Mathematical models of action potentials

Part 2

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Outline: Part 2

Biology

The challenges in understanding neuronal electrophysiology

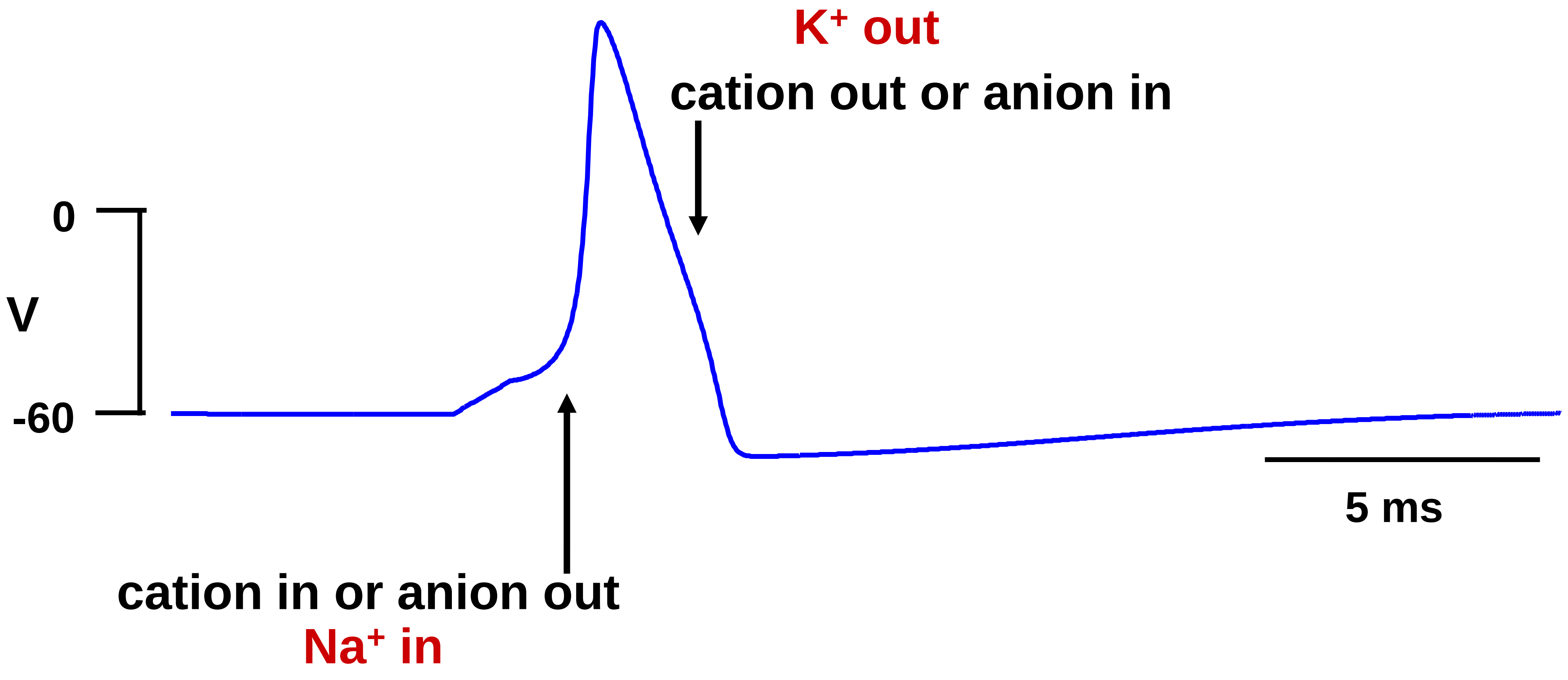
The importance of the voltage-clamp technique

Separating Na^+ and K^+ currents

Theme

Voltage clamp was the key advance that made the Hodgkin-Huxley model possible

Voltage changes result from ion movements



Why do we call this the Hodgkin-Huxley model?

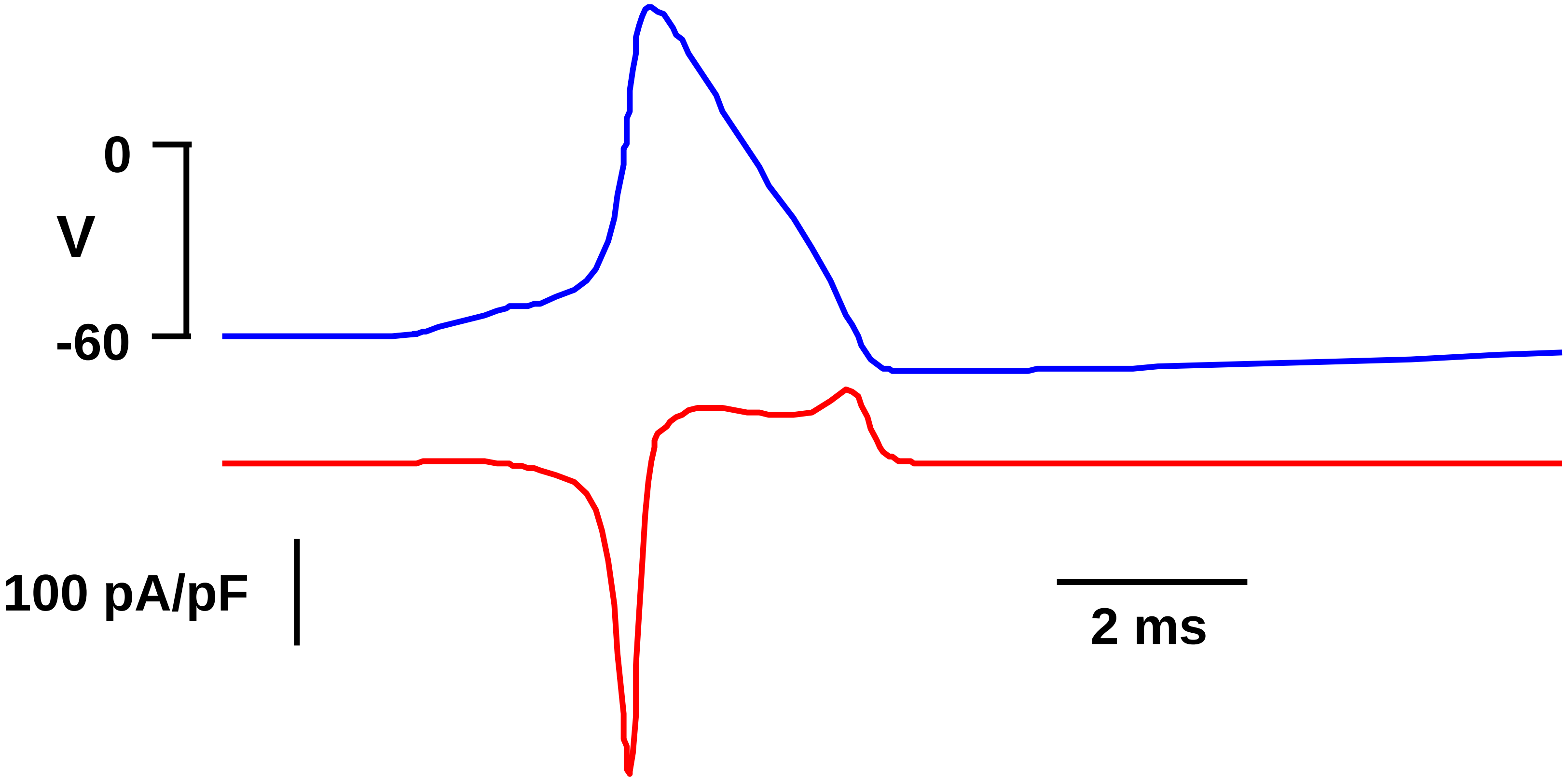
Sir Alan Hodgkin

1914-1998
Nobel Prize 1963

Sir Andrew Huxley

1917-2012
Nobel Prize 1963

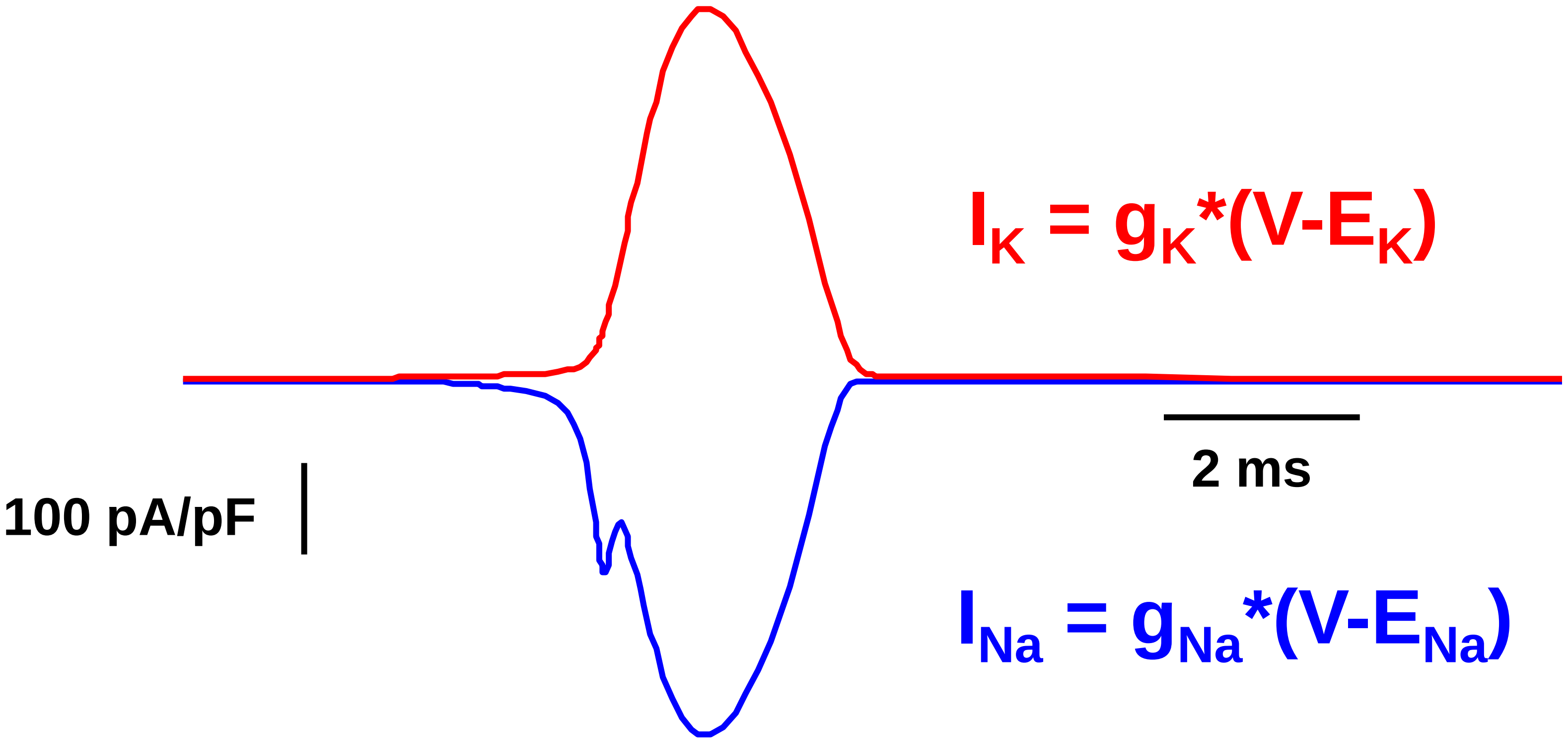
What if Hodgkin & Huxley knew the currents?



$$C_m \frac{dV}{dt} = -I_{ion}$$

Imagine that we can magically separate Na^+ and K^+ currents

What if Hodgkin & Huxley knew the currents?



$I_K = g_K{*}(V-E_K)$

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

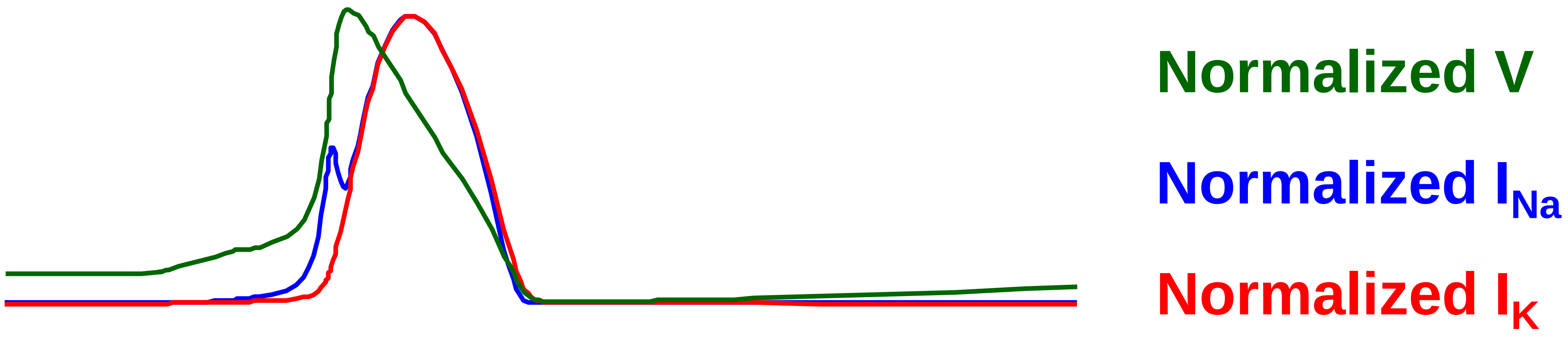
Change in current could result from:

change in conductance g_X, or

change in driving forcre $V\text{-}E_X$

Now let's plot V, I_K, and I_{Na} all on the same scale

What if Hodgkin & Huxley knew the currents?



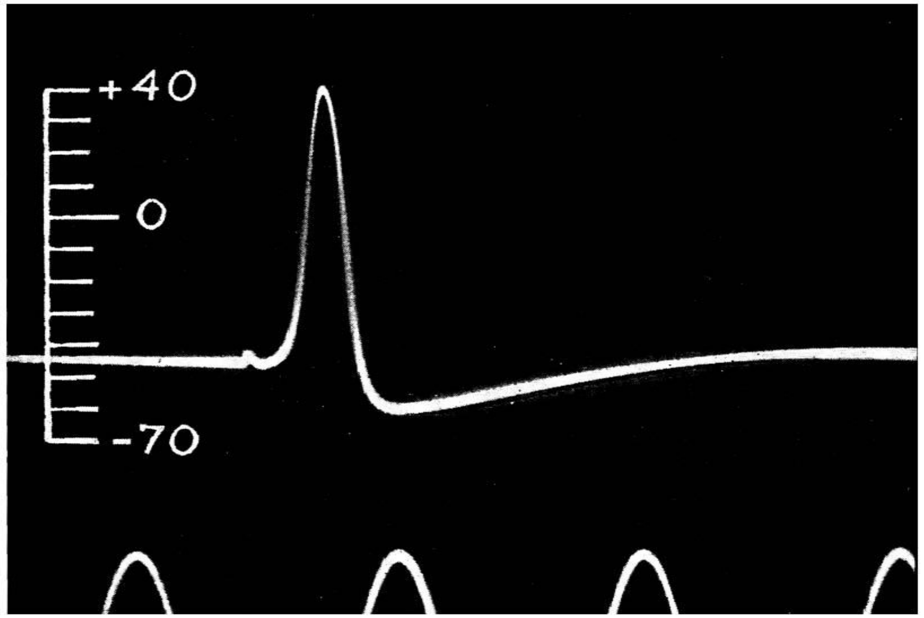
So the problem is:

(1) a change in voltage causes a change in current
(2) a change in current causes a change in voltage

This makes it difficult to separate

Brief historical note

Action potential recorded at Marine Biological Association at Plymouth



Hodgkin & Huxley (1939) *Nature* 144:710-711

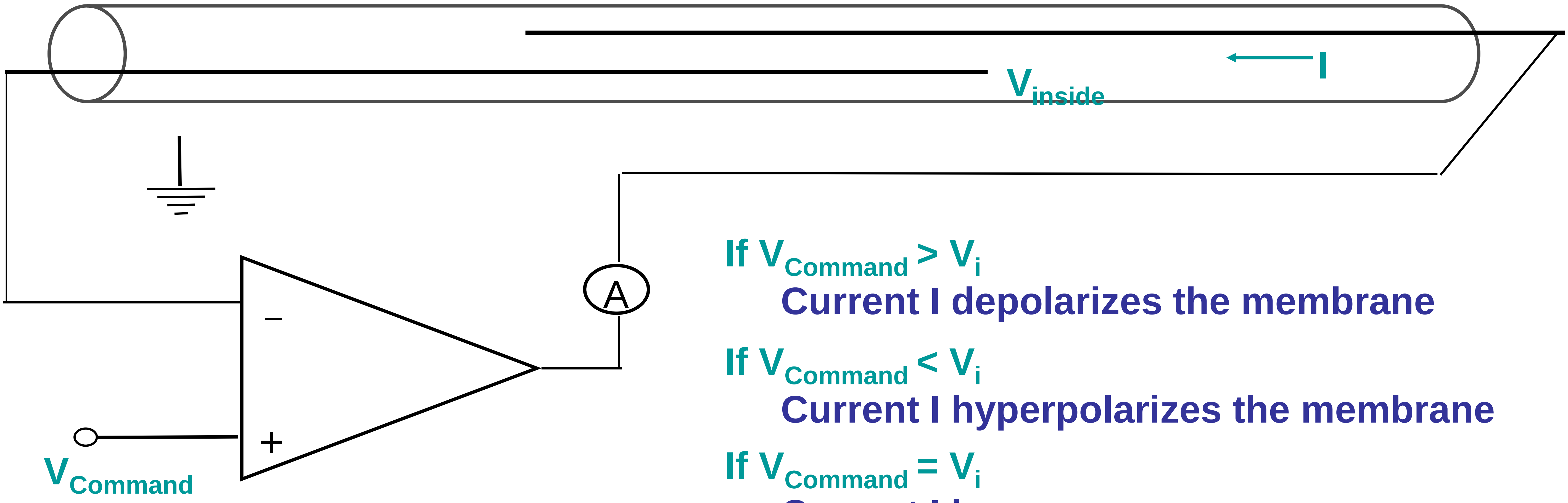
Hodgkin & Huxley left Plymouth: August 30, 1939

Hitler invaded Poland: September 1, 1939

"We published this result in a letter in *Nature* (1939) with no discussion or explanation. In a full paper (1945) we gave four possible explanations, all wrong."

Huxley (2002) *J. Physiol.* 539:2

Voltage clamp of squid giant axon



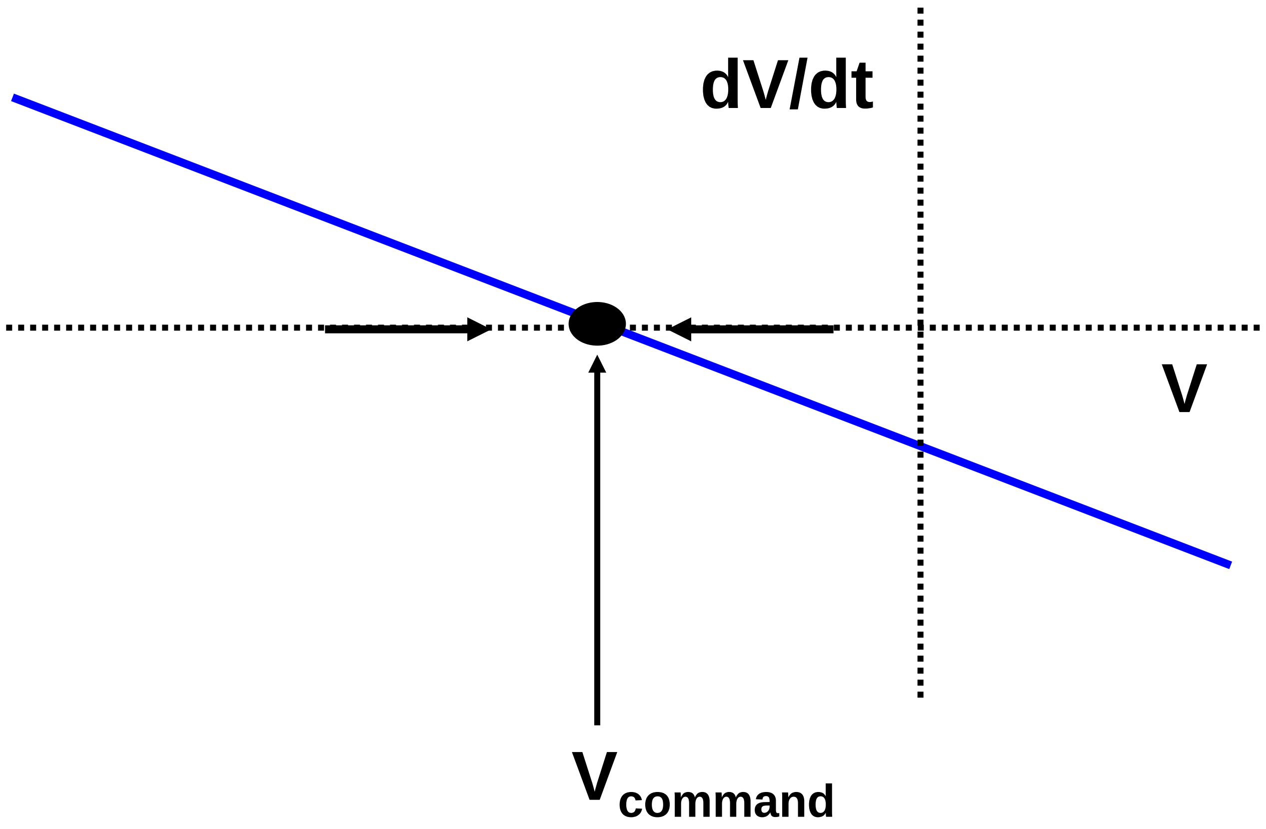
If $V_{Command} > V_i$
Current I depolarizes the membrane

If $V_{Command} < V_i$
Current I hyperpolarizes the membrane

If $V_{Command} = V_i$
Current I is zero

Current I required to keep $V_{command}=V_i$ is equal in magnitude to current flowing across the membrane

Voltage clamp as 1D dynamical system



If $V_{Command} > V_i$

Current I depolarizes the membrane

If $V_{Command} < V_i$

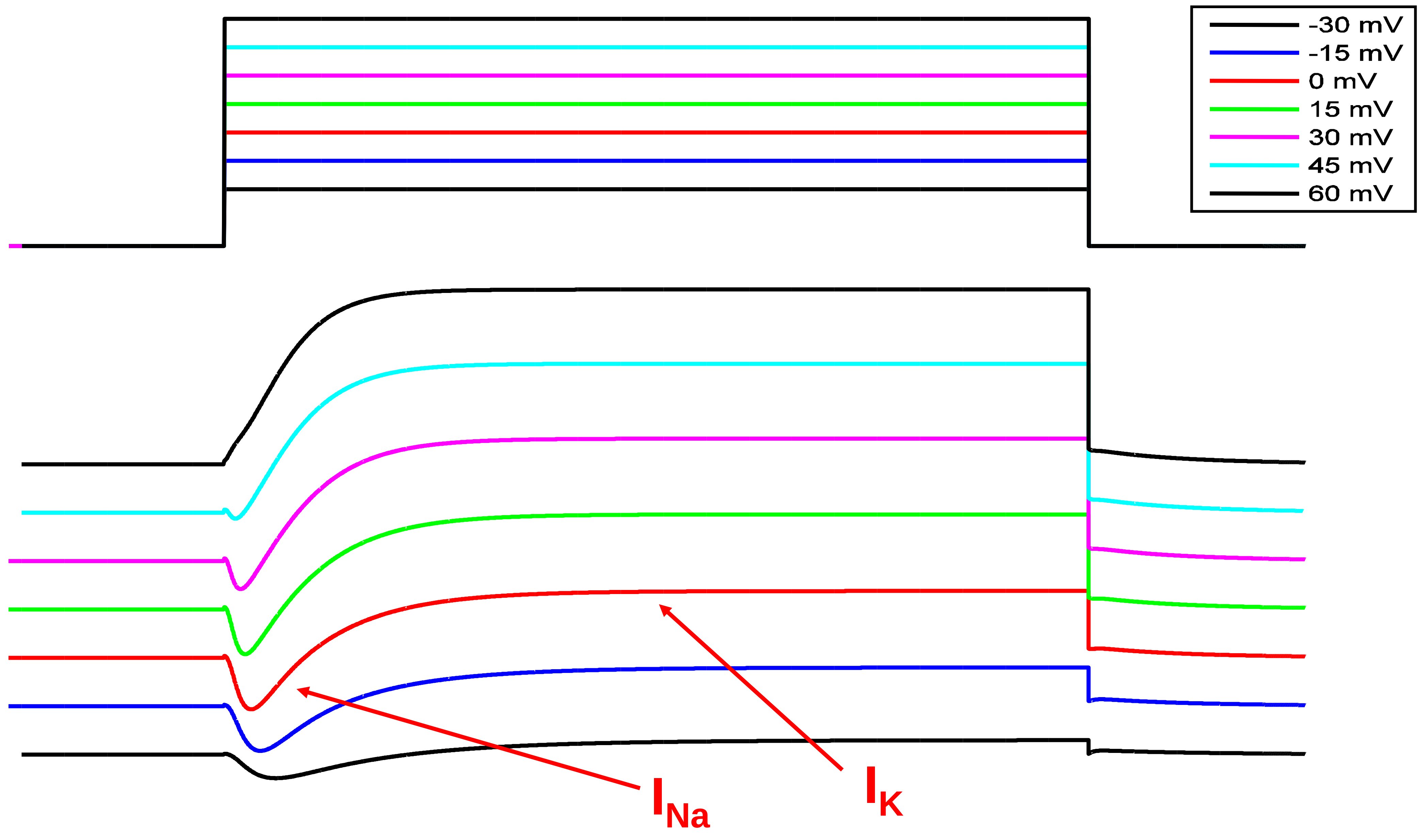
Current I hyperpolarizes the membrane

If $V_{Command} = V_i$

Current I is zero

Command voltage therefore constitutes a stable fixed point

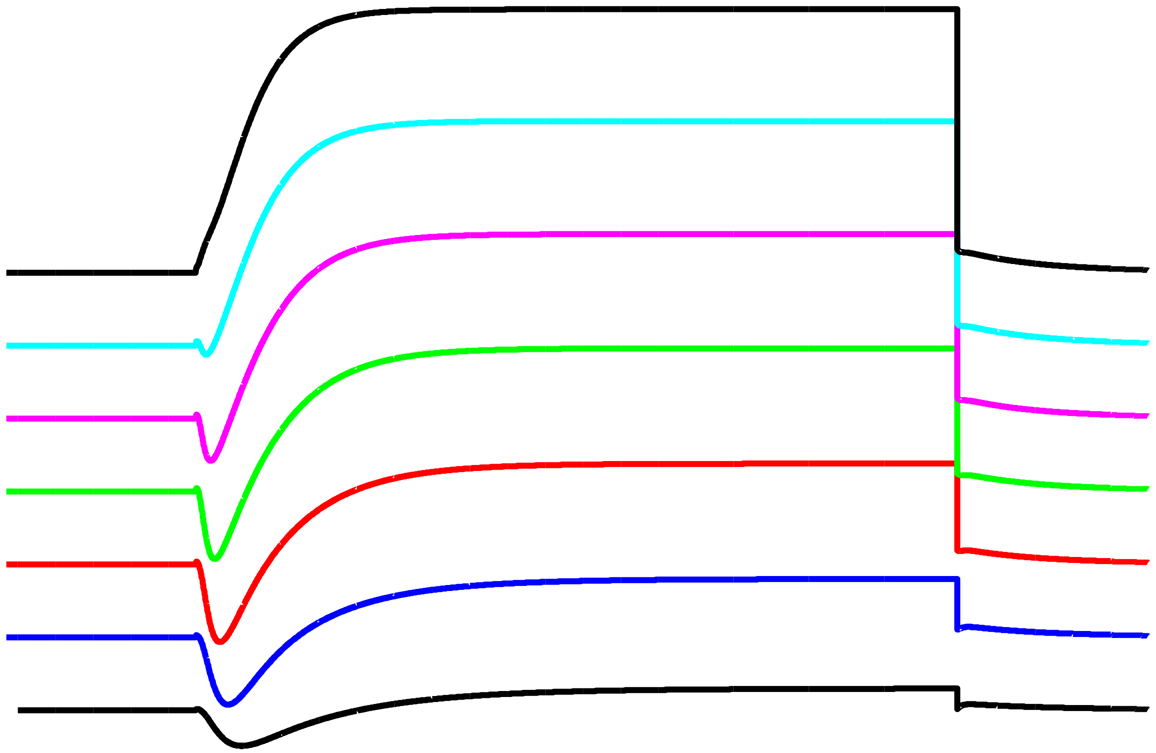
Currents recorded under voltage clamp



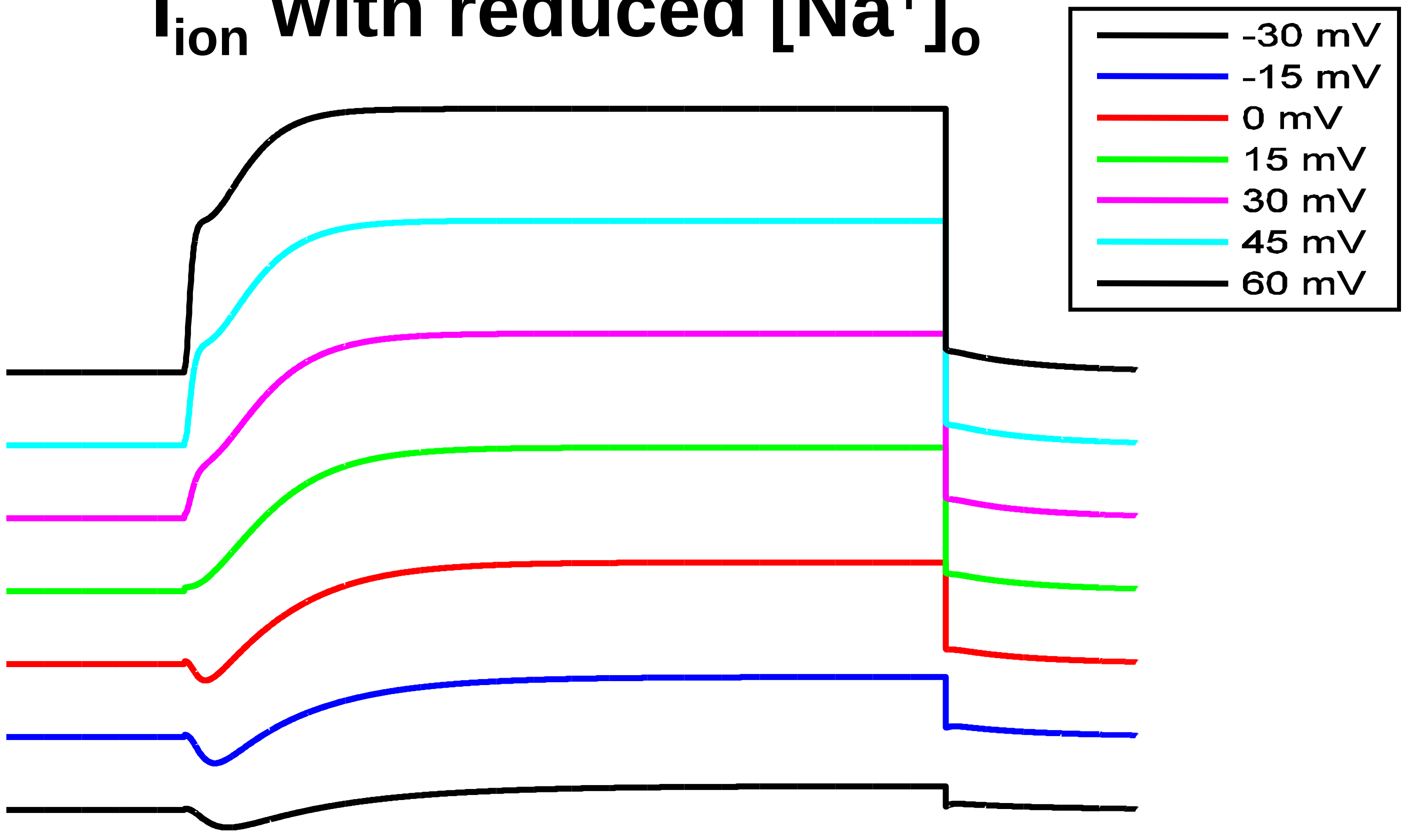
How can I_{Na} and I_K be separated?

A clever technique for separating I_{Na} and I_K

I_{ion} with normal $[Na^+]_o$

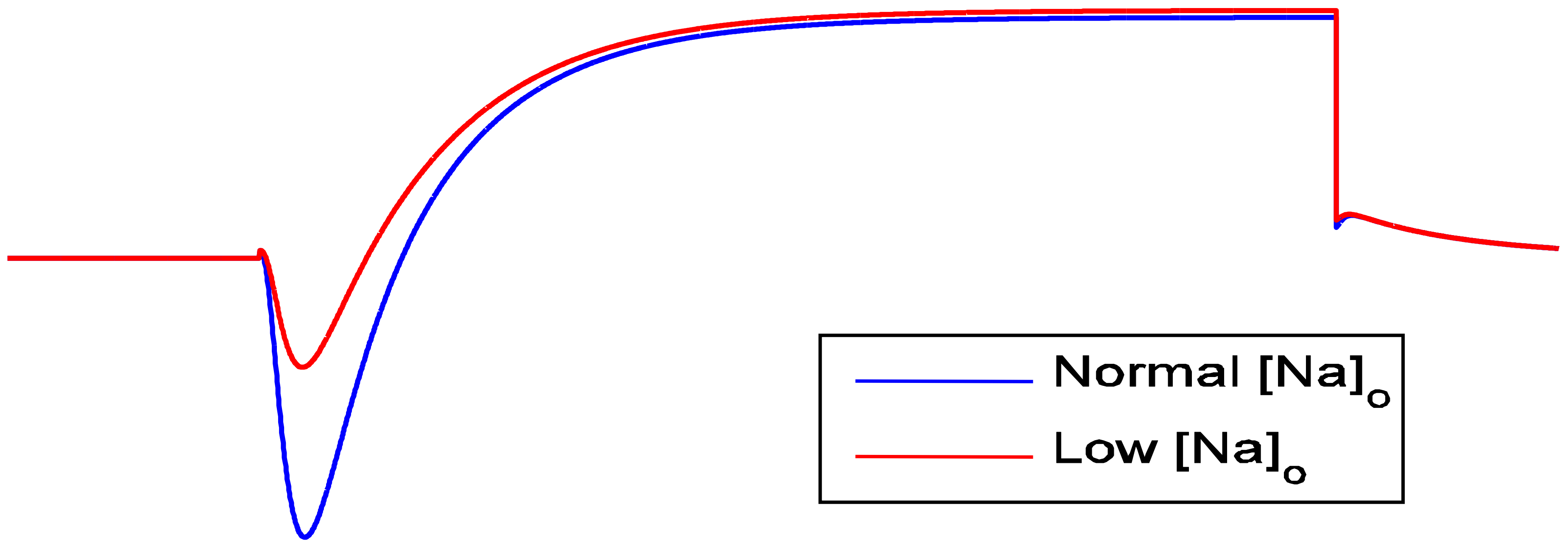


I_{ion} with reduced $[Na^+]_o$



Assume that changing $[Na^+]_o$ only affects I_{Na}, not I_K

A clever technique for separating I_{Na} and I_K



$I_{ion} = I_{Na} + I_K$ $\qquad$ $I'_{ion} = I'_{Na} + I'_K$

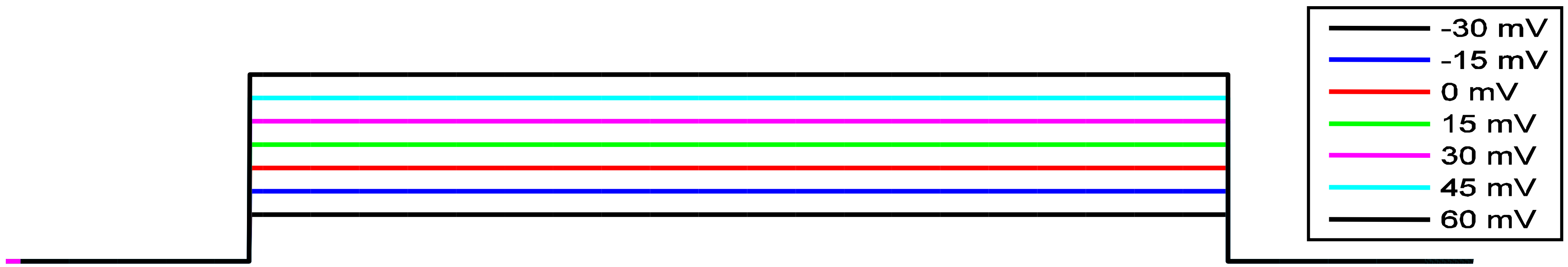
Assume that:

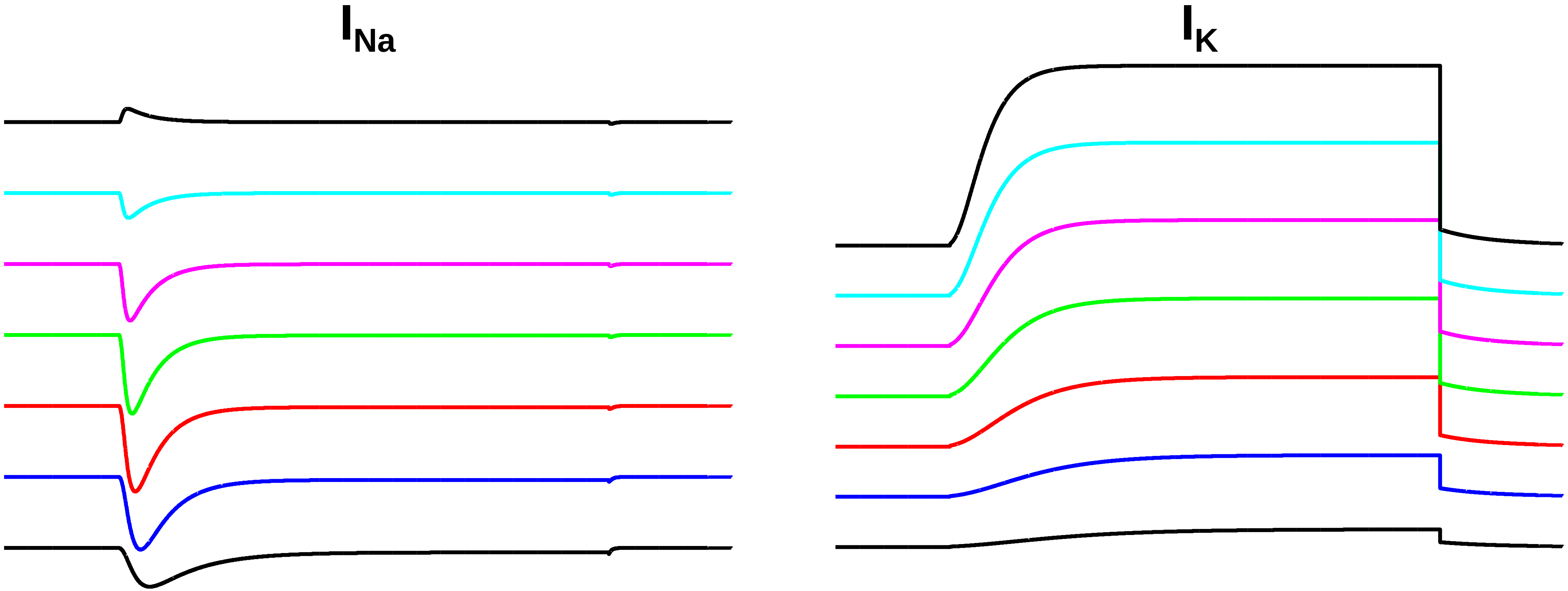
$I'_K = I_K$ $\qquad$ $I'_{Na} = K*I_{Na}$

It follows that:

$I_{Na} = (I_{ion}-I'_{ion})/(1-K)$ $\qquad$ $I_K = (I'_{ion}-K*I_{ion})/(1-K)$

I_{Na} and I_K at different membrane potentials





How do we go from these recordings to the famous equations?

Summary

Membrane voltage and ionic currents in neurons are interdependent, which makes it difficult to develop mathematical representations.

The voltage clamp method, pioneered by Hodgkin and Huxley, allows for the currents to be recorded while voltage is controlled.

Voltage clamp was the key advance that made the Hodgkin-Huxley model possible.