13 State Model

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\begin{tikzcd}
C4 \arrow[r, leftrightarrow] \arrow[d, leftrightarrow] & C3 \arrow[r, leftrightarrow] \arrow[d, leftrightarrow] & C2 \arrow[r, leftrightarrow] \arrow[d, leftrightarrow] & C1 \arrow[r, leftrightarrow] \arrow[d, leftrightarrow] & C0 \arrow[r, leftrightarrow] & OS \arrow[r, leftrightarrow] \arrow[d, leftrightarrow] & IN \arrow[d, leftrightarrow] \\
C4IC1 \arrow[r, leftrightarrow] & C3IC1 \arrow[r, leftrightarrow] & C2IC1 \arrow[r, leftrightarrow] & C1IC1 \arrow[rr, leftrightarrow] & & IC1 \arrow[r, leftrightarrow] & INC1
\end{tikzcd}
$$

This is a 13 state model, representing a potassium channel with 4 independent voltage sensors and two inactivation mechanism. The number of voltage sensors in the closed state is indicated by *C4*, *C3*, *C2*, *C1* and *C0* respectively, C-type inactivation by *IC1* and N-type inactivation by *IN*. Hence *C3IC1* is the state in which 3 of the voltage sensors are in the closed conformation and the channel is C-type inactivated and *INC1* has all 4 sensors in the open conformation but is both C-type and N-type inactivated. *C0* is the pre-activated state, where all voltage sensors are in the open state but the channel is still closed and *OS* is the open state. The transitions rates are given by:

C4 -> C3 : $4\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C3 -> C4 : $\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C3 -> C2 : $3\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C2 -> C3 : $2\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C2 -> C1 : $2\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C1 -> C2 : $3\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C1 -> C0 : $\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C0 -> C1 : $4\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C4IC1 -> C3IC1 : $4\mathrm{v}_c^{ic}\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C3IC1 -> C4IC1 : $\mathrm{r}_c^{ic}\mathrm{v}_c^{ic}\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C3IC1 -> C2IC1 : $3\mathrm{v}_c^{ic}\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C2IC1 -> C3IC1 : $2\mathrm{r}_c^{ic}\mathrm{v}_c^{ic}\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C2IC1 -> C1IC1 : $2\mathrm{v}_c^{ic}\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C1IC1 -> C2IC1 : $3\mathrm{r}_c^{ic}\mathrm{v}_c^{ic}\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C1IC1 -> IC1 : $\mathrm{v}_c^{ic}\mathrm{k}_c \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

IC1 -> C1IC1 : $4\mathrm{r}_c^{ic}\mathrm{v}_c^{ic}\mathrm{k}_c\mathrm{k}_{cf}^{ic} \ \exp(\mathrm{H}_{kc}\Delta\mathrm{T}) \ \exp\left(-\mathrm{Z}_c \frac{\mathrm{F}(\mathrm{V}-\mathrm{V}_c-\mathrm{H}_{vc}\Delta\mathrm{T})}{\mathrm{A}}\right)$

C0 -> OS : k_o
OS -> C0 : $\mathrm{k}_o r_o$

OS -> IC1 : $k_i \exp(H_{ki}\Delta T)$

IC1 -> OS : $k_i r_i \exp(H_{ki}\Delta T) \exp(H_{ri}\Delta T)$

C1IC1 -> C1 : $k_i r_i (v_{ic}^c)^1 \exp(H_{ki}\Delta T) \exp(H_{ri}\Delta T) \exp(H_{vic}^c\Delta T)$

C1 -> C1IC1 : $k_i (r_{ic}^c v_{ic}^c)^1 \exp(H_{ki}\Delta T) \exp(H_{ric}^c\Delta T)\exp(H_{vic}^c\Delta T)$

C2IC1 -> C2 : $k_i r_i (v_{ic}^c)^2 \exp(H_{ki}\Delta T) \exp(H_{ri}\Delta T) \exp(H_{vic}^c\Delta T)$

C2 -> C2IC1 : $k_i (r_{ic}^c v_{ic}^c)^2 \exp(H_{ki}\Delta T) \exp(H_{ric}^c\Delta T)\exp(H_{vic}^c\Delta T)$

C3IC1 -> C3 : $k_i r_i (v_{ic}^c)^3 \exp(H_{ki}\Delta T) \exp(H_{ri}\Delta T) \exp(H_{vic}^c\Delta T)$

C3 -> C3IC1 : $k_i (r_{ic}^c v_{ic}^c)^3 \exp(H_{ki}\Delta T) \exp(H_{ric}^c\Delta T)\exp(H_{vic}^c\Delta T)$

C4IC1 -> C4 : $k_i r_i (v_{ic}^c)^4 \exp(H_{ki}\Delta T) \exp(H_{ri}\Delta T) \exp(H_{vic}^c\Delta T)$

C4 -> C4IC1 : $k_i (r_{ic}^c v_{ic}^c)^4 \exp(H_{ki}\Delta T) \exp(H_{ric}^c\Delta T)\exp(H_{vic}^c\Delta T)$

OS -> IN : $k_n \exp(H_{kn}\Delta T)$

IN -> OS : $k_n r_n \exp(H_{kn}\Delta T) \exp(H_{rn}\Delta T)$

IC1 -> INC1 : $k_n r_n^{ic} v_n^{ic} \exp(H_{kn}\Delta T) \exp\left(H_{rn}^{ic}\Delta T\right)\exp\left(H_{vn}^{ic}\Delta T\right)$

INC1 -> IC1 : $k_n r_n v_n^{ic} \exp(H_{kn}\Delta T) \exp(H_{rn}\Delta T) \ \exp\left(H_{vn}^{ic}\Delta T\right)$

IN -> INC1 : $k_i r_{ic}^n v_{ic}^n \exp(H_{ki}\Delta T) \exp(H_{ric}^n\Delta T)\exp(H_{vic}^n\Delta T)$

INC1 -> IN : $k_i r_i v_{ic}^n \exp(H_{ki}\Delta T) \exp(H_{ri}\Delta T) \exp(H_{vic}^n\Delta T)$

With the conditions (stemming from microreversibility):

$$r_c^{ic} = r_{ic}^c$$
$$r_n^{ic} = r_{ic}^n$$
$$k_{cf}^{ic} = r_o$$
$$H_{ric}^c = 0$$
$$H_{rn}^{ic} = H_{ric}^n$$

and $R = 8.134 \left[\frac{J}{\text{mol K}}\right]$ and $F = 96.485 \left[\frac{J}{\text{mV mol}}\right]$. V [mV] is the transmembrane voltage and $\Delta T = T - 298.15$ [K] is the difference with room temperature. Z_c is the equivalent charge for activation and V_c [mV] the voltage of half activation at 25C.

The model was fit directly to experimental current traces obtained with diverse voltage protocols and measured at 3 different temperatures (15C, 25C and 35C) for a total of 195 traces. The fit was performed with the Data2Dynamics software (https://github.com/Data2Dynamics/d2d).