$$\frac{dh}{dt} = \alpha_1 (1-h-d) - \beta_1 h \; ; \qquad \frac{dd}{dt} = \beta_2 (1-h-d) - \alpha_2 d$$

$$\frac{dh}{dt} = 0 \;) \Rightarrow \; \alpha_1 (1-h-d) = \beta_1 h \; \rightarrow \; h = \frac{\alpha_1 (1-d)}{\alpha_1 + \beta_1} = \frac{\alpha_1 (1-d)}{\alpha_1 + \alpha_1 K}$$

$$\alpha_1 - \alpha_1 h - \alpha_1 d = \beta_1 h$$

$$\boxed{h = \frac{1-d}{1+K}}$$

$$\frac{dd}{dt} = \alpha_2 K \left(1 - \frac{1-d}{1+K} - d\right) - \alpha_2 d = \alpha_2 K - \frac{\alpha_2 K (1-d)}{1+K} - \alpha_2 K d - \alpha_2 d =$$

$$= \frac{\alpha_2 K (1+K) - \alpha_2 K (1-d) - (\alpha_2 K d + \alpha_2 d)(1+K)}{1+K} =$$

$$= \frac{\cancel{\alpha_2 K} + \alpha_2 K^2 - \cancel{\alpha_2 K} + \cancel{\alpha_2 K d} - \cancel{\alpha_2 K d} - \alpha_2 K^2 d - \alpha_2 d - \alpha_2 K d}{1+K} =$$

$$= \frac{\alpha_2 \left(K^2 - (K^2+K+1) d\right)}{1+K}$$

$$\left.\begin{array}{l} K = \dfrac{\beta_2}{\alpha_2} \\[2ex] \tau_2 = \dfrac{1}{\alpha_2 + \beta_2} \end{array}\right) \Rightarrow \quad \beta_2 = K \alpha_2 \qquad \tau_2 = \frac{1}{\alpha_2 (1+K)} \;) \Rightarrow \; \alpha_2 = \frac{1}{\tau_2 (1+K)} \quad \Rightarrow$$

$$) \Rightarrow \; \dot{d} = \frac{K^2 - (K^2+K+1) d}{\tau_2 (1+K)^2} = \frac{\frac{K^2}{K^2+K+1} - d}{h_\infty \tau_2 (1+K)^2} =$$

$$= \frac{h_\infty K^2 - d}{h_\infty \tau_2 (1+K)^2}$$

T-type current

model fit

Activation gate (Wang et al 1991, Kyunghwa et al 2015)

$$\frac{ds}{dt} = \frac{s_\infty(V) - s}{\tau_s(V)}$$

$$s_\infty = \frac{1}{1 + \exp\left[-(V - V_{1/2}^{(s)})/k^{(s)}\right]}$$

$$\delta_s = \frac{1}{a_{\delta_s} + \exp\left[-(V - V_{1/2}^{(\delta_s)})/k^{(\delta_s)}\right]}$$

$$\tau_s = \frac{s_\infty}{\delta_s}$$

$V_{1/2}^{(\delta_s)} \simeq -42.75$

$k^{(\delta_s)} \simeq 7.36$

$a_{\delta_s} \simeq 0.88$

$V_{1/2}^{(\delta_s)} \simeq -23.21$

$k^{(\delta_s)} \simeq 7.23$

Deactivation current

$$h_\infty = \frac{1}{1 + \exp\left[(V - V_{1/2}^{(h)})/k^{(h)}\right]}$$

$V_{1/2}^{(h)} \simeq -58.2$

$k^{(h)} \simeq 7.14$

$$\dot{h} = \frac{1}{\tau_1}\left[\frac{1-d}{1+K} - h\right]$$

$$\dot{d} = \frac{1}{\tau_2}\left[\frac{K(1-h)}{1+K} - d\right]$$

$\tau_1 = \tau_h$

$\tau_2 =$

$$\dot{h} = \alpha_1 (1 - h - d) - \beta_1 h$$

$$\dot{d} = \beta_2 (1 - h - d) - \alpha_2 d$$

$$\left.\begin{aligned} \tau_1 &= \frac{1}{\alpha_1 + \beta_1} \\ K_1 &= \frac{\beta_1}{\alpha_1} \end{aligned}\right) \Rightarrow \begin{aligned} &\beta_1 = \alpha_1 K_1 \\ &\tau_1 = \frac{1}{\alpha_1 + \alpha_1 K_1} = \frac{1}{\alpha_1 (1 + K_1)} \end{aligned} \Bigg) \Rightarrow \boxed{\begin{aligned} \alpha_1 &= \frac{1}{\tau_1 (1 + K_1)} \\ \beta_1 &= \frac{K_1}{\tau_1 (1 + K_1)} \end{aligned}}$$

similarly: $\boxed{\begin{aligned} \alpha_2 &= \frac{1}{\tau_2 (1 + K_2)} \\ \beta_2 &= \frac{K_2}{\tau_2 (1 + K_2)} \end{aligned}}$ $\boxed{K_1 = K_2}$

$$\dot{h} = \frac{1}{\tau_1 (1+K)} (1 - h - d) - \frac{K}{\tau_1 (1+K)} h =$$

$$= \frac{1}{\tau_1 (1+K)} \left[1 - h - d - Kh \right] =$$

$$= \frac{1}{\tau_1 (1+K)} \left[1 - h(1+K) - d \right]$$

$$\dot{d} = \frac{K}{\tau_2 (1+K)} \left[1 - h - d \right] - \frac{1}{\tau_2 (1+K)} d =$$

$$= \frac{1}{\tau_2 (1+K)} \left[K(1 - h - d) - d \right]$$

$$\dot{h} = \frac{1}{\tau_1 (1+K)} \left[1 - h(1+K) - d \right] = \frac{1-d}{\tau_1 (1+K)} - \frac{h}{\tau_1} =$$

$$= \frac{1}{\tau_1} \left[\frac{1-d}{1+K} - h \right]$$

$$\dot{d} = \frac{1}{\tau_2 (1+K)} \left[K(1 - h) - d(1+K) \right] =$$

$$= \frac{1}{\tau_2} \left[\frac{K(1-h)}{1+K} - d \right]$$

$$\frac{d}{dt}\begin{pmatrix} h \\ d \end{pmatrix} = \begin{pmatrix} -\alpha_1-\beta_1 & -\alpha_1 \\ -\beta_2 & -\alpha_2-\beta_2 \end{pmatrix}\begin{pmatrix} h \\ d \end{pmatrix}$$

Sum of exponentials and gating time constants

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \; ; \quad \frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \qquad (1)$$

$$I(t) = g\, m^p h\, (V - E) \qquad (2)$$

$$\left.\begin{array}{l} m(0) = h(0) = 0 \\ p = 3 \end{array}\right) \Rightarrow \left.\begin{array}{l} m(t) = m_\infty (1 - e^{-t/\tau_m}) \\ h(t) = h_\infty (1 - e^{-t/\tau_h}) \\ \qquad (2) \end{array}\right) \Rightarrow$$

$$\Rightarrow I(t) = g\, m_\infty^3 (1 - e^{-t/\tau_m})^3 h_\infty (1 - e^{-t/\tau_h}) (V - E) =$$

$$= g\, m_\infty^3 \left(1 - \cancel{e^{-3t/\tau_m}} - 3e^{-t/\tau_m} + \cancel{3e^{-2t/\tau_m}}\right) h_\infty (1 - e^{-t/\tau_h})(V - E) \simeq$$

$$\simeq g\, m_\infty^3 (1 - 3e^{-t/\tau_m}) h_\infty (1 - e^{-t/\tau_h})(V - E) =$$

$$= g\, m_\infty^3 h_\infty \left(1 - e^{-t/\tau_h} - 3e^{-t/\tau_m} + \cancel{e^{-t/\tau_m - t/\tau_h}}\right)(V - E) \simeq$$

$$\simeq g\, m_\infty^3 h_\infty (1 - e^{-t/\tau_h} - 3e^{-t/\tau_m})(V - E) =$$

$$= \underbrace{g\, m_\infty^3 h_\infty (V - E)}_{\text{Steady state term}} \underbrace{- g\, m_\infty^3 h_\infty (V - E) e^{-t/\tau_h} - 3 g\, m_\infty^3 h_\infty (V - E) e^{-t/\tau_m}}_{\text{Transient term}}$$

$$\boxed{\begin{array}{l} I_{transient}(t) = A_1 e^{-t/\tau_m} + A_2 e^{-t/\tau_h} \\ A_1 = -3 g\, m_\infty^3 h_\infty (V - E) \\ A_2 = -g\, m_\infty^3 h_\infty (V - E) \end{array}}$$

← Thus, τ_m and τ_h can be directly fitted by recorded transient currents $I_{transient}$

$$\frac{dh}{dt} = \alpha_1 (1 - h - d) - \beta_1 h \qquad (1)$$

$$\frac{dd}{dt} = \beta_2 (1 - h - d) - \alpha_2 d \qquad (2)$$

<u>steady state</u>

$$\alpha_1 (1 - h_\infty - d_\infty) = \beta_1 h_\infty \;\Rightarrow\; \alpha_1 (1 - d_\infty) = h_\infty (\alpha_1 + \beta_1) \;\Rightarrow\; h_\infty = \frac{\alpha_1 (1 - d_\infty)}{\alpha_1 + \beta_1}$$

$$\beta_2 (1 - h_\infty - d_\infty) = \alpha_2 d_\infty \;\Rightarrow\; \beta_2 \left(1 - \frac{\alpha_1 (1 - d_\infty)}{\alpha_1 + \beta_1} - d_\infty\right) = \alpha_2 d_\infty$$

$$1 - \frac{\alpha_1 - \alpha_1 d_\infty + \alpha_1 d_\infty + \beta_1 d_\infty}{\alpha_1 + \beta_1} = \frac{\alpha_2}{\beta_2} d_\infty$$

$$\frac{\alpha_1 + \beta_1 d_\infty}{\alpha_1 + \beta_1} = 1 - \frac{\alpha_2}{\beta_2} d_\infty \;\Rightarrow\; \cancel{\alpha_1} + \beta_1 d_\infty = \cancel{\alpha_1} + \beta_1 - \frac{\alpha_2 (\alpha_1 + \beta_1)}{\beta_2} d_\infty$$

$$d_\infty \left(\beta_1 + (\alpha_1 + \beta_1) \frac{\alpha_2}{\beta_2} \right) = \beta_1$$

$$d_\infty \cdot \frac{\beta_1 \beta_2 + \alpha_1 \alpha_2 + \alpha_2 \beta_1}{\beta_2} = \beta_1$$

$$d_\infty = \frac{\beta_1 \beta_2}{\beta_1 \beta_2 + \alpha_2 (\alpha_1 + \beta_1)}$$

$$\beta_1 = \alpha_1 K_1$$

$$\beta_2 = \alpha_2 K_2$$

$$\Rightarrow\; d_\infty = \frac{\alpha_1 K_1 \cancel{\alpha_2} K_2}{\alpha_1 K_1 \cancel{\alpha_2} K_2 + \cancel{\alpha_2} (\alpha_1 + \alpha_1 K_1)} =$$

$$= \frac{\cancel{\alpha_1} K_1 K_2}{\cancel{\alpha_1} K_1 K_2 + \cancel{\alpha_1} (1 + K_1)} = \frac{K_1 K_2}{K_1 K_2 + 1 + K_1} = \frac{K_1 K_2}{1 + K_1 (1 + K_2)}$$

$$h_\infty = \frac{\alpha_1(1-d_\infty)}{\alpha_1+\beta_1} = \frac{\alpha_1}{\alpha_1+K_1\alpha_1}\left(1-\frac{K_1K_2}{1+K_1+K_1K_2}\right) =$$

$$= \frac{1}{1+K_1}\cdot\frac{1+K_1+\cancel{K_1K_2}-\cancel{K_1K_2}}{1+K_1+K_1K_2} = \frac{1}{\cancel{1+K_1}}\cdot\frac{\cancel{1+K_1}}{1+K_1+K_1K_2} =$$

$$= \frac{1}{1+K_1(1+K_2)}$$

$$\boxed{\begin{aligned} h_\infty &= \frac{1}{1+K_1(1+K_2)} \\ d_\infty &= K_1K_2\,h_\infty \end{aligned}} \quad \begin{aligned}&(A2a)\\ &(A2b)\end{aligned}$$

$$K_1=K_2 \Rightarrow \boxed{\begin{aligned} h_\infty &= \frac{1}{1+K+K^2} \\ d_\infty &= K^2 h_\infty \end{aligned}} \quad (A3)$$

$$\begin{matrix}(1)\\(2)\end{matrix} \rightarrow \frac{d}{dt}\begin{pmatrix} h \\ d \end{pmatrix} = \begin{pmatrix} -\alpha_1-\beta_1 & -\alpha_1 \\ -\beta_2 & -\alpha_2-\beta_2 \end{pmatrix}\begin{pmatrix} h \\ d \end{pmatrix} + \begin{pmatrix} \alpha_1 \\ \beta_2 \end{pmatrix}$$

Associated homogeneous equation:

$$\frac{d}{dt}\begin{pmatrix} h \\ d \end{pmatrix} = \begin{pmatrix} -\alpha_1-\beta_1 & -\alpha_1 \\ -\beta_2 & -\alpha_2-\beta_2 \end{pmatrix}\begin{pmatrix} h \\ d \end{pmatrix}$$

$$\begin{pmatrix} h \\ d \end{pmatrix} \equiv \vec{x}$$

$$\begin{pmatrix} -\alpha_1-\beta_1 & -\alpha_1 \\ -\beta_2 & -\alpha_2-\beta_2 \end{pmatrix} \equiv A$$

$\lambda' = -\lambda$ ← eigenvalues

$$\vec{x}' = A\vec{x}$$

$$\det(A+\lambda I) = \det\begin{pmatrix} -\alpha_1-\beta_1+\lambda & -\alpha_1 \\ -\beta_2 & -\alpha_2-\beta_2+\lambda \end{pmatrix} =$$

$$= (-\alpha_1-\beta_1+\lambda)(-\alpha_2-\beta_2+\lambda) - \alpha_1\beta_2 =$$

$$= \alpha_1\alpha_2 + \cancel{\alpha_1\beta_2} - \underline{\lambda\alpha_1} + \alpha_2\beta_1 + \beta_1\beta_2 - \underline{\lambda\beta_1} - \underline{\lambda\alpha_2} - \underline{\lambda\beta_2} + \lambda^2 - \cancel{\alpha_1\beta_2} =$$

$$= \lambda^2 + \lambda\underbrace{(-\alpha_1-\beta_1-\alpha_2-\beta_2)}_{T_r} + \underbrace{\alpha_1\alpha_2 + \beta_1(\alpha_2+\beta_2)}_{D} =$$

$$= \lambda^2 + T_r\cdot\lambda + D$$

$$T_r = -(\alpha_1+\beta_1+\alpha_2+\beta_2) = -\left(\frac{1}{\tau_1}+\frac{1}{\tau_2}\right)$$

$$D = \alpha_1\alpha_2 + \beta_1(\alpha_2+\beta_2) = \alpha_1\alpha_2 + K\alpha_1(\alpha_2+K\alpha_2) =$$

$$= \alpha_1\alpha_2(1+K(1+K))$$

$$K_1 = \frac{\beta_1}{\alpha_1} \Rightarrow \beta_1 = K_1\alpha_1$$

$$\downarrow$$

$$\tau_1 = \frac{1}{\alpha_1+\beta_1} \Rightarrow \tau_1 = \frac{1}{\alpha_1(1+K_1)} \Rightarrow \alpha_1 = \frac{1}{\tau_1(1+K_1)}$$

similarly: $\alpha_2 = \dfrac{1}{\tau_2(1+K_2)}$

$\Rightarrow$

$$\Rightarrow D = \frac{1+K(1+K)}{\tau_1\tau_2(1+K)^2}$$

$$\lambda_1, \lambda_2 = \frac{1}{2}\left[-T_r \pm \sqrt{T_r^2 - 4D}\right]$$

$$T_r^2 - 4D = \left(\frac{1}{\tau_1} + \frac{1}{\tau_2}\right)^2 - \frac{4(1+K(1+K))}{\tau_1\tau_2(1+K)^2} =$$

$$= \left(\frac{1}{\tau_1} - \frac{1}{\tau_2}\right)^2 + \frac{4}{\tau_1\tau_2} - \frac{4(1+K(1+K))}{\tau_1\tau_2(1+K)^2} = \left(\frac{1}{\tau_1} - \frac{1}{\tau_2}\right)^2 + \frac{4(1+K)^2 - 4 - 4K - 4K^2}{\tau_1\tau_2(1+K)^2} =$$

$$= \left(\frac{1}{\tau_1} - \frac{1}{\tau_2}\right)^2 + \frac{\cancel{4} + 8K + \cancel{4K^2} - \cancel{4} - 4K - \cancel{4K^2}}{\tau_1\tau_2(1+K)^2} = \left(\frac{1}{\tau_1} - \frac{1}{\tau_2}\right)^2 + \frac{4K}{\tau_1\tau_2(1+K)^2}$$

$$\lambda_1, \lambda_2 = \frac{1}{2}\left[\left(\frac{1}{\tau_1} + \frac{1}{\tau_2}\right) \pm \sqrt{\left(\frac{1}{\tau_1} - \frac{1}{\tau_2}\right)^2 + \frac{4K}{\tau_1\tau_2(1+K)^2}}\right]$$

$$\Big\downarrow \text{(from the paper)}$$

$$\tau_1^{-1}, \tau_2^{-2} = \frac{1}{2}\left[(\lambda_1 + \lambda_2) \pm \sqrt{(\lambda_1 + \lambda_2)^2 - \frac{4(1+K)^2\lambda_1\lambda_2}{1+K(1+K)}}\right]$$

Measurable time constants in experiments are λ_1^{-1} and λ_2^{-1} (i.e. τ_R and τ_r).

general solution for d and h:

$$A_0^{(\ell)} + A_1^{(\ell)}\exp(-\lambda_1 t) + A_2^{(\ell)}\exp(-\lambda_2 t)$$

where $\ell = \{d, h\}$

Approximations:

$$\boxed{\begin{aligned}\tilde{\tau}_1 &\simeq \lambda_1^{-1} \\ \tilde{\tau}_2 &\simeq \lambda_2^{-1}\left[1+K(1+K)\right]/(1+K)^2\end{aligned}}$$

$$\dot{h} = \alpha_1(1-h-d) - \beta_1 h \qquad (1)$$

$$\dot{d} = \beta_2(1-h-d) - \alpha_2 d \qquad (2)$$

As (1) describes much faster process than (2), the authors used rapid equilibrium hypothesis on the former: assume steady state $\frac{dh}{dt} = 0$. Then:

$$\left.\begin{aligned} h &= \frac{\alpha_1(1-d)}{\alpha_1+\beta_1} \\ &(2) \end{aligned}\right) \Rightarrow$$

$$) \Rightarrow \quad \dot{d} = \beta_2\left(1 - \frac{\alpha_1(1-d)}{\alpha_1+\beta_1} - d\right) - \alpha_2 d =$$

$$= \beta_2 - \frac{\alpha_1\beta_2(1-d)}{\alpha_1+\beta_1} - \beta_2 d - \alpha_2 d =$$

$$= \frac{\cancel{\alpha_1\beta_2} + \beta_1\beta_2 - \cancel{\alpha_1\beta_2} + \cancel{\alpha_1\beta_2 d} - \cancel{\alpha_1\beta_2 d} - \beta_1\beta_2 d - \alpha_1\alpha_2 d - \alpha_2\beta_1 d}{\alpha_1+\beta_1} =$$

$$= \frac{\alpha_1\alpha_2 K^2(1-d) - \alpha_1\alpha_2 d - \alpha_1\alpha_2 K d}{\alpha_1+\beta_1}$$

$$\dot{d} = \frac{\alpha_1\alpha_2K^2(1-d) - \alpha_1\alpha_2 d - \alpha_1\alpha_2 K d}{\alpha_1 + \alpha_1 K} =$$

$$= \frac{\alpha_2K^2(1-d) - \alpha_2 d - \alpha_2 K d}{1+K} = \frac{\alpha_2\left(K^2 - K^2 d - d - Kd\right)}{1+K} =$$

$$= \frac{\alpha_2\left(K^2 - d\left(1+K(1+K)\right)\right)}{1+K} = -\frac{\alpha_2\left(1+K(1+K)\right)}{1+K}\, d + \frac{\alpha_2 K^2}{1+K}.$$

$$\frac{1+K}{\alpha_2\left(1+K(1+K)\right)}\,\dot{d} = -d + \frac{\cancel{\alpha_2}K^2}{\cancel{1+K}} \cdot \frac{\cancel{1+K}}{\cancel{\alpha_2}\left(1+K(1+K)\right)}$$

$$\frac{1+K}{\alpha_2\left(1+K(1+K)\right)} \equiv \lambda_2^{-1}$$

$$\boxed{\lambda_2^{-1}\dot{d} = -d + \frac{K^2}{1+K(1+K)}} \quad (*)$$

$$\alpha_1 = \frac{1}{\tau_1(1+K_1)}$$

$$\left.\begin{aligned} \lambda_2^{-1} &= \frac{1+K}{\alpha_2\left(1+K(1+K)\right)} \\ \alpha_2 &= \frac{1}{\tau_2(1+K)} \end{aligned}\right) \Rightarrow \lambda_2^{-1} = \frac{\tau_2(1+K)^2}{1+K(1+K)}$$

$$\boxed{\tau_2 = \frac{\lambda_2^{-1}\left(1+K(1+K)\right)}{(1+K)^2}}$$

$$\frac{dh}{dt} = \frac{\phi\,(h_\infty - h)}{\tau_h(V)}$$

$$h_\infty(V) = \frac{1}{1+\exp\left[(V-\theta_h)/k_h\right]}$$

$$\tau_h(V) = h_\infty(V)\exp\left((V+162.3)/17.8\right) + 20$$

$$\tau_2 \simeq \lambda_2^{-1}\,\frac{1+K(1+K)}{(1+K)^2} = \lambda_2^{-1}\,\frac{1+K+K^2}{(1+K)^2} =$$

$$= \lambda_2^{-1}\,\frac{1+K+K^2}{1+K+K^2+K} = \lambda_2^{-1}\frac{h_\infty^{-1}}{h_\infty^{-1}+K} = \lambda_2^{-1}\,\frac{1}{1+h_\infty K} =$$

$$= \lambda_2^{-1}\,\frac{1}{1+h_\infty\left(\sqrt{h_\infty^{-1}-0.75}-0.5\right)} =$$

$$= \frac{\lambda_2^{-1}}{1+\sqrt{h_\infty - 0.75\,h_\infty^2}-0.5\,h_\infty}$$