Appendix A. The foot of a propagated action potential

Propagation of a planar wavefront along a given direction x in a homogeneous medium can be described by the one-dimensional monodomain equation given as

$$\sigma_x \frac{\partial^2 V_m}{\partial x^2} = \beta \left(C_m \frac{\partial V_m}{\partial t} + I_{ion} \right). \quad (37)$$

Under such conditions a depolarization wavefront propagates at a sufficient distance to any tissue boundary uniformly at a constant velocity without any spatial variation in the shape of the wavefront. Mathematically, this can be expressed as

$$V_m(x,t) = V_m(x - vt) \quad (38)$$

or, equivalently, as a differential equation by

$$\frac{\partial^2 V_m}{\partial x^2} = \frac{1}{v^2} \frac{\partial^2 V_m}{\partial t^2} \quad (39)$$

where v denotes the conduction velocity of the propagating wavefront. Under subthreshold conditions, that is, the range of transmembrane voltages V_m below the firing threshold, V_{th}, referred to as the foot of the action potential, the membrane behavior is characterized as passive and linear. The transmembrane current I_m is composed then of a capacitive current I_c

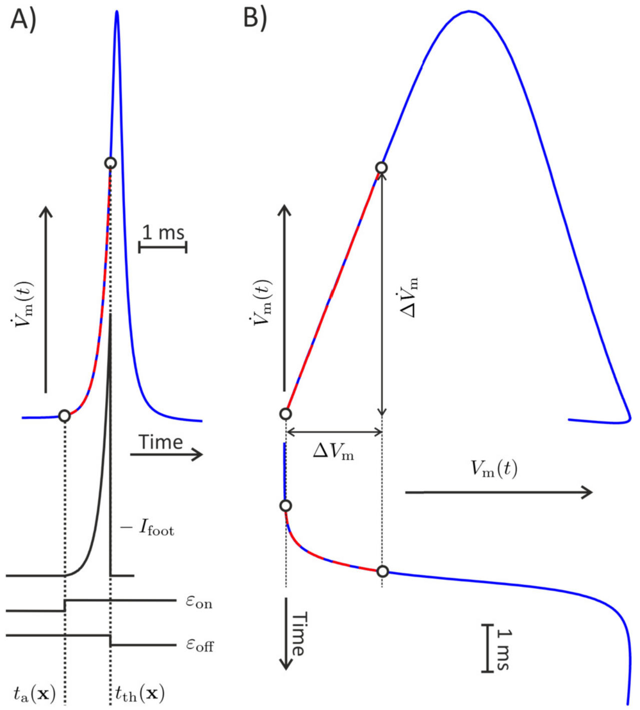

Fig. 10. Fitting of current I_{foot}. Shown are traces derived from a simulated propagated action potential (solid blue lines) and traces derived from the fitted current I_{foot} (red dashed lines). Fitting yielded $A = 0.91$ mV and $\tau_F = 0.25$ ms. A) Trace of $\dot{V}_m$, foot current $-I_{foot}/C_m$ and the step functions $\varepsilon_{on} = \varepsilon(t - t_a(x))$ and $\varepsilon_{off} = \varepsilon(t_{th}(x) - t)$. B) Phase plane trajectory of propagated action potential. During the foot of the action potential the ratio $\Delta\dot{V}_m/\Delta V_m$ is $\approx$ constant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

and an ionic current I_{ion} where $I_{ion} = G_m V_m$ is ohmic. Thus using (37) with (39) the time course of the action potential at any given point in space can be described by

$$\frac{\sigma_x}{\beta G_m v^2}\frac{\partial^2 V_m}{\partial t^2} - R_m C_m \frac{\partial V_m}{\partial t} - V_m = 0. \tag{40}$$

Using the definition of the time constant of the membrane, τ_m, and the space constant along the direction x, λ_x,

$$\tau_m = R_m C_m; \quad \lambda_x = \sqrt{\frac{\sigma_x}{\beta G_m}} \tag{41}$$

yields the differential equation of the foot of a propagating action potential

$$\left(\frac{\lambda_x}{v}\right)^2 \frac{\partial^2 V_m}{\partial t^2} - \tau_m \frac{\partial V_m}{\partial t} - V_m = 0 \tag{42}$$

for which an analytical solution is found as

$$V_m = A \cdot \exp\left[\left(\frac{\tau_m v^2}{2\lambda_x^2} + \frac{v}{2\lambda_x}\sqrt{\frac{\tau_m^2 v^2}{\lambda_x^2} + 4}\right) t\right] + B \cdot \exp\left[\left(\frac{\tau_m v^2}{2\lambda_x^2} - \frac{v}{2\lambda_x}\sqrt{\frac{\tau_m^2 v^2}{\lambda_x^2} + 4}\right) t\right]. \tag{43}$$

In the case of a propagating depolarization wavefront the foot of the action potential traverses its rising phase implying that $B = 0$ must hold. Further, in general the assumption $\tau_m^2 v^2/\lambda_x^2 \gg 4$ holds, allowing to represent the foot of the action potential as a mono-exponential process

$$V_m = A\, e^{kt} \quad \text{with} \quad k = \frac{\tau_m v^2}{\lambda_x^2} = \frac{1}{\tau_F}, \tag{44}$$

where τ_F denotes the time constant of the foot of the action potential. The time constant τ_F can be determined experimentally [40] or from a simulated propagated action potential through phase plane analysis (Fig. 10). At the arrival time of a propagating depolarization wavefront at the location x in space, $t_a(x)$, the change in transmembrane voltage during the foot of the action potential is described by a function

$$V_m(x,t) = \left[A \cdot e^{\frac{t - t_a(x)}{\tau_F}} + B \right] \cdot \varepsilon_{on}(t - t_a(x)) \cdot \varepsilon_{off}(t_{th}(x) - t), \tag{45}$$

where ε_{on} and ε_{off} are step functions delimiting the time interval $[t_a(x), t_{th}(x)]$ of the foot of the action potential marking the onset of the AP foot and the instant of V_m crossing a given transmembrane voltage threshold at location x. The change of V_m during the foot is driven by the foot current I_{foot} given as

$$I_{foot} = I_{ion} - \nabla \cdot \boldsymbol{\sigma} \nabla V_m = -C_m \frac{V_m}{dt} = -\frac{A}{\tau_F} \cdot e^{\frac{t - t_a(x)}{\tau_F}} \cdot \varepsilon(t - t_a(x)) \cdot \varepsilon(t_{th}(x) - t), \tag{46}$$

which represents the combined effect of electronic currents due to diffusion, represented by $\nabla \cdot \boldsymbol{\sigma} \nabla V_m$, and the ionic currents, I_{ion} where $I_{ion} \approx 0$ can be assumed during the foot phase of an action potential. The constant A of the current I_{foot} can be determined by fitting the function in Eq. (46) to the foot of a propagated action potential (Fig. 10).

According to Eq. (44) τ_F depends on the velocity of propagation, suggesting that the foot of the action potential may vary as a function of direction of propagation. However, taking into account the known proportionality relation for conduction velocity

$$v_x \propto K \sqrt{\frac{\sigma_x}{\beta}} \tag{47}$$

it becomes apparent, by inserting Eqs. (47) and (41) into Eq. (44) that the ratio v_x/λ_x is a constant factor $K\sqrt{G_m}$. Thus the potentially space-dependent terms cancel out in Eq. (44) and the time course of the foot of the action potential is governed by local membrane properties, that is, the conductivity G_m of the membrane under subthreshold conditions.