{K}^+]_i = 145$; $[\mathrm{Na}^+]_i = 10$, and no initial values were given for x_{s1} and x_{s2}.

Physical Constants

$$R = 8314 \tag{36}$$
$$F = 96485 \tag{37}$$
$$T = 310 \tag{38}$$

Cell geometry

$$
\begin{aligned}
L =& 0.01 && (39)\\
r =& 0.0011 && (40)\\
V_{cell} =& 3.801 \times 10^{-5} && (41)\\
A_{Geo} =& 2\pi r^2 + 2\pi r L && (42)\\
A_{Cap} =& 2A_{Geo} && (43)\\
V_{myo} =& 2.58468 \times 10^{-5} && (44)\\
V_{\mathrm{NSR}} =& 0.0552 V_{cell} && (45)\\
V_{\mathrm{JSR}} =& 0.0048 V_{cell} && (46)
\end{aligned}
$$

Na^+-K^+ *pump :* I_{NaK}

$$
\begin{aligned}
I_{\mathrm{NaK}} =& 1.5 f_{\mathrm{NaK}} \frac{1}{1 + (10/[\mathrm{Na}^+]_i)^{1.5}} \cdot \frac{[\mathrm{K}^+]_o}{[\mathrm{K}^+]_o + 1.5} && (47)\\
f_{\mathrm{NaK}} =& \frac{1}{1 + 0.1245 \exp\left(-0.1 \cdot \frac{V_m F}{RT}\right) + 0.0365 \sigma \exp((-V_m F)/(RT))} && (48)\\
\sigma =& \frac{1}{7} \exp\left(\frac{[\mathrm{Na}^+]_o}{67.3}\right) - 1 && (49)
\end{aligned}
$$

which is identical to [9]

$I_{\mathrm{K}s}$, the Slow Component of the Delayed Rectifier K^+ Current

$$
\begin{aligned}
I_{\mathrm{K}s} =& \bar{G}_{\mathrm{K}s} x_{s1} x_{s2} (V_m - E_{\mathrm{K}s}) && (50)\\
E_{\mathrm{K}s} =& (RT/F) \log((4.5 + P_{\mathrm{NaK}} 150)/([\mathrm{K}^+]_i + P_{\mathrm{NaK}} [\mathrm{Na}^+]_o)) \quad \# && (51)\\
P_{\mathrm{NaK}} =& 0.01833 && (52)\\
\bar{G}_{\mathrm{K}s} =& (0.433(1 + 0.6/(1 + (0.000038/[\mathrm{Ca}^{2+}]_i)^{1.4}))) \cdot 0.615 \quad \# && (53)\\
x_{s1\infty} =& 1/(1 + \exp(-(V_m - 1.5)/16.7)) && (54)\\
x_{s2\infty} =& x_{s1\infty} && (55)\\
\tau_{xs1} =& \left(0.0000719 \frac{V_m + 30}{1 - \exp(-0.148(V_m + 30))} + 0.000131 \frac{V_m + 30}{\exp(0.0687(V_m + 30)) - 1}\right)^{-1} && (56)\\
\tau_{xs2} =& 4\tau_{xs1} && (57)
\end{aligned}
$$

The definition of $E_{\mathrm{K}s}$ in equation (51) differs from [11] by the hard-coded term for the $[\mathrm{K}^+]_o = 4.5$ and $[\mathrm{Na}^+]_o = 150$ rather than values defined by equations (20,21) where $[\mathrm{K}^+]_o = 4.5$ and $[\mathrm{Na}^+]_o = 140$ are parameters.

The definition of $\bar{G}_{\mathrm{K}s}$ in equation (53) is multiplied by 0.615 "to simulate the intramural heterogeneity", which is slightly different from the factor 0.652 used in Viswanathan et al. (1999) [11] to simulate epicardial cell.

Otherwise the $I_{\mathrm{K}s}$ definition is identical to [11].

$$
\begin{aligned}
\frac{\mathrm{d}x_{s1}}{\mathrm{d}t} =& \frac{x_{s1\infty} - x_{s1}}{\tau_{xs1}} && (58)\\
\frac{\mathrm{d}x_{s2}}{\mathrm{d}t} =& \frac{x_{s2\infty} - x_{s2}}{\tau_{xs2}} && (59)
\end{aligned}
$$

$I_{\mathrm{K}r}$, the Fast Component of the Delayed Rectifier K^+ Current

$$
\begin{aligned}
I_{\mathrm{K}r} =& \bar{G}_{\mathrm{K}r} X_r R_{\mathrm{K}r} (V_m - E_{\mathrm{K}r}) && (60)\\
\bar{G}_{\mathrm{K}r} =& 0.02614 \sqrt{[\mathrm{K}^+]_o/5.4} && (61)\\
X_{r\infty} =& 1/(1 + \exp(-(V_m + 21.5)/7.5)) && (62)
\end{aligned}
$$

$$R_{\mathrm{K}r} = 1/(1+\exp((V_m+9)/22.4)) \quad (63)$$
$$E_{\mathrm{K}r} = ((RT)/F)\log([\mathrm{K}^+]_o/[\mathrm{K}^+]_i) \quad (64)$$
$$\tau_{xr} = \left(0.00138\frac{V_m+14.2}{1-\exp(-0.123(V_m+14.2))}+0.00061\frac{V_m+38.9}{\exp(0.145(V_m+38.9))-1}\right)^{-1} \quad (65)$$

which is identical to [10]. The original notation for $R_{\mathrm{K}r}$ was R; we use R for the gas constant in this section, and for one of the state occupancies of the Markov Chain model elsewhere in the rest of the paper.

$$\frac{\mathrm{d}X_r}{\mathrm{d}t} = \frac{X_{r\infty}-X_r}{\tau_{xr}} \quad (66)$$

Time-independent K^+ *current:* I_{K1}

$$I_{\mathrm{K1}} = \bar{G}_{\mathrm{K1}}\mathrm{K1}_\infty(V_m-E_{\mathrm{K1}}) \quad (67)$$
$$E_{\mathrm{K1}} = (RT/F)\log([\mathrm{K}^+]_o/[\mathrm{K}^+]_i) \quad (68)$$
$$\bar{G}_{\mathrm{K1}} = 0.75\cdot\sqrt{([\mathrm{K}^+]_o/5.4)} \quad (69)$$
$$\alpha_{\mathrm{K1}} = 1.02/(1+\exp(0.2385(V_m-E_{\mathrm{K1}}-59.215))) \quad (70)$$
$$\beta_{\mathrm{K1}} = \frac{0.49124\exp(0.08032(V_m-E_{\mathrm{K1}}+5.476))+\exp(0.06175(V_m-E_{\mathrm{K1}}-594.31))}{1+\exp(-0.5143(V_m-E_{\mathrm{K1}}+4.753))} \quad (71)$$

which is identical to [9].

$$\mathrm{K1}_\infty = \alpha_{\mathrm{K1}}/(\alpha_{\mathrm{K1}}+\beta_{\mathrm{K1}}) \quad (72)$$
$$(73)$$

Plateau K^+ *current:* $I_{\mathrm{K}p}$

$$I_{\mathrm{K}p} = 0.00552K_p(V_m-E_{\mathrm{K1}}) \quad (74)$$
$$K_p = 1/(1+\exp((7.488-V_m)/5.98)) \quad (75)$$

equivalent to [9] with an update from [10].

$$I_{\mathrm{K}} = I_{\mathrm{K1}}+I_{\mathrm{K}p} \quad (76)$$

Currents through the L-type Ca^{+2} *channel* $I_{\mathrm{Ca}L}$

$$I_{\mathrm{Ca}L} = I_{\mathrm{Ca}}+I_{\mathrm{CaK}}+I_{\mathrm{CaNa}} \quad (77)$$
$$I_{\mathrm{Ca}} = dff_{\mathrm{Ca}}\bar{I}_{\mathrm{Ca}} \quad (78)$$
$$I_{\mathrm{CaK}} = dff_{\mathrm{Ca}}\bar{I}_{\mathrm{CaK}} \quad (79)$$
$$I_{\mathrm{CaNa}} = dff_{\mathrm{Ca}}\bar{I}_{\mathrm{CaNa}} \quad (80)$$
$$\bar{I}_{\mathrm{Ca}} = P_{\mathrm{Ca}}z_{\mathrm{Ca}}^2\frac{(V_mF^2)}{RT}\frac{\gamma_{\mathrm{Ca}i}[\mathrm{Ca}^{2+}]_i\exp((z_{\mathrm{Ca}}V_mF)/(RT))-\gamma_{\mathrm{Ca}o}[\mathrm{Ca}^{2+}]_o}{\exp((z_{\mathrm{Ca}}V_mF)/(RT))-1} \quad (81)$$
$$\bar{I}_{\mathrm{CaNa}} = P_{\mathrm{Na}}z_{\mathrm{Na}}^2\frac{(V_mF^2)}{RT}\frac{\gamma_{\mathrm{Na}i}[\mathrm{Na}^+]_i\exp((z_{\mathrm{Na}}V_mF)/(RT))-\gamma_{\mathrm{Na}o}[\mathrm{Na}^+]_o}{\exp((z_{\mathrm{Na}}V_mF)/(RT))-1} \quad (82)$$
$$\bar{I}_{\mathrm{CaK}} = P_{\mathrm{K}}z_{\mathrm{K}}^2\frac{(V_mF^2)}{RT}\frac{\gamma_{\mathrm{K}i}[\mathrm{K}^+]_i\exp((z_{\mathrm{K}}V_mF)/(RT))-\gamma_{\mathrm{K}o}[\mathrm{K}^+]_o}{\exp((z_{\mathrm{K}}V_mF)/(RT))-1} \quad (83)$$
$$P_{\mathrm{Ca}} = 5.4\times10^{-4} \qquad \gamma_{\mathrm{Ca}i}=1 \qquad \gamma_{\mathrm{Ca}o}=0.341 \quad (84)$$
$$P_{\mathrm{Na}} = 6.75\times10^{-7} \qquad \gamma_{\mathrm{Na}i}=0.75 \qquad \gamma_{\mathrm{Na}o}=0.75 \quad (85)$$
$$P_{\mathrm{K}} = 1.93\times10^{-7} \qquad \gamma_{\mathrm{K}i}=0.75 \qquad \gamma_{\mathrm{K}o}=0.75 \quad (86)$$
$$f_{\mathrm{Ca}} = 1/(1+[\mathrm{Ca}^{2+}]_i/K_{m\mathrm{Ca}}) \quad (87)$$
$$K_{m\mathrm{Ca}} = 0.0006 \quad (88)$$

$$d_\infty = 1/(1+\exp(-(V_m+10)/6.24)) \tag{89}$$
$$\tau_d = d_\infty(1-\exp(-(V_m+10)/6.24))/(0.035(V_m+10)) \tag{90}$$
$$f_\infty = (1/(1+\exp((V_m+32)/8))) + (0.6/(1+\exp((50-V_m)/20))) \quad \# \tag{91}$$
$$\tau_f = 1/(0.0197\exp(-(0.0337(V_m+10)^2)) + 0.02) \tag{92}$$

Equation (91) differs from [9] which has 8.6 rather than 8 in the denominator of the argument of the first exponential. Otherwise, these equations are exactly the same as in [9].

$$z_{\mathrm{Na}} = 1 \tag{93}$$
$$z_{\mathrm{K}} = 1 \tag{94}$$
$$z_{\mathrm{Ca}} = 2 \tag{95}$$
$$\frac{\mathrm{d}d}{\mathrm{d}t} = \frac{d_\infty - d}{\tau_d} \tag{96}$$
$$\frac{\mathrm{d}f}{\mathrm{d}t} = \frac{f_\infty - f}{\tau_f} \tag{97}$$

Ca^{2+} *Current Through T-Type* Ca^{2+} *Channels* $I_{\mathrm{Ca}(T)}$

$$I_{\mathrm{Ca}(T)} = \bar{G}_{\mathrm{Ca}(T)} b^2 g(V_m - E_{\mathrm{Ca}}) \tag{98}$$
$$\bar{G}_{\mathrm{Ca}(T)} = 0.05 \tag{99}$$
$$b_\infty = 1/(1+\exp(-(V_m+14)/10.8)) \tag{100}$$
$$g_\infty = 1/(1+\exp((V_m+60)/5.6)) \tag{101}$$
$$E_{\mathrm{Ca}} = (RT/(2F))\,\log([\mathrm{Ca}^{2+}]_o/[\mathrm{Ca}^{2+}]_i) \tag{102}$$
$$\tau_b = 3.7 + 6.1/(1+\exp((V_m+25)/4.5)) \tag{103}$$
$$\tau_g = -0.875V_m + 12 \text{ for: } V_m \le 0\text{; and } \tau_g = 12 \text{ for: } V_m > 0 \tag{104}$$

which correspond exactly to [10].

$$\frac{\mathrm{d}b}{\mathrm{d}t} = \frac{b_\infty - b}{\tau_b} \tag{105}$$
$$\frac{\mathrm{d}g}{\mathrm{d}t} = \frac{g_\infty - g}{\tau_g} \tag{106}$$

Na^+-Ca^+ *exchanger:* I_{NaCa}

$$I_{\mathrm{NaCa}} = \frac{2.5\times10^{-4}\exp((\eta-1)V_m\frac{F}{RT})(\exp(V_m\frac{F}{RT})[\mathrm{Na}^+]_i^3[\mathrm{Ca}^{2+}]_o - [\mathrm{Na}^+]_o^3[\mathrm{Ca}^{2+}]_i)}{1+1\times10^{-4}\exp((\eta-1)V_m\frac{F}{RT})(\exp(V_m\frac{F}{RT})[\mathrm{Na}^+]_i^3[\mathrm{Ca}^{2+}]_o + [\mathrm{Na}^+]_o^3[\mathrm{Ca}^{2+}]_i)} \quad \# \tag{107}$$
$$\eta = 0.15 \quad \# \tag{108}$$

Here I_{NaCa} depends on external $[\mathrm{Ca}^{2+}]_o, [\mathrm{Na}^+]_o$ as well as internal $[\mathrm{Na}^+]_i, [\mathrm{Ca}^{2+}]_i$ concentrations, which is different from [9] where it depended only on external concentrations $[\mathrm{Ca}^{2+}]_o, [\mathrm{Na}^+]_o$. The variable $\eta = 0.35$ in [9].

Nonspecific Ca^{2+}*-activated current:* $I_{ns(\mathrm{Ca})}$

$$\bar{I}_{ns\mathrm{K}} = 1.75\times10^{-7}\frac{V_m F^2}{RT}\cdot\frac{0.75[\mathrm{K}^+]_i\exp((V_mF)/(RT)) - 0.75[\mathrm{K}^+]_o}{\exp(V_mF/(RT))-1} \tag{109}$$
$$I_{ns\mathrm{K}} = \bar{I}_{ns\mathrm{K}}\frac{1}{1+(0.0012/[\mathrm{Ca}^{2+}]_i)^3} \tag{110}$$
$$\bar{I}_{ns\mathrm{Na}} = 1.75\times10^{-7}\frac{V_m F^2}{RT}\cdot\frac{0.75[\mathrm{Na}^+]_i\exp((V_mF)/(RT)) - 0.75[\mathrm{Na}^+]_o}{\exp(V_mF/(RT))-1} \tag{111}$$
$$I_{ns\mathrm{Na}} = \bar{I}_{ns\mathrm{Na}}\frac{1}{1+(0.0012/[\mathrm{Ca}^{2+}]_i)^3} \tag{112}$$
$$I_{ns(\mathrm{Ca})} = I_{ns\mathrm{K}} + I_{ns\mathrm{Na}} \tag{113}$$
$$P_{ns(\mathrm{Ca})} = 1.75\times10^{-7} \tag{114}$$

This is almost identical to [9] except the latter also made a definition for $E_{ns(\mathrm{Ca})}$ which however was not used.

Sarcolemmal Ca^{+2} *pump:* $I_{p(\mathrm{Ca})}$

$$I_{p(\mathrm{Ca})} = 1.15 \frac{[\mathrm{Ca}^{2+}]_i}{0.0005 + [\mathrm{Ca}^{2+}]_i} \tag{115}$$

identical to [9].

Ca^{+2} *background current:* $I_{\mathrm{Ca}b}$

$$I_{\mathrm{Ca}b} = 0.003016(V_m - E_{\mathrm{Ca}}) \tag{116}$$
$$E_{\mathrm{Ca}} = RT/(2F)\log([\mathrm{Ca}^{2+}]_o/[\mathrm{Ca}^{2+}]_i) \tag{117}$$

identical to [9].

Na^{+} *background current:* $I_{\mathrm{Na}b}$

$$E_{\mathrm{Na}} = ((RT)/F)\log([\mathrm{Na}^{+}]_o/[\mathrm{Na}^{+}]_i) \tag{118}$$
$$I_{\mathrm{Na}b} = 0.00141(V_m - E_{\mathrm{Na}}) \tag{119}$$

identical to [9].

Ca^{2+} *uptake and leakage of NSR:* I_{up} *and* I_{leak}

$$I_{up} = 0.00875[\mathrm{Ca}^{2+}]_i/([\mathrm{Ca}^{2+}]_i + 0.00092) \quad \# \tag{120}$$
$$K_{leak} = 0.005/15 \tag{121}$$
$$I_{leak} = K_{leak}[\mathrm{Ca}^{2+}]_{\mathrm{NSR}} \tag{122}$$

The definition of I_{up} in [9] is ambiguous. This version is consistent with one possible understanding.

Ca^{+2} *Fluxes in NSR*

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{\mathrm{NSR}}}{\mathrm{d}t} = (I_{up} - I_{leak} - I_{tr}V_{\mathrm{JSR}}/V_{\mathrm{NSR}}) \tag{123}$$

Ca^{2+} *Fluxes in Myoplasm*

$$I_{t\mathrm{Ca}} = I_{\mathrm{Ca}} + I_{\mathrm{Ca}b} + I_{p(\mathrm{Ca})} - 2I_{\mathrm{NaCa}} + I_{\mathrm{Ca}(T)} \tag{124}$$
$$\Delta[\mathrm{Ca}^{2+}]_i = -\Delta t(((I_{t\mathrm{Ca}}A_{Cap})/(V_{myo}2F)) + ((I_{up} - I_{leak})V_{\mathrm{NSR}}/V_{myo}) - (I_{rel}V_{\mathrm{JSR}}/V_{myo})) \tag{125}$$
$$[\mathrm{Ca}^{2+}]_{ion} = \mathrm{TRPN} + \mathrm{CMDN} + \Delta[\mathrm{Ca}^{2+}]_i + [\mathrm{Ca}^{2+}]_i \tag{126}$$
$$B = 0.05 + 0.07 - [\mathrm{Ca}^{2+}]_{ion} + 0.0005 + 0.00238 \tag{127}$$
$$C = (0.00238 \cdot 0.0005) - ([\mathrm{Ca}^{2+}]_{ion}(0.0005 + 0.00238)) + (0.07 \cdot 0.00238) + (0.05 \cdot 0.0005) \tag{128}$$
$$D = -0.0005 \cdot 0.00238[\mathrm{Ca}^{2+}]_{ion} \tag{129}$$
$$F_{ab} = \sqrt{(B^2 - 3C)} \tag{130}$$
$$[\mathrm{Ca}^{2+}]_i = 1.5F_{ab}\cos(\arccos((9BC - 2B^3 - 27D)/(2(B^2 - 3C)^{1.5}))/3) - (B/3) \tag{131}$$

This definition merely summarises computations that are done in the code, which *de facto* describe a time-stepping algorithm for a system of a differential equation and a finite constraint, rather than the equation and the constraint themselves, hence the time step Δt is present in (125). Any attempts of higher-order numerical approximations would have to take this into account. The explicit solution of the finite constraint given by the cubic formula (131) follows [10] whereas [9] used Steffensen's iterations for that purpose.

Ca^{2+} Fluxes in JSR

$$\Delta[\mathrm{Ca}^{2+}]_{\mathrm{JSR}} = \Delta t(I_{tr} - I_{rel}) \tag{132}$$
$$b_{\mathrm{JSR}} = 10 - \mathrm{CSQN} - \Delta[\mathrm{Ca}^{2+}]_{\mathrm{JSR}} - [\mathrm{Ca}^{2+}]_{\mathrm{JSR}} + 0.8 \tag{133}$$
$$c_{\mathrm{JSR}} = 0.8(\mathrm{CSQN} + \Delta[\mathrm{Ca}^{2+}]_{\mathrm{JSR}} + [\mathrm{Ca}^{2+}]_{\mathrm{JSR}}) \tag{134}$$
$$[\mathrm{Ca}^{2+}]_{\mathrm{JSR}} = (\sqrt{(b_{\mathrm{JSR}}^2 + 4c_{\mathrm{JSR}})} - b_{\mathrm{JSR}})/2 \tag{135}$$

Ditto: Δt is present in (132).

Sodium Ion Fluxes

$$I_{t\mathrm{Na}} = I_{\mathrm{Na}} + I_{\mathrm{Na}b} + I_{\mathrm{CaNa}} + I_{ns\mathrm{Na}} + 3I_{\mathrm{NaK}} + 3I_{\mathrm{NaCa}} \tag{136}$$
$$\frac{\mathrm{d}[\mathrm{Na}^+]_i}{\mathrm{d}t} = -(I_{t\mathrm{Na}}A_{Cap})/(V_{myo}F) \tag{137}$$

$[\mathrm{Na}^+]_i$ is constant in [9], [10], [11].

Potassium Ion Fluxes

$$I_{t\mathrm{K}} = I_{\mathrm{K}r} + I_{\mathrm{K}s} + I_{\mathrm{K}} + I_{\mathrm{CaK}} + I_{ns\mathrm{K}} - 2I_{\mathrm{NaK}} + I_{to} + I_{st} \tag{138}$$
$$\frac{\mathrm{d}[\mathrm{K}^+]_i}{\mathrm{d}t} = -(I_{t\mathrm{K}}A_{Cap})/(V_{myo}F) \tag{139}$$

$[\mathrm{K}^+]_i$ is constant in [9], [10], [11].

Ca^{2+} buffers in the myoplasm

$$\mathrm{TRPN} = 0.07[\mathrm{Ca}^{2+}]_i/([\mathrm{Ca}^{2+}]_i + 0.0005) \tag{140}$$
$$\mathrm{CMDN} = 0.05[\mathrm{Ca}^{2+}]_i/([\mathrm{Ca}^{2+}]_i + 0.00238) \tag{141}$$

identical to [9].

Ca^{2+} buffer in JSR and SCQN

$$\mathrm{CSQN} = 10([\mathrm{Ca}^{2+}]_{\mathrm{JSR}}/([\mathrm{Ca}^{2+}]_{\mathrm{JSR}} + 0.8)) \tag{142}$$
$$\tag{143}$$

identical to [9].

CICR From Junctional SR (JSR)

$$I_{rel} = G_{rel}\mathrm{ryr}_{open}\mathrm{ryr}_{close}([\mathrm{Ca}^{2+}]_{\mathrm{JSR}} - [\mathrm{Ca}^{2+}]_i) \tag{144}$$
$$G_{rel} = 150/(1 + \exp(I_{t\mathrm{Ca}} + 5)/0.9) \quad \# \tag{145}$$
$$\mathrm{ryr}_{open} = 1/(1 + \exp((-t_c + 4)/0.5)) \quad \# \tag{146}$$
$$\mathrm{ryr}_{close} = 1 - (1/(1 + \exp((-t_c + 4)/0.5))) \quad \# \tag{147}$$

Here is another deviation of the model description from the standard form of a system of ODEs, and this also would have to be taken into account in any attempts of higher-order schemes. Variables ryr_{close} and $\mathrm{ryr}_{open} = 1 - \mathrm{ryr}_{close}$ ensure that the calcium release channel is open at a fuzzy time interval around 4 ms after the steepest point of the upstroke of the action potential. This is done using an additional time variable t_c which is linked to the t, that is $\mathrm{d}t_c/\mathrm{d}t = 1$ most of the time, except t_c is reset to zero each time the $\frac{\mathrm{d}V_m}{\mathrm{d}t}$ reaches a *significant* local maximum, "significant" meaning $\frac{\mathrm{d}V_m}{\mathrm{d}t} > 1\,\mathrm{mV/ms}$. In [9], G_{rel} is defined differently from (145) and calcium release proceeds with a different dynamics from (146,147), e.g. it starts sharply 2 ms after the the time of the maximum $\frac{\mathrm{d}V_m}{\mathrm{d}t}$.

Translocation of Ca^{2+} *ions from NSR to JSR:* I_{tr}

$$I_{tr} = ([\mathrm{Ca}^{2+}]_{\mathrm{NSR}} - [\mathrm{Ca}^{2+}]_{\mathrm{JSR}})/180 \tag{148}$$

identical to [9].

Total time-independent current: I_v

$$I_v = I_{\mathrm{Na}b} + I_{\mathrm{NaK}} + I_{p(\mathrm{Ca})} + I_{\mathrm{K}p} + I_{\mathrm{Ca}b} + I_{\mathrm{K1}} \tag{149}$$

identical to [9].

Total Current

$$\begin{aligned} I_t = & I_{\mathrm{K}r} + I_{\mathrm{K}s} + I_{\mathrm{K}} + I_{\mathrm{CaK}} + I_{ns\mathrm{K}} - 2I_{\mathrm{NaK}} + I_{\mathrm{Na}} + I_{\mathrm{Na}b} + I_{\mathrm{CaNa}} + I_{ns\mathrm{Na}} + 3I_{\mathrm{NaK}} + \\ & 3I_{\mathrm{NaCa}} + I_{\mathrm{Ca}} + I_{\mathrm{Ca}b} + I_{p(\mathrm{Ca})} - 2I_{\mathrm{NaCa}} + I_{\mathrm{Ca}(T)} \end{aligned} \tag{150}$$

Membrane Potential

$$\frac{\mathrm{d}V_m}{\mathrm{d}t} = -I_t. \tag{151}$$

II. I_{Na} Markov Chain Model Definition

Up to the choice of notation, we use the model described in [8]. The fast sodium current is defined by

$$I_{\mathrm{Na}} = G_{\mathrm{Na}}(V_m - E_{\mathrm{Na}})O, \tag{152}$$

where the channel open probability O is defined by the system of ODEs

$$\frac{\mathrm{d}O}{\mathrm{d}t} = \alpha_{PO}P + \alpha_{UO}U - (\alpha_{OP} + \alpha_{OU})O \tag{153}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \alpha_{QP}Q + \alpha_{UP}U + \alpha_{OP}O - (\alpha_{PQ} + \alpha_{PU} + \alpha_{PO})P \tag{154}$$

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \alpha_{RQ}R + \alpha_{TQ}T + \alpha_{PQ}P - (\alpha_{QR} + \alpha_{QT} + \alpha_{QP})Q \tag{155}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \alpha_{SR}S + \alpha_{QR}Q - (\alpha_{RS} + \alpha_{RQ})R \tag{156}$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \alpha_{TS}T + \alpha_{RS}R - (\alpha_{ST} + \alpha_{SR})S \tag{157}$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \alpha_{QT}Q + \alpha_{ST}S + \alpha_{UT}U - (\alpha_{TQ} + \alpha_{TS} + \alpha_{TU})T \tag{158}$$

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \alpha_{TU}T + \alpha_{PU}P + \alpha_{VU}V + \alpha_{OU}O - (\alpha_{UT} + \alpha_{UP} + \alpha_{UO} + \alpha_{UV})U \tag{159}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = \alpha_{UV}U + \alpha_{WV}W - (\alpha_{VU} + \alpha_{VW})V \tag{160}$$

$$\frac{\mathrm{d}W}{\mathrm{d}t} = \alpha_{VW}V - \alpha_{WV}W \tag{161}$$

with the transition rates defined by

$$\begin{aligned} \alpha_{RQ} = \alpha_{ST} = \alpha_{11} = & \frac{3.802}{0.1027\,\mathrm{e}^{-V_m/17.0} + 0.20\,\mathrm{e}^{-V_m/150}} \\ \alpha_{QP} = \alpha_{TU} = \alpha_{12} = & \frac{3.802}{0.1027\,\mathrm{e}^{-V_m/15.0} + 0.23\,\mathrm{e}^{-V_m/150}} \\ \alpha_{PO} = \alpha_{13} = & \frac{3.802}{0.1027\,\mathrm{e}^{-V_m/12.0} + 0.25\,\mathrm{e}^{-V_m/150}} \\ \alpha_{QR} = \alpha_{TS} = \beta_{11} = & 0.1917\,\mathrm{e}^{-V_m/20.3} \\ \alpha_{PQ} = \alpha_{UT} = \beta_{12} = & 0.20\,\mathrm{e}^{-(V_m-5)/20.3} \end{aligned}$$

$$\begin{aligned}
\alpha_{OP} = \beta_{13} =& 0.22\,\mathrm{e}^{-(V_m-10)/20.3}\\
\alpha_{UP} = \alpha_{TQ} = \alpha_{SR} = \alpha_3 =& 3.7933 \cdot 10^{-7}\,\mathrm{e}^{-V_m/7.7}\\
\alpha_{PU} = \alpha_{QT} = \alpha_{RS} = \beta_3 =& 8.4 \cdot 10^{-3} + 2 \cdot 10^{-5} V_m\\
\alpha_{OU} = \alpha_2 =& 9.178\,\mathrm{e}^{V_m/29.68}\\
\alpha_{UO} = \beta_2 =& \frac{\alpha_{13}\alpha_2\alpha_3}{\beta_{13}\beta_3}\\
\alpha_{UV} = \alpha_4 =& \alpha_2/100\\
\alpha_{VU} = \beta_4 =& \alpha_3\\
\alpha_{VW} = \alpha_5 =& \alpha_2/(9.5 \cdot 10^4)\\
\alpha_{WV} = \beta_5 =& \alpha_3/50
\end{aligned}$$

III. Details of the hybrid Operator Splitting method

In the hybrid method we use operator splitting. The system of equations (153)–(161) is considered as an ODE

$$\frac{\mathrm{d}\vec{u}}{\mathrm{d}t} = \boldsymbol{A}(V_m(t))\vec{u}, \tag{9}$$

for the vector-function $\vec{u} = (O, P, Q, R, S, T, U, V, W)^\top = \vec{u}(t)$, and the transition matrix is split into the sum

$$\boldsymbol{A} = \boldsymbol{A}_0 + \boldsymbol{A}_1 + \boldsymbol{A}_2 \tag{162}$$

of the matrix $\boldsymbol{A}_0$ of transition rates that are fast at high values of V_m,

$$\boldsymbol{A}_0 = \begin{bmatrix}
-\alpha_{OU} & \alpha_{PO} & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & -\alpha_{PO} & \alpha_{QP} & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & -\alpha_{QP} & \alpha_{RQ} & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & -\alpha_{RQ} & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & -\alpha_{ST} & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & \alpha_{ST} & -\alpha_{TU} & 0 & 0 & 0\\
\alpha_{OU} & 0 & 0 & 0 & 0 & \alpha_{TU} & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}, \tag{163}$$

the matrix $\boldsymbol{A}_1$ of transition rates that are fast at low values of V_m,

$$\boldsymbol{A}_1 = \begin{bmatrix}
-\alpha_{OP} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
\alpha_{OP} & -\alpha_{PQ} & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & \alpha_{PQ} & -\alpha_{QR} & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & \alpha_{QR} & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & \alpha_{TS} & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & -\alpha_{TS} & \alpha_{UT} & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & -\alpha_{UT} & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}, \tag{164}$$

and the matrix $\boldsymbol{A}_2$ of uniformly slow transition rates,

$$\boldsymbol{A}_2 = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & \alpha_{UO} & 0 & 0\\
0 & -\alpha_{PU} & 0 & 0 & 0 & 0 & \alpha_{UP} & 0 & 0\\
0 & 0 & -\alpha_{QT} & 0 & 0 & \alpha_{TQ} & 0 & 0 & 0\\
0 & 0 & 0 & -\alpha_{RS} & \alpha_{SR} & 0 & 0 & 0 & 0\\
0 & 0 & 0 & \alpha_{RS} & -\alpha_{SR} & 0 & 0 & 0 & 0\\
0 & 0 & \alpha_{QT} & 0 & 0 & -\alpha_{TQ} & 0 & 0 & 0\\
0 & \alpha_{PU} & 0 & 0 & 0 & 0 & -(\alpha_{UP} + \alpha_{UO} + \alpha_{UV}) & \alpha_{VU} & 0\\
0 & 0 & 0 & 0 & 0 & 0 & \alpha_{UV} & -(\alpha_{VU} + \alpha_{VW}) & \alpha_{WV}\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_{VW} & -\alpha_{WV}
\end{bmatrix}. \tag{165}$$

Every timestep is then done in three substeps, each using one of the three matrices $\boldsymbol{A}_m$, $m = 0, 1, 2$:

$$\vec{u}_{n+1/3} = \exp(\Delta t \boldsymbol{A}_0(V_m(t_n)))\,\vec{u}_n, \tag{17}$$

$$\vec{u}_{n+2/3} = \exp(\Delta t \boldsymbol{A}_1(V_m(t_n)))\,\vec{u}_{n+1/3}, \tag{18}$$

$$\vec{u}_{n+1} = \vec{u}_{n+2/3} + \Delta t \boldsymbol{A}_2(V_m(t_n))\, \vec{u}_{n+2/3}. \tag{19}$$

Note that V_m in all cases is evaluated at $t = t_n$, in which we simply follow the original Rush-Larsen idea of "freezing" V_m for the duration of the time step. The matrix exponentials in (17) and (18) can be understood in terms of matrix Taylor series [7], or the product of the matrix exponential by the corresponding vector $\vec{u}$ can be understood just as the solutions of an initial-value problem for the corresponding system of ODEs with constant coefficients. The mapping (17) is calculated by solving the following initial-value problem, defined by the matrix $\boldsymbol{A}_0$ (163),

$$\frac{\mathrm{d}O}{\mathrm{d}t} = -\alpha_{OU} O + \alpha_{PO} P, \qquad O(0) = O_n, \tag{166}$$
$$\frac{\mathrm{d}P}{\mathrm{d}t} = -\alpha_{PO} P + \alpha_{QP} Q, \qquad P(0) = P_n, \tag{167}$$
$$\frac{\mathrm{d}Q}{\mathrm{d}t} = -\alpha_{QP} Q + \alpha_{RQ} R, \qquad Q(0) = Q_n, \tag{168}$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = -\alpha_{RQ} R, \qquad R(0) = R_n, \tag{169}$$
$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha_{ST} S, \qquad S(0) = S_n, \tag{170}$$
$$\frac{\mathrm{d}T}{\mathrm{d}t} = \alpha_{ST} S - \alpha_{TU} T, \qquad T(0) = T_n, \tag{171}$$
$$\frac{\mathrm{d}U}{\mathrm{d}t} = \alpha_{OU} O + \alpha_{TU} T, \qquad U(0) = U_n, \tag{172}$$
$$\frac{\mathrm{d}V}{\mathrm{d}t} = 0, \qquad V(0) = V_n, \tag{173}$$
$$\frac{\mathrm{d}W}{\mathrm{d}t} = 0, \qquad W(0) = W_n, \tag{174}$$

and then evaluating the result at $t = \Delta t$ to give $O_{n+1/3}, \ldots, W_{n+1/3}$. We note now that equations (169) and (170) are decoupled and we can solve them to get

$$R(t) = R_n\, \mathrm{e}^{-\alpha_{RQ} t}, \tag{175}$$
$$S(t) = S_n\, \mathrm{e}^{-\alpha_{ST} t}. \tag{176}$$

We then substitute (175) into (168) to obtain a closed initial-value problem for $Q(t)$,

$$\frac{\mathrm{d}Q}{\mathrm{d}t} + \alpha_{QP} Q = R_n \alpha_{RQ}\, \mathrm{e}^{-\alpha_{RQ} t}, \quad Q(0) = Q_n, \tag{177}$$

the solution of which is

$$Q(t) = Q_n\, \mathrm{e}^{-\alpha_{QP} t} - R_n \frac{\alpha_{RQ}(\,\mathrm{e}^{-\alpha_{QP} t} - \,\mathrm{e}^{-\alpha_{RQ} t})}{\alpha_{QP} - \alpha_{RQ}}. \tag{178}$$

(179)

Similarly, we substitute (176) into (171) to obtain

$$T(t) = T_n\, \mathrm{e}^{-\alpha_{TU} t} - S_n \frac{\alpha_{ST}(\,\mathrm{e}^{-\alpha_{TU} t} - \,\mathrm{e}^{-\alpha_{ST} t})}{\alpha_{TU} - \alpha_{ST}}. \tag{180}$$

(181)

We then proceed in the same manner, by substituting the obtained solution (178) for $Q(t)$ into (167) to obtain $P(t)$, and the solution (180) for $T(t)$ into (172) to obtain $U(t)$, and finally the found solution for $P(t)$ into (166) to obtain $O(t)$. With the obvious solutions to (173) and (174), the result of all these steps is mapping

$$O_{n+1/3} = \mu_{OU} O_n + K_{PO} P_n + K_{QO} Q_n + K_{RO} R_n, \tag{182}$$
$$P_{n+1/3} = \mu_{PO} P_n + K_{QP} Q_n + K_{RP} R_n, \tag{183}$$
$$Q_{n+1/3} = \mu_{QP} Q_n + K_{RQ} R_n, \tag{184}$$
$$R_{n+1/3} = \mu_{RQ} R_n, \tag{185}$$
$$S_{n+1/3} = \mu_{ST} S_n, \tag{186}$$
$$T_{n+1/3} = \mu_{TU} T_n + K_{ST} S_n, \tag{187}$$
$$U_{n+1/3} = U_n + (1 - \mu_{TU}) T_n + K_{SU} S_n + (1 - \mu_{OU}) O_n + K_{PU} P_n + K_{QU} Q_n + K_{RU} R_n, \tag{188}$$
$$V_{n+1/3} = V_n, \tag{189}$$

$$W_{n+1/3} = W_n, \tag{190}$$

where $\mu_{jk} = \mathrm{e}^{-\alpha_{jk}\Delta t}$ and

$$K_{PO} = \frac{\alpha_{PO}(\mu_{PO} - \mu_{OU})}{\alpha_{OU} - \alpha_{PO}}, \tag{191}$$

$$K_{QO} = \frac{\alpha_{PO}\alpha_{QP}(\mu_{QP} - \mu_{OU})}{(\alpha_{PO} - \alpha_{QP})(\alpha_{OU} - \alpha_{QP})} - \frac{\alpha_{PO}\alpha_{QP}(\mu_{PO} - \mu_{OU})}{(\alpha_{PO} - \alpha_{QP})(\alpha_{OU} - \alpha_{PO})}, \tag{192}$$

$$\begin{aligned} K_{RO} = &- \frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{QP} - \mu_{OU})}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{QP})(\alpha_{OU} - \alpha_{QP})} + \frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{PO} - \mu_{OU})}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{QP})(\alpha_{OU} - \alpha_{PO})} +, \\ &+ \frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{RQ} - \mu_{OU})}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{RQ})(\alpha_{OU} - \alpha_{RQ})} - \frac{\alpha_{PO}\alpha_{QP}\alpha_{RQ}(\mu_{PO} - \mu_{OU})}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{RQ})(\alpha_{OU} - \alpha_{PO})}, \end{aligned} \tag{193}$$

$$K_{QP} = \frac{\alpha_{QP}(\mu_{QP} - \mu_{PO})}{\alpha_{PO} - \alpha_{QP}}, \tag{194}$$

$$K_{RP} = - \frac{\alpha_{QP}\alpha_{RQ}(\mu_{QP} - \mu_{PO})}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{QP})} + \frac{\alpha_{QP}\alpha_{RQ}(\mu_{RQ} - \mu_{PO})}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{RQ})}, \tag{195}$$

$$K_{RQ} = - \frac{\alpha_{RQ}(\mu_{QP} - \mu_{RQ})}{\alpha_{QP} - \alpha_{RQ}}, \tag{196}$$

$$K_{ST} = - \frac{\alpha_{ST}(\mu_{TU} - \mu_{ST})}{\alpha_{TU} - \alpha_{ST}}, \tag{197}$$

$$K_{SU} = 1 + \frac{\alpha_{ST}\mu_{TU} - \alpha_{TU}\mu_{ST}}{\alpha_{TU} - \alpha_{ST}}, \tag{198}$$

$$K_{PU} = 1 - \frac{\alpha_{OU}\mu_{PO} - \alpha_{PO}\mu_{OU}}{\alpha_{OU} - \alpha_{PO}}, \tag{199}$$

$$K_{QU} = \frac{\alpha_{PO}}{\alpha_{PO} - \alpha_{QP}} \left(1 - \frac{\alpha_{OU}\mu_{QP} - \alpha_{QP}\mu_{OU}}{\alpha_{OU} - \alpha_{QP}}\right) - \frac{\alpha_{QP}}{\alpha_{PO} - \alpha_{QP}} \left(1 - \frac{\alpha_{OU}\mu_{PO} - \alpha_{PO}\mu_{OU}}{\alpha_{OU} - \alpha_{PO}}\right), \tag{200}$$

$$\begin{aligned} K_{RU} = &- \frac{\alpha_{PO}\alpha_{RQ}}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{QP})} \left(1 - \frac{\alpha_{OU}\mu_{QP} - \alpha_{QP}\mu_{OU}}{\alpha_{OU} - \alpha_{QP}}\right) + \\ &+ \frac{\alpha_{QP}\alpha_{RQ}}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{QP})} \left(1 - \frac{\alpha_{OU}\mu_{PO} - \alpha_{PO}\mu_{OU}}{\alpha_{OU} - \alpha_{PO}}\right) + \\ &+ \frac{\alpha_{PO}\alpha_{QP}}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{RQ})} \left(1 - \frac{\alpha_{OU}\mu_{RQ} - \alpha_{RQ}\mu_{OU}}{\alpha_{OU} - \alpha_{RQ}}\right) - \\ &- \frac{\alpha_{QP}\alpha_{RQ}}{(\alpha_{QP} - \alpha_{RQ})(\alpha_{PO} - \alpha_{RQ})} \left(1 - \frac{\alpha_{OU}\mu_{PO} - \alpha_{PO}\mu_{OU}}{\alpha_{OU} - \alpha_{PO}}\right). \end{aligned} \tag{201}$$

At the second sub-step, the mapping (18) is calculated by solving the following initial-value problem, defined by the matrix $\boldsymbol{A}_1$ (164),

$$\frac{\mathrm{d}O}{\mathrm{d}t} = -\alpha_{OP}O, \qquad O(0) = O_{n+1/3}, \tag{202}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \alpha_{OP}O - \alpha_{PQ}P, \qquad P(0) = P_{n+1/3}, \tag{203}$$

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \alpha_{PQ}P - \alpha_{QR}Q, \qquad Q(0) = Q_{n+1/3}, \tag{204}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \alpha_{QR}Q, \qquad R(0) = R_{n+1/3}, \tag{205}$$

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \alpha_{TS}T, \qquad S(0) = S_{n+1/3}, \tag{206}$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \alpha_{UT}U - \alpha_{TS}T, \qquad T(0) = T_{n+1/3}, \tag{207}$$

$$\frac{\mathrm{d}U}{\mathrm{d}t} = -\alpha_{UT}U, \qquad U(0) = U_{n+1/3}, \tag{208}$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = 0, \qquad V(0) = V_{n+1/3}, \tag{209}$$

$$\frac{\mathrm{d}W}{\mathrm{d}t} = 0, \qquad W(0) = W_{n+1/3}. \tag{210}$$

Here we proceed similar to the first sub-step. We note that the equations (202) and (208) are decoupled, and solve them to get $O(t)$ and $U(t)$. The result for $O(t)$ is substituted to (203) and the result for $U(t)$ is substituted to (207) to obtain closed initial value problems, which are solved to produce $P(t)$ and $T(t)$. The solution for $P(t)$ is substituted to the (204) to give $Q(t)$. Finally, we substitute the $Q(t)$ into (205) and $T(t)$ to (206) which yield $R(t)$ and $S(t)$ respectively. With the obvious solution to V and W the mapping is as follows:

$$O_{n+2/3} = \mu_{OP} O_{n+1/3}, \tag{211}$$
$$P_{n+2/3} = L_{OP} O_{n+1/3} + \mu_{PQ} P_{n+1/3}, \tag{212}$$
$$Q_{n+2/3} = L_{OQ} O_{n+1/3} + L_{PQ} P_{n+1/3} + \mu_{QR} Q_{n+1/3}, \tag{213}$$
$$R_{n+2/3} = L_{OR} O_{n+1/3} + L_{PR} P_{n+1/3} + (1 - \mu_{QR}) Q_{n+1/3} + R_{n+1/3}, \tag{214}$$
$$S_{n+2/3} = L_{US} U_{n+1/3} + (1 - \mu_{TS}) T_{n+1/3} + S_{n+1/3}, \tag{215}$$
$$T_{n+2/3} = L_{UT} U_{n+1/3} + \mu_{TS} T_{n+1/3}, \tag{216}$$
$$U_{n+2/3} = \mu_{UT} U_{n+1/3}, \tag{217}$$
$$V_{n+2/3} = V_{n+1/3}, \tag{218}$$
$$W_{n+2/3} = W_{n+1/3}, \tag{219}$$

where $\mu_{jk} = \mathrm{e}^{-\alpha_{jk}\Delta t}$ again, and

$$L_{OP} = \frac{\alpha_{OP}(\mu_{OP} - \mu_{PQ})}{\alpha_{PQ} - \alpha_{OP}}, \tag{220}$$
$$L_{OQ} = \frac{\alpha_{PQ}\alpha_{OP}(\mu_{OP} - \mu_{QR})}{(\alpha_{PQ} - \alpha_{OP})(\alpha_{QR} - \alpha_{OP})} - \frac{\alpha_{PQ}\alpha_{OP}(\mu_{PQ} - \mu_{QR})}{(\alpha_{PQ} - \alpha_{OP})(\alpha_{QR} - \alpha_{PQ})}, \tag{221}$$
$$L_{PQ} = \frac{\alpha_{PQ}(\mu_{PQ} - \mu_{QR})}{\alpha_{QR} - \alpha_{PQ}}, \tag{222}$$
$$L_{OR} = 1 + \frac{\alpha_{PQ}(\alpha_{OP}\mu_{QR} - \alpha_{QR}\mu_{OP})}{(\alpha_{PQ} - \alpha_{OP})(\alpha_{QR} - \alpha_{OP})} - \frac{\alpha_{OP}(\alpha_{PQ}\mu_{QR} - \alpha_{QR}\mu_{PQ})}{(\alpha_{PQ} - \alpha_{OP})(\alpha_{QR} - \alpha_{PQ})}, \tag{223}$$
$$L_{PR} = 1 + \frac{\alpha_{PQ}\mu_{QR} - \alpha_{QR}\mu_{PQ}}{\alpha_{QR} - \alpha_{PQ}}, \tag{224}$$
$$L_{US} = 1 + \frac{\alpha_{UT}\mu_{TS} - \alpha_{TS}\mu_{UT}}{\alpha_{TS} - \alpha_{UT}}, \tag{225}$$
$$L_{UT} = \frac{\alpha_{UT}(\mu_{UT} - \mu_{TS})}{\alpha_{TS} - \alpha_{UT}}. \tag{226}$$

The third sub-step mapping (19) is calculated by solving the following initial-value problem, defined by the matrix $\boldsymbol{A}_2$ (165),

$$\frac{\mathrm{d}O}{\mathrm{d}t} = \alpha_{UO} U, \qquad O(0) = O_{n+2/3}, \tag{227}$$
$$\frac{\mathrm{d}P}{\mathrm{d}t} = \alpha_{UP} U - \alpha_{PU} P, \qquad P(0) = P_{n+2/3}, \tag{228}$$
$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \alpha_{TQ} T - \alpha_{QT} Q, \qquad Q(0) = Q_{n+2/3}, \tag{229}$$
$$\frac{\mathrm{d}R}{\mathrm{d}t} = \alpha_{SR} S - \alpha_{RS} R, \qquad R(0) = R_{n+2/3}, \tag{230}$$
$$\frac{\mathrm{d}S}{\mathrm{d}t} = \alpha_{RS} R - \alpha_{SR} S, \qquad S(0) = S_{n+2/3}, \tag{231}$$
$$\frac{\mathrm{d}T}{\mathrm{d}t} = \alpha_{QT} Q - \alpha_{TQ} T, \qquad T(0) = T_{n+2/3}, \tag{232}$$
$$\frac{\mathrm{d}U}{\mathrm{d}t} = \alpha_{PU} P + \alpha_{VU} V - (\alpha_{UP} + \alpha_{UO} + \alpha_{UV}) U, \qquad U(0) = U_{n+2/3}, \tag{233}$$
$$\frac{\mathrm{d}V}{\mathrm{d}t} = \alpha_{UV} U + \alpha_{WV} W - (\alpha_{VU} + \alpha_{VW}) V, \qquad V(0) = V_{n+2/3}, \tag{234}$$
$$\frac{\mathrm{d}W}{\mathrm{d}t} = \alpha_{VW} V - \alpha_{WV} W, \qquad W(0) = W_{n+2/3}. \tag{235}$$

Unlike the previous sub-steps, this system is not solved exactly, but its solution is approximated by the forward Euler method as follows:

$$O_{n+1} = O_{n+2/3} + (\alpha_{UO} U_{n+2/3})\Delta t, \tag{236}$$
$$P_{n+1} = P_{n+2/3} + (\alpha_{UP} U_{n+2/3} - \alpha_{PU} P_{n+2/3})\Delta t, \tag{237}$$
$$Q_{n+1} = Q_{n+2/3} + (\alpha_{TQ} T_{n+2/3} - \alpha_{QT} Q_{n+2/3})\Delta t, \tag{238}$$

$$R_{n+1} = R_{n+2/3} + (\alpha_{SR} S_{n+2/3} - \alpha_{RS} R_{n+2/3})\Delta t, \tag{239}$$
$$S_{n+1} = S_{n+2/3} + (\alpha_{RS} R_{n+2/3} - \alpha_{SR} S_{n+2/3})\Delta t, \tag{240}$$
$$T_{n+1} = T_{n+2/3} + (\alpha_{QT} Q_{n+2/3} - \alpha_{TQ} T_{n+2/3})\Delta t, \tag{241}$$
$$U_{n+1} = U_{n+2/3} + \left[\alpha_{PU} P_{n+2/3} + \alpha_{VU} V_{n+2/3} - (\alpha_{UP} + \alpha_{UO} + \alpha_{UV}) U_{n+2/3}\right]\Delta t, \tag{242}$$
$$V_{n+1} = V_{n+2/3} + \left[\alpha_{UV} U_{n+2/3} + \alpha_{WV} W_{n+2/3} - (\alpha_{VU} + \alpha_{VW}) V_{n+2/3}\right]\Delta t, \tag{243}$$
$$W_{n+1} = W_{n+2/3} + (\alpha_{VW} V_{n+2/3} - \alpha_{WV} W_{n+2/3})\Delta t. \tag{244}$$

This completes the definition of the hybrid method.

IV. Details of error analysis

As proclaimed in the main text and as we shall see below, the local truncation errors at time step $[t_n, t_n + \Delta t]$ in all three methods are given by expressions of the form

$$\mathcal{E}(t_n)\Delta t^2 + \mathcal{O}\left(\Delta t^3\right), \tag{245}$$

giving the upper estimate of a global error for the interval $t \in [t_{\min}, t_{\max}]$ of the first order,

$$\sup_{[t_{\min}, t_{\max}]} \|\vec{u}^{\text{exact}} - \vec{u}^{\text{numeric}}\| \leq \sup_{[t_{\min}, t_{\max}]} (\mathcal{E}(t))\,(t_{\max} - t_{\min})\Delta t + \mathcal{O}\left(\Delta t^2\right), \tag{246}$$

where the estimates of the coefficients $\mathcal{E}$ are different for the three methods.

To obtain these estimates, let us consider the quasi-linear system (9), rewritten as

$$\frac{\mathrm{d}\vec{u}}{\mathrm{d}t} = \boldsymbol{A}(V_m(t))\vec{u} = \boldsymbol{A}(t)\vec{u}$$

on the interval $t \in [t_n, t_{n+1}]$, $t_{n+1} = t_n + \Delta t$. Using matrix exponential, the result can be written in the form

$$\vec{u}(t_{n+1}) = \exp\left[\int\limits_{t_n}^{t_n+\Delta t} \boldsymbol{A}(t')\,\mathrm{d}t'\right]\vec{u}(t_n) \equiv \boldsymbol{T}(t_n, \Delta t)\,\vec{u}(t_n) \tag{247}$$

The accuracy in finding $\vec{u}(t_{n+1})$ at a given $\vec{u}(t_n)$ depends on accuracy of the approximation of operator $\boldsymbol{T}$ and on the norm of vector $\vec{u}(t_n)$. Since each component of $\vec{u}$ is restricted to the interval $[0, 1]$ and sum of its components is fixed to 1, we have $\|\vec{u}\| \leq 1$ for any choice of norm, in which any vector, that has exactly one component equal to unity and the rest equal to zero, is a unit vector.

Hence from this point on we focus on the approximation of the timestep transition operator $\boldsymbol{T}$.

Expanding (247), first the integral, then the exponential, in the Taylor series, we have

$$\begin{aligned}\boldsymbol{T} &= \exp\left[\int\limits_{t_n}^{t_n+\Delta t}\left(\boldsymbol{A}(t_n) + \dot{\boldsymbol{A}}(t_n)(t'-t_n) + \mathcal{O}\left((t'-t_n)^2\right)\right)\mathrm{d}t'\right] = \exp\left[\boldsymbol{A}(t_n)\Delta t + \frac{1}{2}\dot{\boldsymbol{A}}(t_n)\Delta t^2 + \mathcal{O}\left(\Delta t^3\right)\right] \\ &= 1 + \left[\boldsymbol{A}(t_n)\Delta t + \frac{1}{2}\dot{\boldsymbol{A}}(t_n)\Delta t^2 + \mathcal{O}\left(\Delta t^3\right)\right] + \frac{1}{2}\left[\boldsymbol{A}(t_n)\Delta t + \frac{1}{2}\dot{\boldsymbol{A}}(t_n)\Delta t^2 + \mathcal{O}\left(\Delta t^3\right)\right]^2 + \mathcal{O}\left(\Delta t^3\right) \\ &= 1 + \boldsymbol{A}(t_n)\Delta t + \frac{1}{2}\left[\dot{\boldsymbol{A}}(t_n) + \boldsymbol{A}^2(t_n)\right]\Delta t^2 + \mathcal{O}\left(\Delta t^3\right),\end{aligned}$$

where the dot designates time differentiation. FE approximates this operator as

$$\boldsymbol{T}_{\text{EF}}(t_n, \Delta t) = 1 + \boldsymbol{A}(t_n)\Delta t,$$

hence for the principal term of the norm of the error we have

$$\mathcal{E}_{\text{FE}} = \lim_{\Delta t \to 0} \|\boldsymbol{T}_{\text{EF}} - \boldsymbol{T}\|/\Delta t^2 = \frac{1}{2}\|\boldsymbol{A}^2 + \dot{\boldsymbol{A}}\| \leq \frac{1}{2}\left(\|\boldsymbol{A}\|^2 + \|\dot{\boldsymbol{A}}\|\right).$$

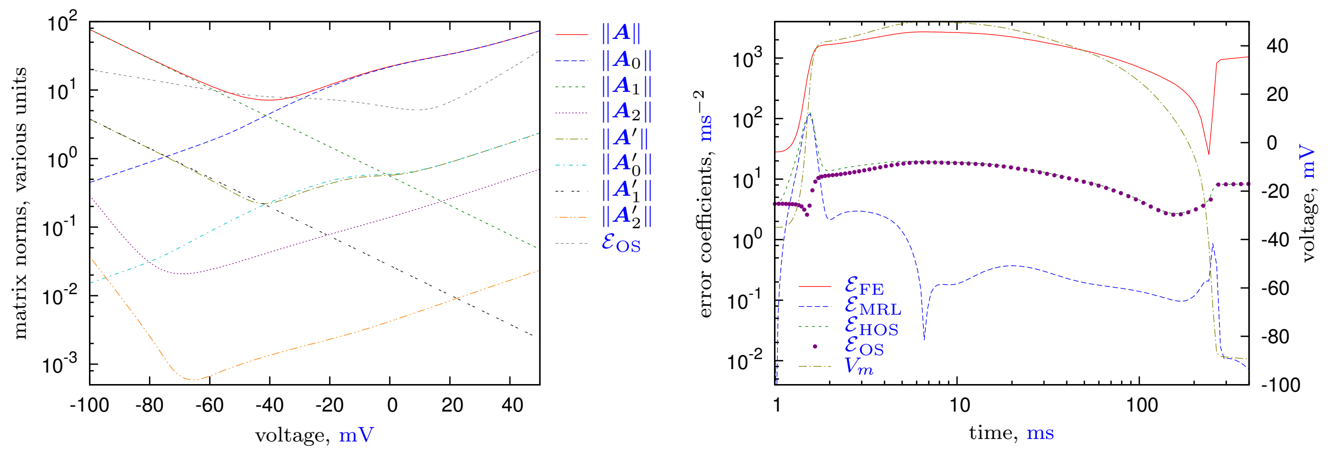
For the MRL, we have

$$\boldsymbol{T}_{\text{MRL}} = \exp\left(\boldsymbol{A}(t_n)\Delta t\right) = 1 + \boldsymbol{A}(t_n)\Delta t + \frac{1}{2}\boldsymbol{A}^2(t_n)\Delta t^2 + \mathcal{O}\left(\Delta t^3\right),$$

therefore

$$\mathcal{E}_{\text{MRL}} = \frac{1}{2}\|\dot{\boldsymbol{A}}\| = \frac{1}{2}\|\boldsymbol{A}'\||\dot{V}_m|$$

where the prime designates differentiation by V_m.



(a) (b)

Fig. 1. (a) Matrix norms affecting the apriori error estimates, as functions of the transmembrane voltage. Norms $\|\boldsymbol{A}\|$,$\|\boldsymbol{A}_m\|$ are in ms^{-1}, $\|\boldsymbol{A}'\|$,$\|\boldsymbol{A}'_m\|$,$\mathcal{E}_{\mathrm{OS}}$ are in ms^{-2}. (b) The coefficients of the apriori error estimates, as functions of time. $\mathcal{E}_{\mathrm{OS}}$ component shown by points as it overlaps with $\mathcal{E}_{\mathrm{HOS}}$ most of the time. The action potential $V_m(t)$ is shown for reference.

The errors of the three substeps of HOS are described by the above formulas for FE (for $\boldsymbol{A}_2$) and for MRL (for $\boldsymbol{A}_0$, $\boldsymbol{A}_1$), and in addition to those, we have the error due to operator splitting. To estimate the latter, let us compare the exact solution with the result of the successive application of the substeps as if they were done exactly. Let $\boldsymbol{B}_m = \int\limits_{t_n}^{t_n+\Delta t} \boldsymbol{A}_m(t)\,\mathrm{d}t$, $m = 0, 1, 2$. Then the exact solution is

$$\begin{aligned}\boldsymbol{T} &= 1 + (\boldsymbol{B}_0 + \boldsymbol{B}_1 + \boldsymbol{B}_2) + \frac{1}{2}(\boldsymbol{B}_0 + \boldsymbol{B}_1 + \boldsymbol{B}_2)^2 + \mathcal{O}\left(\Delta t^3\right) \\ &= 1 + (\boldsymbol{B}_0 + \boldsymbol{B}_1 + \boldsymbol{B}_2) + \frac{1}{2}(\boldsymbol{B}_0^2 + \boldsymbol{B}_1^2 + \boldsymbol{B}_2^2 + \boldsymbol{B}_0\boldsymbol{B}_1 + \boldsymbol{B}_1\boldsymbol{B}_0 + \boldsymbol{B}_0\boldsymbol{B}_2 + \boldsymbol{B}_2\boldsymbol{B}_0 + \boldsymbol{B}_1\boldsymbol{B}_2 + \boldsymbol{B}_2\boldsymbol{B}_1) + \mathcal{O}\left(\Delta t^3\right),\end{aligned}$$

and the result of the three substeps, with $\mathrm{e}^{\boldsymbol{B}_0}$ applied first and $\mathrm{e}^{\boldsymbol{B}_2}$ applied last, is

$$\begin{aligned}\boldsymbol{T}_{\mathrm{OS}} &= \left(1 + \boldsymbol{B}_2 + \frac{1}{2}\boldsymbol{B}_2^2 + \mathcal{O}\left(\Delta t^3\right)\right)\left(1 + \boldsymbol{B}_1 + \frac{1}{2}\boldsymbol{B}_1^2 + \mathcal{O}\left(\Delta t^3\right)\right)\left(1 + \boldsymbol{B}_0 + \frac{1}{2}\boldsymbol{B}_0^2 + \mathcal{O}\left(\Delta t^3\right)\right) \\ &= 1 + \boldsymbol{B}_2 + \boldsymbol{B}_1 + \boldsymbol{B}_0 + \frac{1}{2}\left(\boldsymbol{B}_2^2 + \boldsymbol{B}_1^2 + \boldsymbol{B}_0^2 + 2\boldsymbol{B}_2\boldsymbol{B}_1 + 2\boldsymbol{B}_2\boldsymbol{B}_0 + 2\boldsymbol{B}_1\boldsymbol{B}_0\right) + \mathcal{O}\left(\Delta t^3\right),\end{aligned}$$

so

$$\boldsymbol{T}_{\mathrm{OS}} - \boldsymbol{T} = \frac{1}{2}\left([\boldsymbol{B}_2, \boldsymbol{B}1] + [\boldsymbol{B}_2, \boldsymbol{B}_0] + [\boldsymbol{B}_1, \boldsymbol{B}_0]\right) + \mathcal{O}\left(\Delta t^3\right) = \frac{1}{2}\left([\boldsymbol{A}_2, \boldsymbol{A}1] + [\boldsymbol{A}_2, \boldsymbol{A}_0] + [\boldsymbol{A}_1, \boldsymbol{A}_0]\right)\Delta t^2 + \mathcal{O}\left(\Delta t^3\right)$$

where we use the standard notation for the matrix commutator, $[\boldsymbol{X}, \boldsymbol{Y}] \equiv \boldsymbol{X}\boldsymbol{Y} - \boldsymbol{Y}\boldsymbol{X}$. Finally, by the triangle inequality (subadditivity) of a matrix norm, the upper estimate of the error coefficient $\mathcal{E}_{\mathrm{HOS}}$ is given by the sum of the error coefficients of the three constituent steps and of the operator splitting.

To summarize, we have the following estimates of the leading terms of the approximation errors for the three methods as

$$\begin{aligned}\mathcal{E}_{\mathrm{FE}} &\leq \frac{1}{2}\left(\|\boldsymbol{A}\|^2 + \|\mathrm{d}\boldsymbol{A}/\mathrm{d}V_m\||\mathrm{d}V_m/\mathrm{d}t|\right) \\ \mathcal{E}_{\mathrm{MRL}} &= \frac{1}{2}\|\mathrm{d}\boldsymbol{A}/\mathrm{d}V_m\||\mathrm{d}V_m/\mathrm{d}t| \\ \mathcal{E}_{\mathrm{HOS}} &\leq \frac{1}{2}|\mathrm{d}V_m/\mathrm{d}t|\left(\|\mathrm{d}\boldsymbol{A}_0/\mathrm{d}V_m\| + \|\mathrm{d}\boldsymbol{A}_1/\mathrm{d}V_m\| + \|\mathrm{d}\boldsymbol{A}_2/\mathrm{d}V_m\|\right) + \frac{1}{2}||\boldsymbol{A}_2||^2 + \mathcal{E}_{\mathrm{OS}}, \\ \mathcal{E}_{\mathrm{OS}} &= \frac{1}{2}\|[\boldsymbol{A}_1, \boldsymbol{A}_0] + [\boldsymbol{A}_2, \boldsymbol{A}_0] + [\boldsymbol{A}_2, \boldsymbol{A}_1]\|.\end{aligned} \tag{248}$$

An important observation is that the apriori estimates of the errors cannot be made based on the properties of the MC alone as they depend on the rate of change of the voltage.

The graphs of the Frobenius norms of the matrices involved in the estimates (248) are shown in Fig. 1(a). Evidently $\|\boldsymbol{A}\|$ dominates other norms throughout the voltage range; however, it is relatively small for intermediate values of V_m and this is precisely when $\mathrm{d}V_m/\mathrm{d}t$ is large during a typical AP, making the related components of the errors more significant. So a more adequate idea of the relative magnitudes of the errors of the three methods should take into account properties of specific solutions. Figure 1(b) shows the values of the error estimates (248) for the typical AP which was used for other numerical illustrations in the paper. We see that the error associated with FE is the largest of the three, with the maximal magnitude of about $2700\,\mathrm{ms}^{-2}$, achieved early during the plateau of the AP, thus guaranteeing no more than 10% global error on a time interval of $1\,\mathrm{ms}$ long for time steps as short as $\Delta t \approx 0.04\,\mu\mathrm{s}$, and its main contributor is $\|\boldsymbol{A}\|^2$ rather than $\|\dot{\boldsymbol{A}}\|$. The error associated with MRL is the smallest of the three, with the maximal magnitude of about $118\,\mathrm{ms}^{-2}$, achieved during the upstroke of the action potential, giving 10% global accuracy on $1\,\mathrm{ms}$ interval for $\Delta t \approx 0.8\,\mu\mathrm{s}$. The error of the HOS is intermediate between the two. Its maximum of about $125\,\mathrm{ms}^{-2}$, i.e. very similar to that of MRL and achieved at the same time, as its main contributors are the same $\dot{V}_m$-dependent errors of the exponential integrator substeps as in $\mathcal{E}_{\mathrm{MRL}}$. Outside the AP upstroke, the error of HOS is dominated by the operator splitting error $\mathcal{E}_{\mathrm{OS}}$, which however never exceeds $19\,\mathrm{ms}^{-2}$. The ratio of the error coefficients of the two methods varies widely during the AP solution: $\mathcal{E}_{\mathrm{FE}}/\mathcal{E}_{\mathrm{MRL}} \in (3.18, \infty)$ (remember $\mathcal{E}_{\mathrm{MRL}} = 0$ when $\mathrm{d}V_m/\mathrm{d}t = 0$) and $\mathcal{E}_{\mathrm{FE}}/\mathcal{E}_{\mathrm{HOS}} \in (2.30, 161)$, with the smallest values achieved during the upstroke when the exponential solvers are least accurate.

Clearly, the estimate of the global error given by (246) is over-cautious, or "pessimistic", as it presumes that local errors take maximal values allowed by the matrix norms, and accumulate but not compensate on the whole interval $[t_{\min}, t_{\max}]$. As the numerical experiments described in the main text show, the actual errors are much smaller. Still, the analysis done here can be useful in identifying relative contribution of different sources of errors and identifying "bottlenecks". Specifically, we see that

- the exponential solvers are more accurate than FE: even in the worst case, during the upstroke, they give two to three times smaller error;
- the principal limitation of the accuracy of both exponential solvers is the dependence on $\dot{V}_m$, which affects accuracy mostly during the upstroke, hence any attempts to improve the accuracy should in the first instance address this issue.

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