Supporting Material

Inter beat interval modulation in the sinoatrial node due to membrane current stochasticity – a theoretical and numerical study

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A. Derivation of equation 4 for a basic Hodgkin-Huxley model

We demonstrate the derivation of Eq. 4 for the following original Hodgkin-Huxley model for the squid's giant axon that incorporates capacitive, ion (sodium and potassium), leakage and stimulation currents [1]:

$$\frac{\partial v_m}{\partial t} = -\left(g_{Na}(v_m - E_{Na}) + g_K(v_m - E_K) + g_L(v_m - E_L) - I_p\right), \qquad \text{(A1)}$$

where g_{Na} and g_K [μS/μF] are the sodium and potassium channel conductivities (both nonlinear functions of v_m and t due to gating kinetics), g_L [μS/μF] is the membrane leakage conductivity, E_x [mV] is the reversal potential of the x current, where $x \in \{Na, K, L\}$, and I_p [nA/nF] is a prescribed external current. By defining,

$$g(v_m, t) \triangleq g_{Na} + g_K + g_L$$

$$\mu(v_m, t) \triangleq \frac{g_{Na}E_{Na} + g_K E_K + g_L E_L + I_p}{g_{Na} + g_K + g_L} \qquad \text{(A2)}$$

Eq. A1 can be written as,

$$\frac{\partial v_m}{\partial t} = -g_m(v_m, t)[v_m - \mu(v_m, t)], \qquad \text{(A3)}$$

which is similar to Eq. 4.

B. Analytical expression for deterministic $g_m(v_m, t)$

An analytical expression for $g_m(v_m, t)$ was derived from the kinetics model of Severi et al. [2], as follows,

$$\mathrm{g_m(v_m, t) = G1 + G2 + G3 + G4 + G5 + G6 + G7 + G8 + G9}, \qquad \text{(B1)}$$

where,

$$G1 = g_{Na} \cdot m^3 \cdot h \qquad \text{(B2)}$$

$$G2 = \left(\frac{y^2 \cdot K_o}{K_o + Km_f}\right) \cdot gf_{Na} \qquad \text{(B3)}$$

$$G3 = \left(\frac{y^2 \cdot K_o}{K_o + Km_f}\right) \cdot gf_K \qquad \text{(B4)}$$

$$G4 = g_{Kr} \cdot (0.9 \cdot p_{aF} + 0.1 \cdot p_{aS}) \cdot p_i \qquad \text{(B5)}$$

$$G5 = g_{Ks} \cdot n^2 \qquad \text{(B6)}$$

$$G6 = g_{to} \cdot q \cdot r \qquad \text{(B7)}$$

$$G7 = \left[\frac{2 \cdot P_{CaL}}{\frac{R \cdot T}{F} \cdot \left(1 - exp\left(\frac{-2 \cdot v_m}{\frac{R \cdot T}{F}}\right)\right)} \cdot \left(Ca_{sub} - Ca_o \cdot exp\left(\frac{-2 \cdot v_m}{\frac{R \cdot T}{F}}\right)\right) \cdot d_L \cdot f_L \cdot f_{Ca}\right] +$$

$$\left[\frac{0.000365\cdot P_{CaL}}{\frac{R\cdot T}{F}\cdot\left(1-exp\left(\frac{-v_m}{\frac{R\cdot T}{F}}\right)\right)}\cdot\left(K_i - K_o\cdot exp\left(\frac{-v_m}{\frac{R\cdot T}{F}}\right)\right)\cdot d_L\cdot f_L\cdot f_{Ca}\right]+\left[\frac{1.85\cdot 10^{-5}\cdot P_{CaL}}{\frac{R\cdot T}{F}\cdot\left(1-exp\left(\frac{-v_m}{\frac{R\cdot T}{F}}\right)\right)}\cdot\right.$$

$$\left.\left(Na_i - Na_o\cdot exp\left(\frac{-v_m}{\frac{R\cdot T}{F}}\right)\right)\cdot d_L\cdot f_L\cdot f_{Ca}\right] \quad \text{(B8)}$$

$$G8 = \frac{2\cdot P_{CaT}}{\frac{R\cdot T}{F}\cdot\left(1-exp\left(\frac{-2\cdot v_m}{\frac{R\cdot T}{F}}\right)\right)}\cdot\left(Ca_{sub} - Ca_o\cdot exp\left(\frac{-2\cdot v_m}{\frac{R\cdot T}{F}}\right)\right)\cdot d_T\cdot f_T$$

(B9)

$$G9 = \begin{cases} g_{KACh}\cdot\left(1+exp\left(\frac{v_m+20}{20}\right)\right)\cdot a & ACh > 0 \\ 0 & o.w. \end{cases} \quad \text{(B10)}$$

For the definition of variables and coefficients in Eqs. B2-B10, refer to Severi et al. model [2]. $g_m(v_m)$ was calculated using Eq. B1 using the state variable values during a deterministic action potential, and is shown in Fig. S1 in the vicinity of v_{min} and for voltages corresponding to phase 4 depolarization (panels A and B, respectively).

In Eq. 22, the deterministic values of μ and g_m during phase 4 depolarization, and the values of g_m and $\left.\frac{\partial g_m}{\partial v_m}\right|_{v_{min}+\delta}$ in the vicinity of v_{min} are needed. Given the deterministic action potential $v_m(t)$, $\mu(v_m)$ during phase 4 depolarization was calculated according to Eq. 4 (setting $\xi = 0$) using the g_m values from Fig. S1 panel B. The results given in Fig. S1 panel C demonstrate a monotonic, non-linear relationship between μ and v_m, with μ varying between -42 to -32 mV for voltages between -55 to -45 mV, that correspond to the major segment of phase 4 depolarization. Therefore, we took $\mu = -37mV$ as an approximated constant value during that phase. As shown in panel B, during phase 4 depolarization g_m increases with v_m in an approximately linear curve, albeit with a relatively small slope of $\frac{\partial g_m}{\partial v_m} \sim 0.34\ s^{-1}/mV$. We therefore approximated g_m as constant during that phase with a value of $g_m \approx 10\mu S/\mu F$. At v_{min}, $g_m(v_m)$ is non-differentiable, as seen in panel D. We therefore considered in Eq. 13 and forward the values of $g_m(v_m)$ and

$\frac{\partial g_m}{\partial v_m}$ in the vicinity of v_{min}, i.e., $v_{min} + \delta$. Panels A and D suggest that $g_m(v_{min} + \delta, t) \approx 6.6\mu S/\mu F$ and $\left.\frac{\partial g_m(v_m)}{\partial v_m}\right|_{v_{min}+\delta} \approx -10s^{-1}/\text{mV}$.

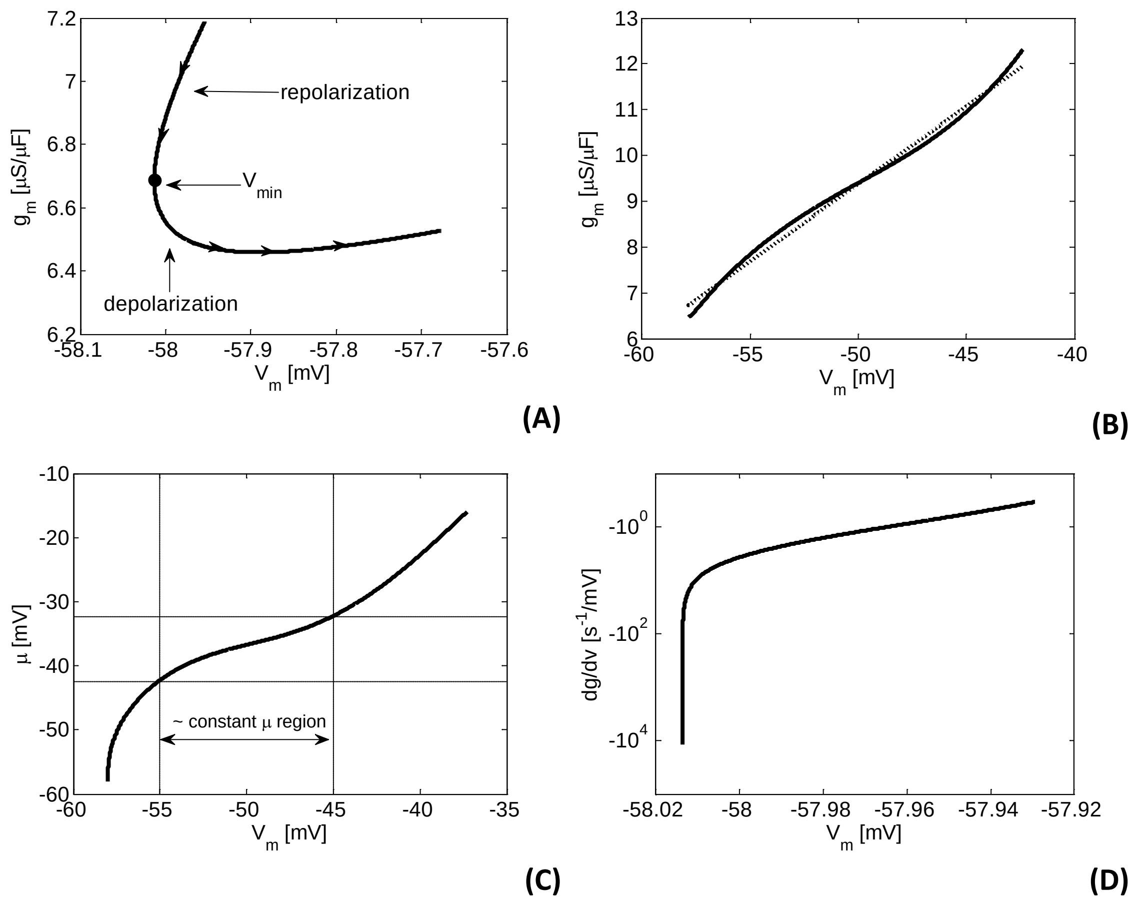

Figure S1. Mathematical analysis of the deterministic general conductivity, $g_m(v_m)$ and the general voltage term, $\mu(v_m)$. (A) $g_m(v_m)$ for "end-diastolic" voltage region. (B-C) $g_m(v_m)$ (panel B) and $\mu(v_m)$ (panel C) for phase 4 depolarization voltage region. (D) $\frac{\partial g_m(v_m)}{\partial v_m}$ for "end-diastolic" voltage region.

SUPPORTING REFERENCES

1. Hille, B., 2001. Ion channels of excitable membranes. Sunderland, MA: Sinauer.
2. Severi, S., M. Fantini, L. A. Charawi, & D. DiFrancesco, 2012. An updated computational model of rabbit sinoatrial action potential to investigate the mechanisms of heart rate modulation. The Journal of Physiology, 590:4483-4499.