Mathematical models of action potentials

Part 3

Icahn School of Medicine at Mount Sinai

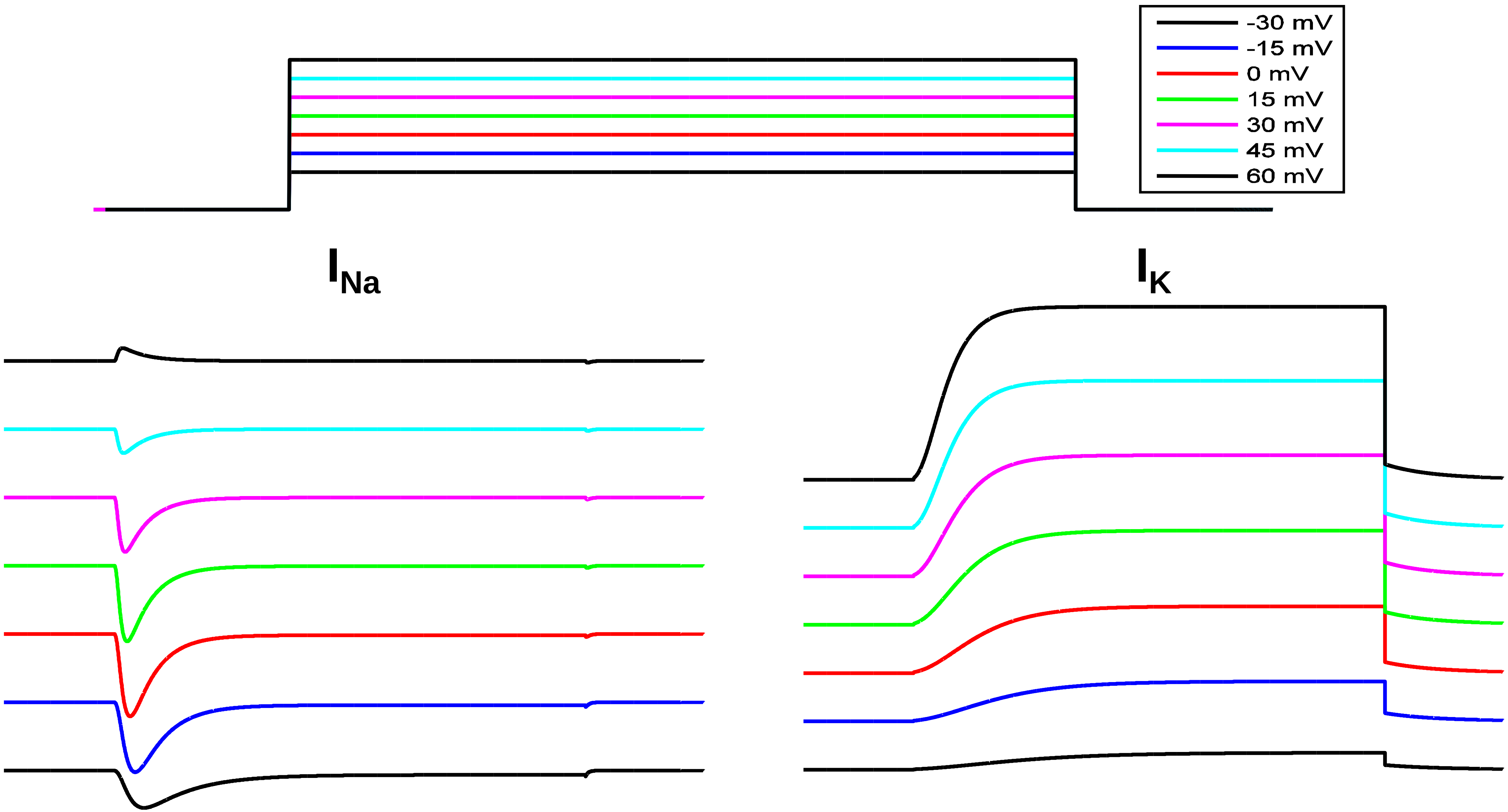
SBCNY

Outline: Part 3

The Hodgkin-Huxley (1952) action potential model

- **Deriving the model equations from the experimental records**
- **Converting from currents to conductances**
- **K^+ conductance: increases with a delay**
- **Na^+ conductance: increases then decreases (inactivates)**

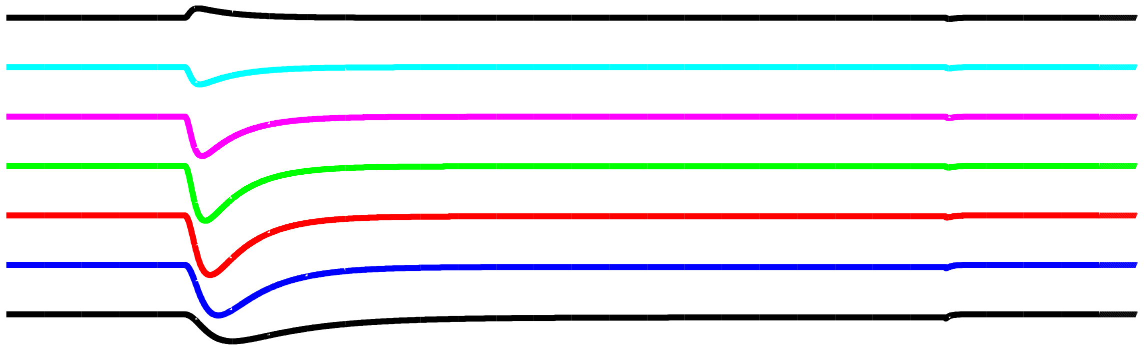
I_{Na} and I_K at different membrane potentials



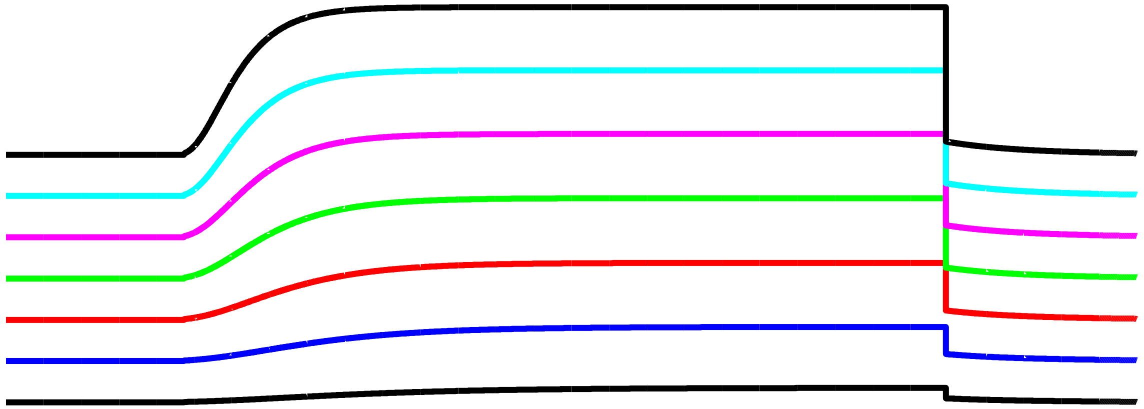
$I_X = g_X*(V-E_X)$, change in current can reflect conductance or driving force

Convert from currents to conductances

I_{Na}



I_K



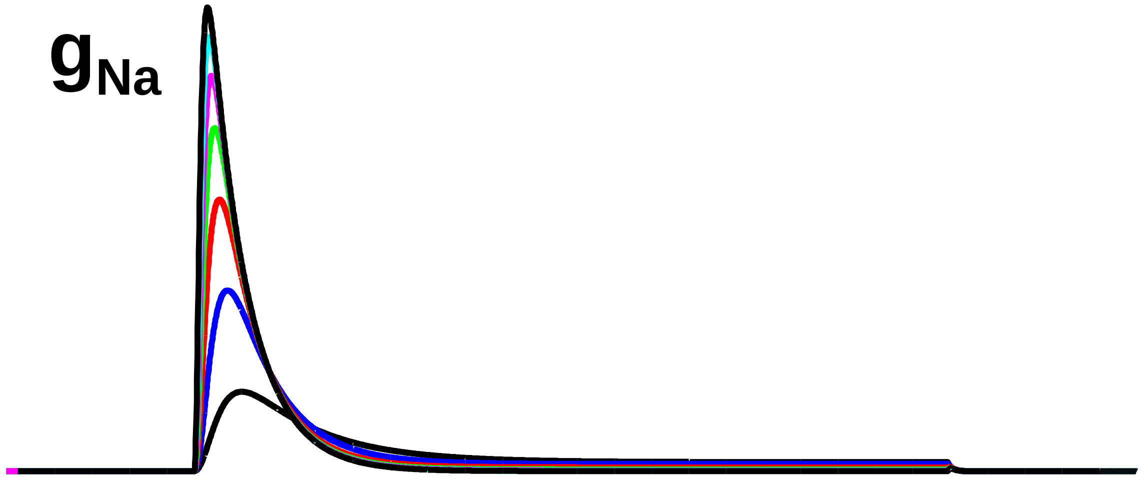
$I_{Na} = g_{Na}*(V - E_{Na})$

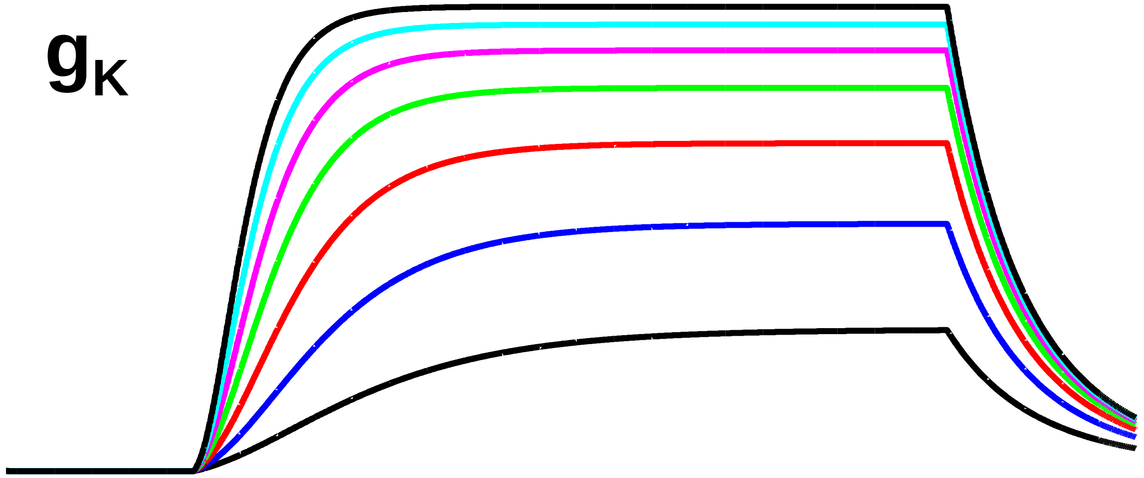
$I_K = g_K*(V - E_K)$

therefore:

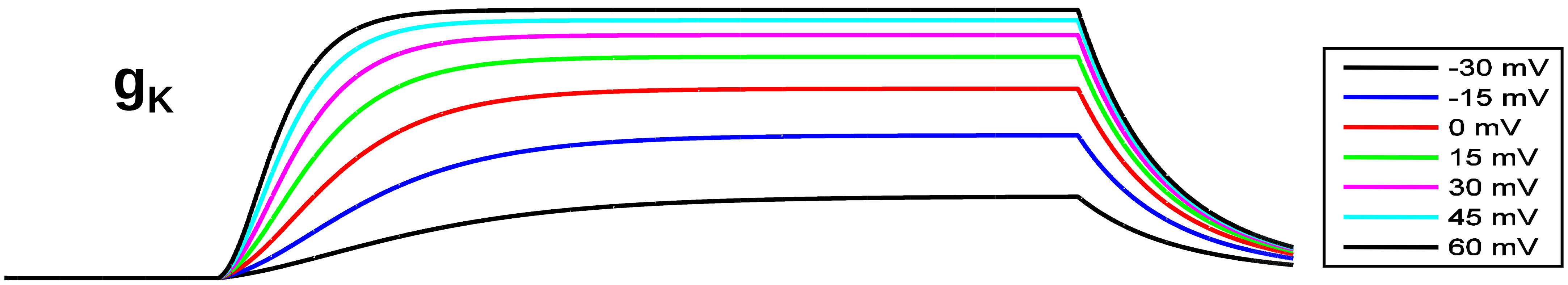
$g_{Na} = I_{Na}/(V - E_{Na})$

$g_K = I_K/(V - E_K)$



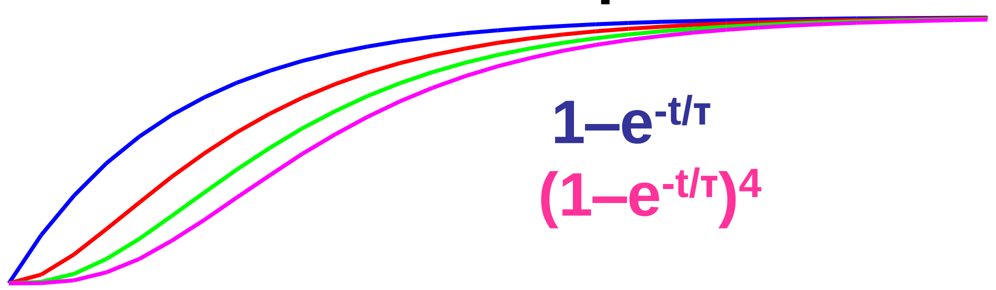


Focus on potassium conductance



1) Changing V changes both steady-state g_K and rate of rise

2) Time course of g_K increase similar to an exponential raised to a power



These facts suggest the following model:

n = fraction of particles in "permissive" state

conductance proportional to n^4

$$g_K = g_{K,max} n^4$$

$$(1-n) \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} n$$

$dn/dt = \alpha(1-n) - \beta n$

α and β are functions of voltage

gating variable n
always between 0 and 1

How are the functions for $\alpha(V)$ and $\beta(V)$ determined?

$$dn/dt = \alpha(1-n) - \beta n = \alpha - (\alpha + \beta)n$$

This equation has the steady-state ($t=\infty$) solution:

$$n_\infty = \alpha/(\alpha + \beta)$$

The steady-state value is reached with a time constant:

$$\tau = 1/(\alpha + \beta)$$

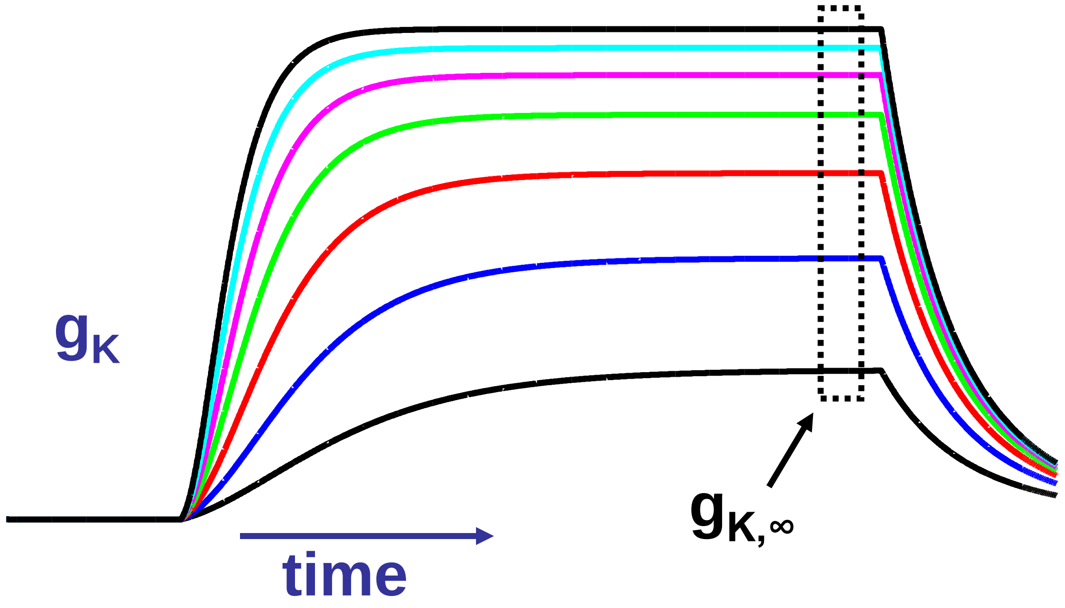
Rearranging terms: $\alpha = n_\infty/\tau \quad \beta = (1 - n_\infty)/\tau$

So if we know $n_\infty(V)$ and $\tau(V)$, we can determine $\alpha(V)$ and $\beta(V)$

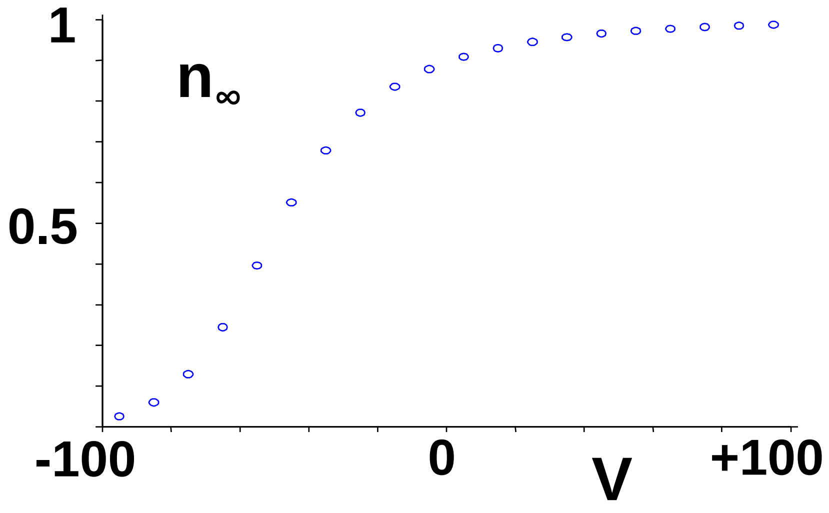
$n_\infty(V)$ and $\tau(V)$ can be extracted from the data. How?

How are the functions for α(V) and β(V) determined?

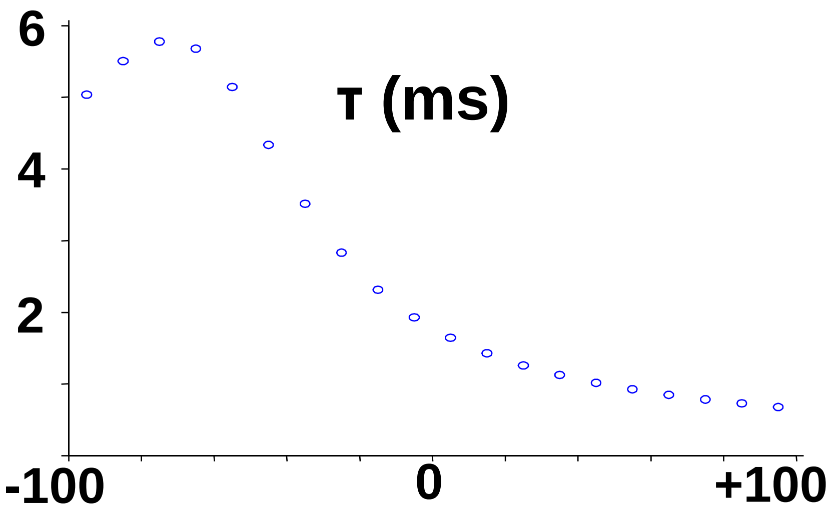
g_K as a function of time and voltage tells us n_∞ and τ



$g_K \sim n^4$ $\quad n_\infty \sim \sqrt[4]{g_{K_\infty}}$



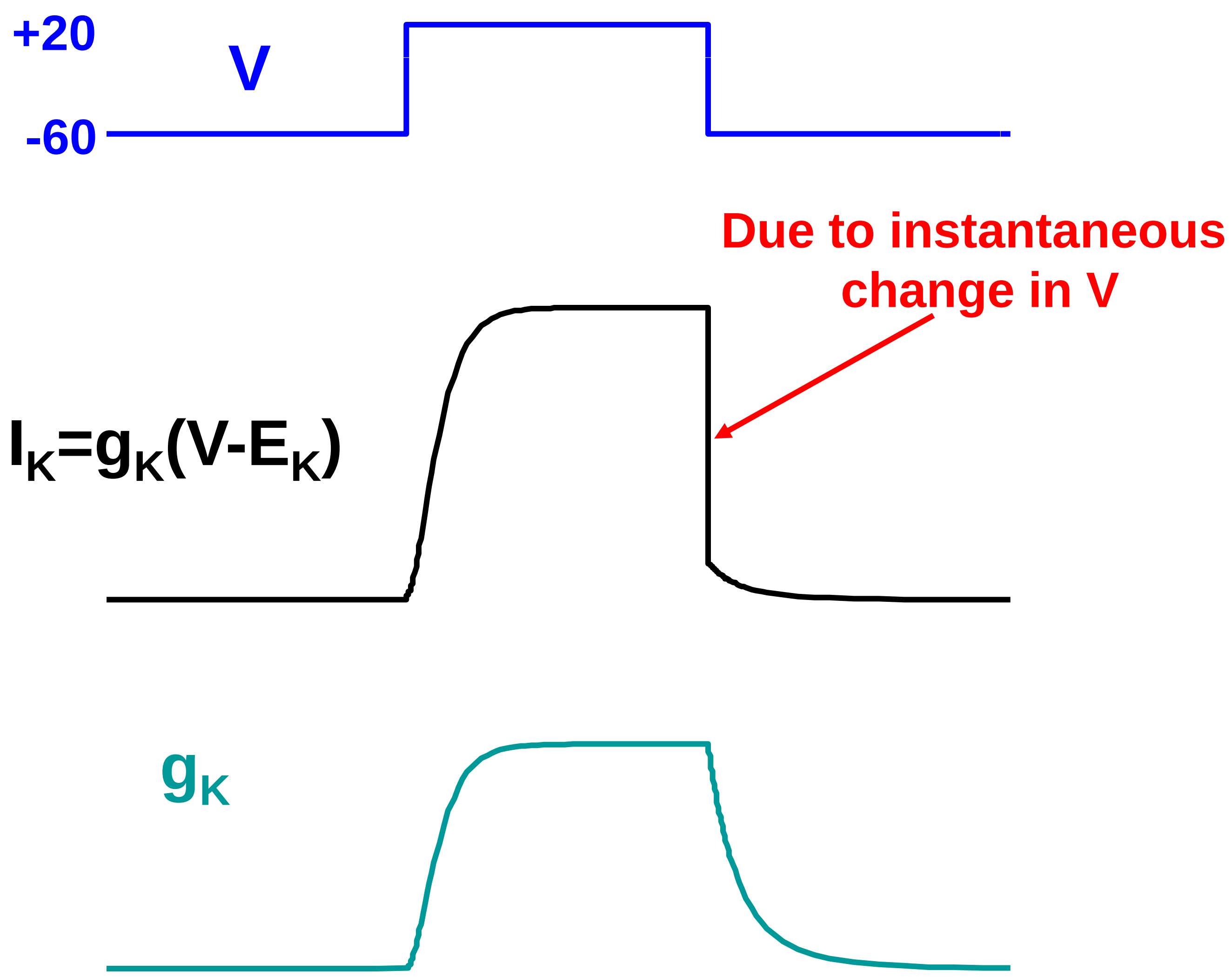
To determine τ(V), plot $\left(1 - e^{-t/\tau}\right)^4$ for different τ, choose best fit

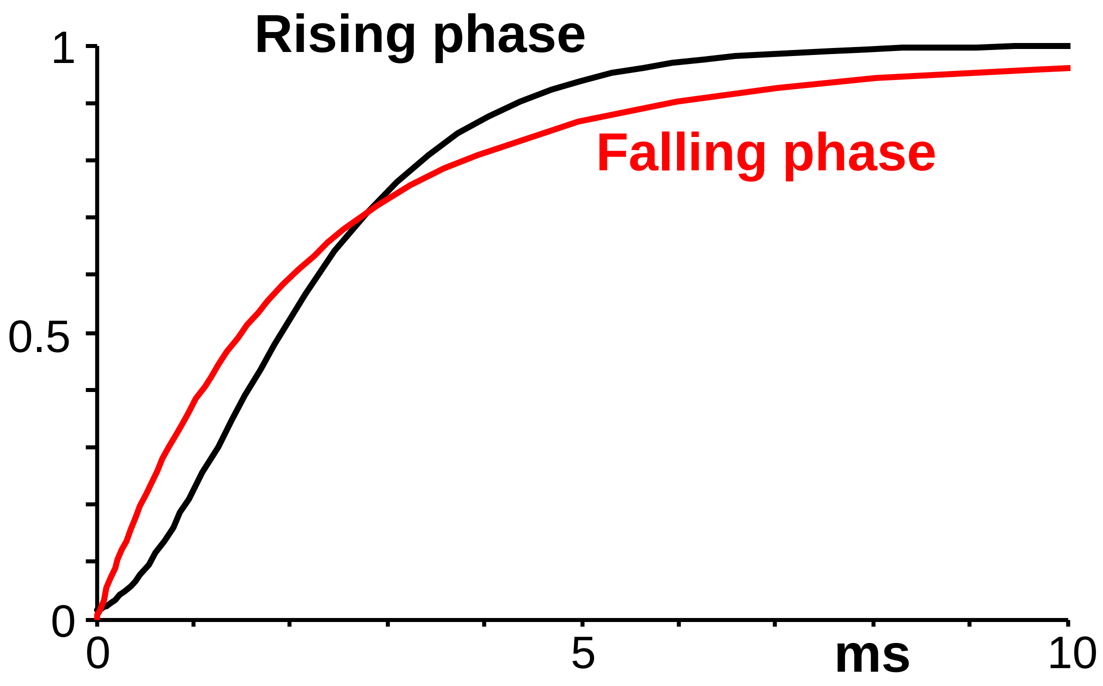


Then solve: $\alpha = n_\infty / \tau$ $\quad \beta = (1 - n_\infty)/\tau$

Time course of conductance changes

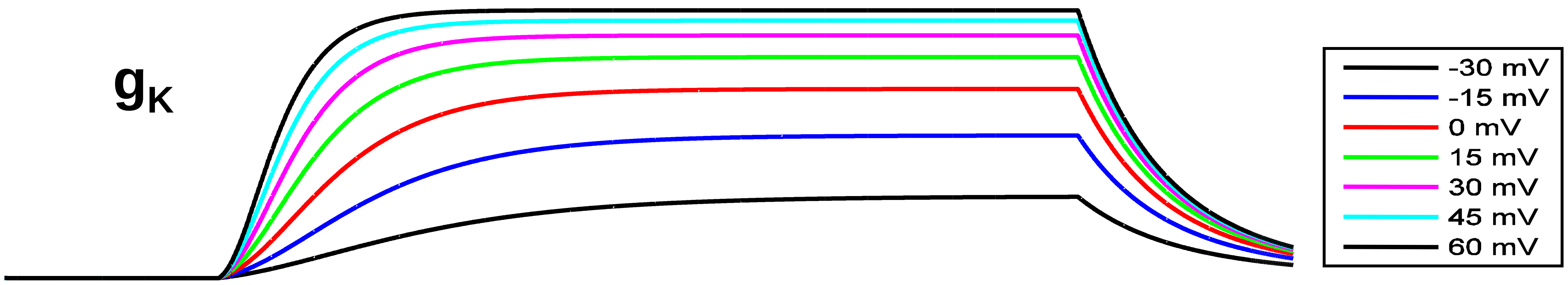
Rising phase has a delay, falling phase does not!





Time course of conductance changes

Rising phase has a delay, falling phase does not!



This is a consequence of $g_K \sim n^4$

$$(1-n) \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} n$$

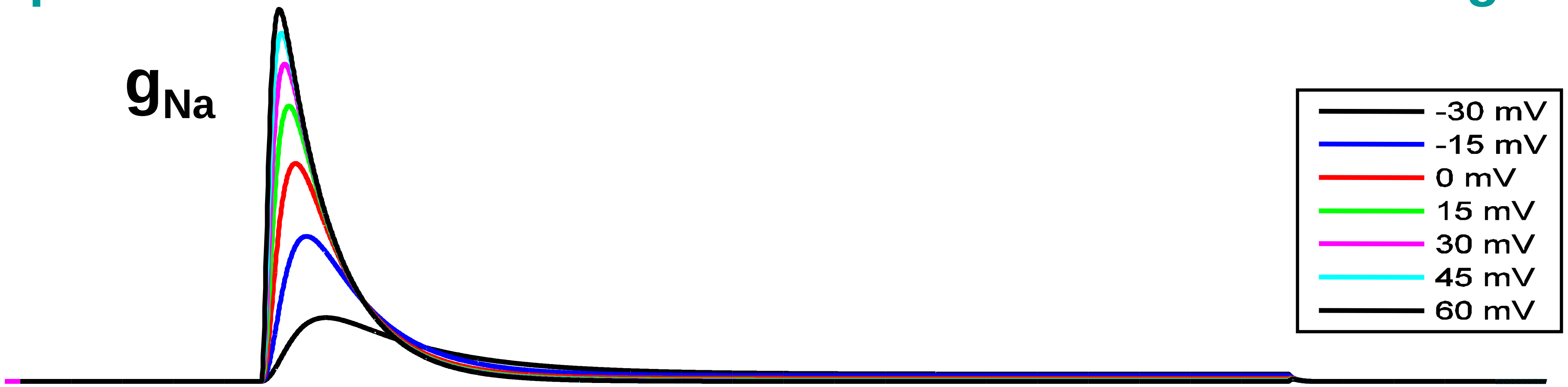
When conductance increases, all 4 charged particles must move
When conductances decreases, 1 out of 4 is sufficient

This model now has a well-established physical basis, namely that as most ion channels are tetramers.

Focus on sodium conductance

Slightly more complicated than g_K

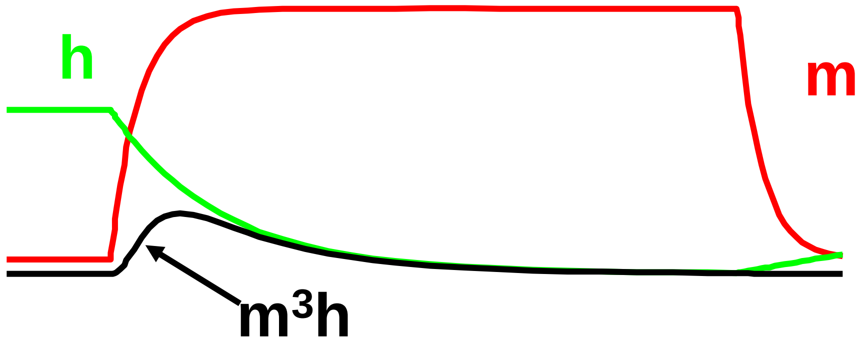
How to explain both the increase and decrease at constant voltage?



H & H postulated separate activation and inactivation processes

$g_{Na} \sim m^3h$

Both must be > 0 for appreciable g_{Na}



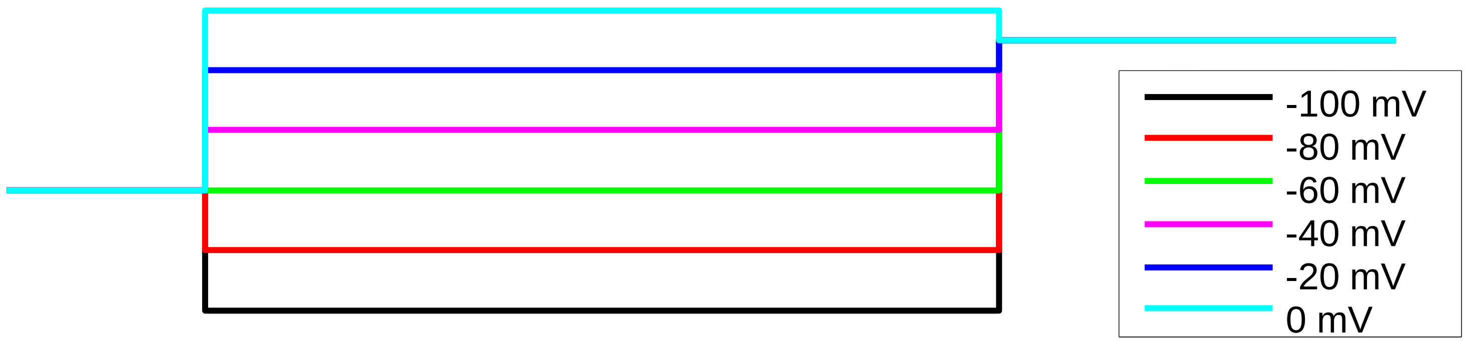
m must be faster than h

This idea also now has a physical basis, "ball-and-chain" inactivation.

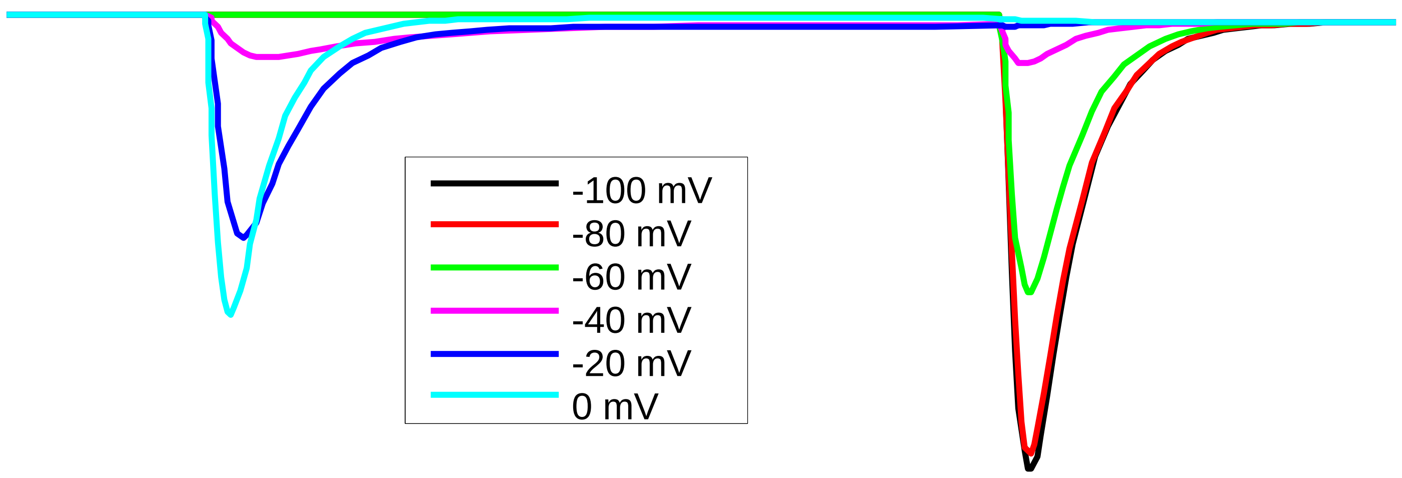
Focus on sodium conductance

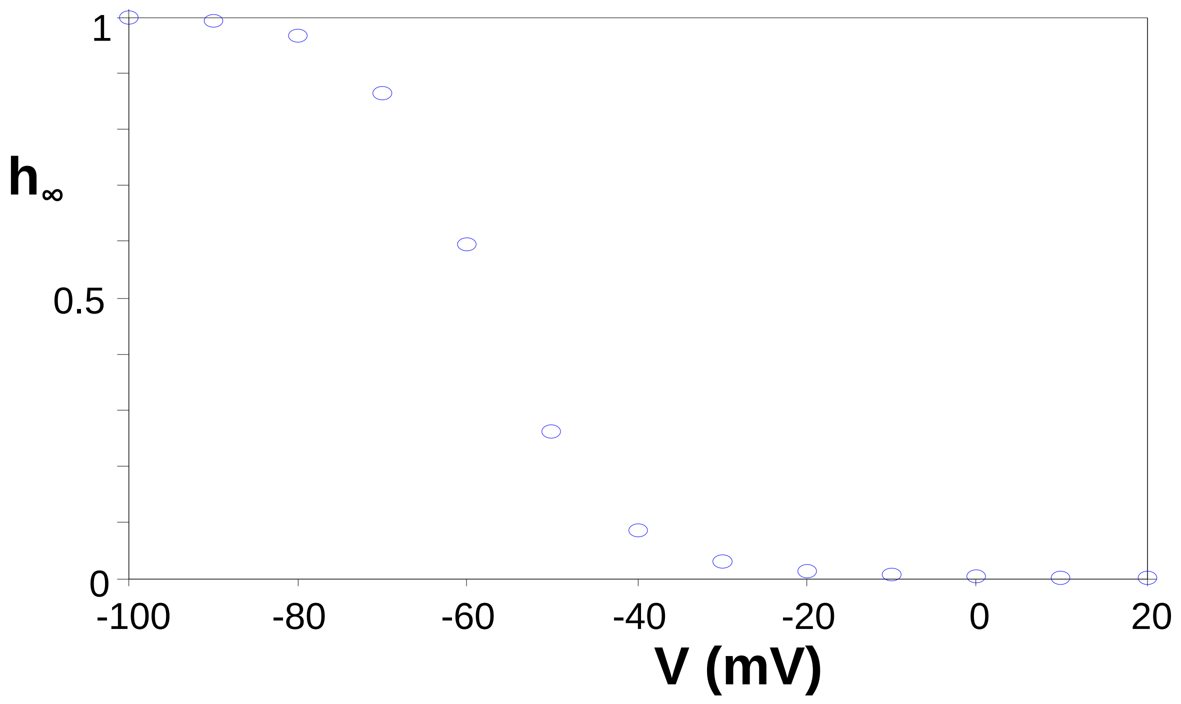
How to derive both m and h from the data?

A clever experiment to measure steady-state value of h



Measure I_{Na} due to *second* pulse





If first pulse is long, this gives value of steady-state inactivation, h_∞

Summary

Changes in K^+ conductance and Na^+ conductance can be described by "gating variables" that range from 0 to 1.

K^+ conductance is described by a single variable (n). Na^+ conductance is described by the product of an activation variable (m) and an inactivation variable (h).

The terms describing how gating variables depend on voltage are extracted directly from the experimental voltage clamp data.