11 State Model

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

This is an 11 state model, representing a potassium channel with 4 independent voltage sensors and one inactivation mechanism. The number of voltage sensors in the closed state is indicated by *C4*, *C3*, *C2*, *C1* and *C0* respectively, and inactivation by *IC1*. Hence *C3IC1* is the state in which 3 of the voltage sensors are in the closed conformation and the channel is 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 : $4\mathrm{k}_c \exp\left(\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

C3 -> C4 : $\mathrm{k}_c \exp\left(-\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

C3 -> C2 : $3\mathrm{k}_c \exp\left(\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

C2 -> C3 : $2\mathrm{k}_c \exp\left(-\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

C2 -> C1 : $2\mathrm{k}_c \exp\left(\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

C1 -> C2 : $3\mathrm{k}_c \exp\left(-\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

C1 -> C0 : $\mathrm{k}_c \exp\left(\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

C0 -> C1 : $4\mathrm{k}_c \exp\left(-\mathrm{Z}_c \frac{\mathrm{F(V-V}_c)}{\mathrm{A}}\right)$

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

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

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

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

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

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

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

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

C0 -> OS : k_o

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

OS -> IC1 : k_i
IC1 -> OS : $\mathrm{k}_i \mathrm{r}_i$

C1IC1 -> C1 : $\mathrm{k}_i \mathrm{r}_i (\mathrm{v}_{ic}^{c})^1$
C1 -> C1IC1 : $\mathrm{k}_i (\mathrm{r}_{ic}^{c} \mathrm{v}_{ic}^{c})^1$
C2IC1 -> C2 : $\mathrm{k}_i \mathrm{r}_i (\mathrm{v}_{ic}^{c})^2$
C2 -> C2IC1 : $\mathrm{k}_i (\mathrm{r}_{ic}^{c} \mathrm{v}_{ic}^{c})^2$
C3IC1 -> C3 : $\mathrm{k}_i \mathrm{r}_i (\mathrm{v}_{ic}^{c})^3$
C3 -> C3IC1 : $\mathrm{k}_i (\mathrm{r}_{ic}^{c} \mathrm{v}_{ic}^{c})^3$
C4IC1 -> C4 : $\mathrm{k}_i \mathrm{r}_i (\mathrm{v}_{ic}^{c})^4$
C4 -> C4IC1 : $\mathrm{k}_i (\mathrm{r}_{ic}^{c} \mathrm{v}_{ic}^{c})^4$

With the conditions (stemming from microreversibility):

$$\mathrm{r}_{c}^{ic} = \mathrm{r}_{ic}^{c}$$
$$\mathrm{k}_{cf}^{ic} = \mathrm{r}_o$$

and $\mathrm{R} = 8.134 \left[\frac{\mathrm{J}}{\mathrm{mol\ K}}\right]$ and $\mathrm{F} = 96.485 \left[\frac{\mathrm{J}}{\mathrm{mV\ mol}}\right]$. V [mV] is the transmembrane voltage. Z_c is the equivalent charge for activation and V_c [mV] the voltage of half activation.

The model was fit directly to experimental current traces obtained with diverse voltage protocols and measured at 35C for a total of 65 traces. The fit was performed with the Data2Dynamics software (https://github.com/Data2Dynamics/d2d).