6 State Model

$$CS \longleftrightarrow OS \longleftrightarrow IN$$

$$\updownarrow \qquad \updownarrow \qquad \updownarrow$$

$$CIC1 \longleftrightarrow IC1 \longleftrightarrow INC1$$
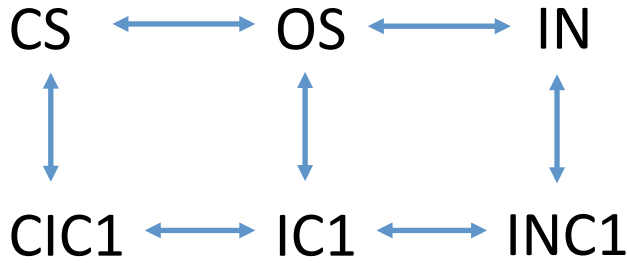
This is a 6 state model, with a closed state *CS*, an open state *OS*, a C-type inactivated state *IC1* and a closed C-type inactivated state *CIC1*, an N-type inactivated state *IN* and an N and C-type inactivated state *INC1*. The transitions rates are given by:

CS -> OS : $k_c \exp\left(Z_c \frac{F(V-V_c)}{A}\right)$

OS -> CS : $k_c \exp\left(-Z_c \frac{F(V-V_c)}{A}\right)$

OS -> IC1 : k_i

IC1 -> OS : $k_i r_i$

IC1 -> CIC1 : $r_c^{ic} v_c^{ic} k_c \exp\left(-Z_c \frac{F(V-V_c)}{A}\right)$

CIC1 -> IC1 : $v_c^{ic} k_c \exp\left(Z_c \frac{F(V-V_c)}{A}\right)$

CIC1 -> CS : $k_i r_i v_{ic}^c$

CS -> CIC1 : $k_i r_{ic}^c v_{ic}^c$

OS -> IN : k_n

IN -> OS : $k_n r_n$

IC1 -> INC1 : $k_n r_n^{ic} v_n^{ic}$

INC1 -> IC1 : $k_n r_n v_n^{ic}$

IN -> INC1 : $k_i r_{ic}^n v_{ic}^n$

INC1 -> IN : $k_i r_i v_{ic}^n$

With the conditions (stemming from microreversibility):
$$r_c^{ic} = r_{ic}^c$$
$$r_n^{ic} = r_{ic}^n$$

and R $= 8.134 \left[\frac{J}{mol\,K}\right]$ and F $= 96.485 \left[\frac{J}{mV\,mol}\right]$. 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).