Mathematical models of action potentials

Part 4

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Outline: Part 4

Example results with Hodgkin-Huxley model

Sub-threshold and supra-threshold responses

Refractoriness

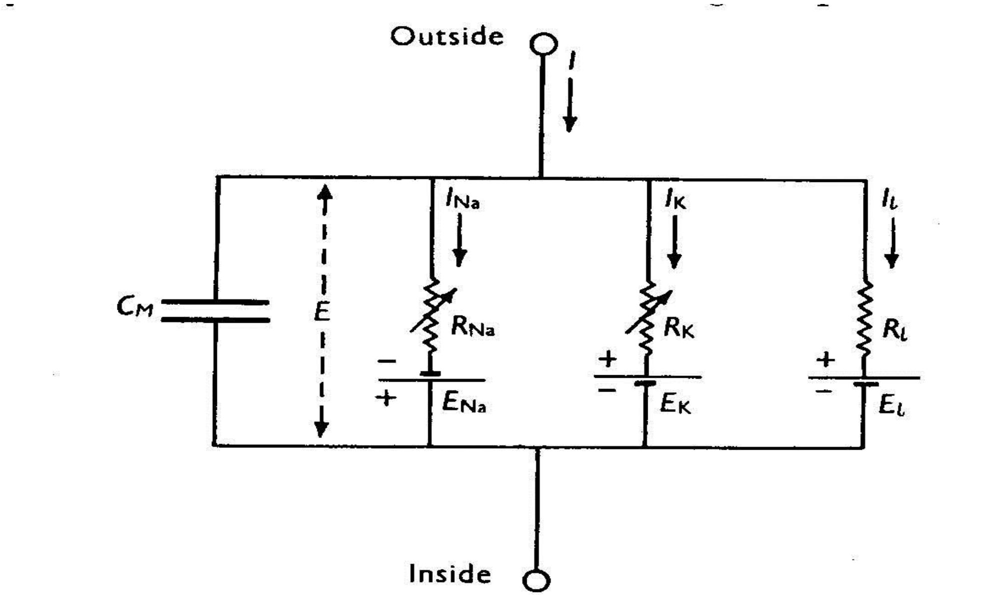
Anode break excitation

Theme

Each of these simulations represented an independent validation of the model.

Overall Hodgkin-Huxley model

Membrane represented as parallel conductances



Hodgkin & Huxley (1952), *J. Physiol.* 117:400.

Four ODEs

$$C_m \frac{dV}{dt} = -g_L\left(V - V_L\right) - \bar{g}_{Na} m^3 h\left(V - V_{Na}\right) - \bar{g}_K n^4\left(V - V_K\right)$$

$$\frac{dm}{dt} = \alpha_m\left(V\right)\left(1 - m\right) - \beta_m\left(V\right)m$$

$$\frac{dh}{dt} = \alpha_h\left(V\right)\left(1 - h\right) - \beta_h\left(V\right)h$$

$$\frac{dn}{dt} = \alpha_n\left(V\right)\left(1 - n\right) - \beta_n\left(V\right)n$$

Voltage-dependent rate constants

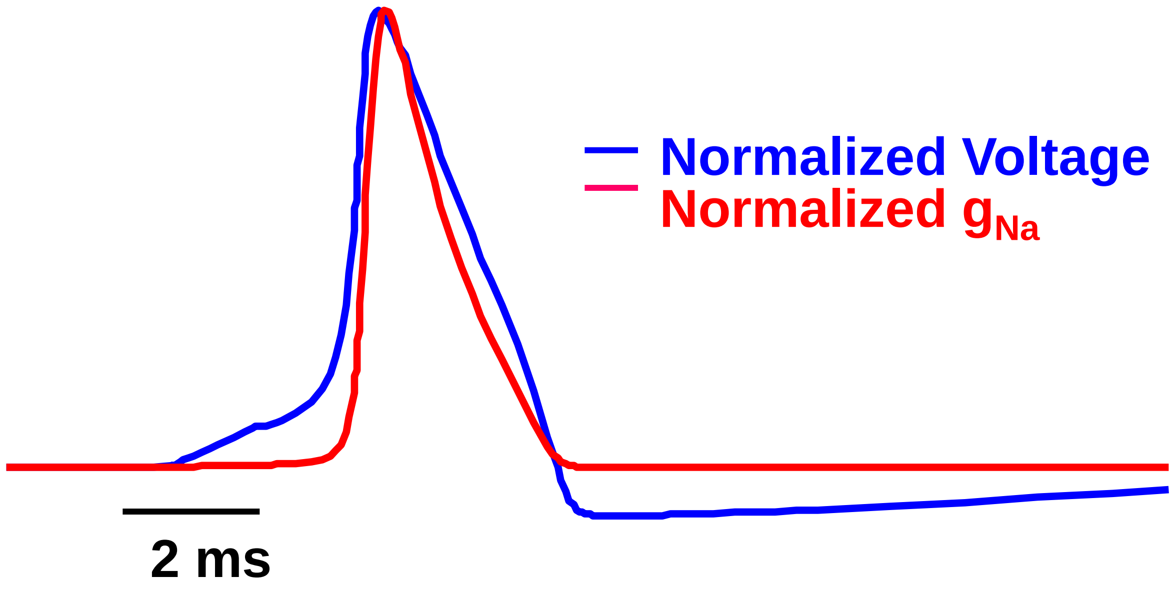
$$\alpha_m = 0.1(V_m + 35.0)/(1. - e^{(-(V_m+35.0)/10.0)})$$
$$\beta_m = 4.0\, e^{(-(V_m+60.0)/18.0)}$$

$$\alpha_h = 0.07\, e^{(-(V_m+60.0)/20.0)}$$
$$\beta_h = 1./(1 + e^{(-(V_m+30.0)/10.0)})$$

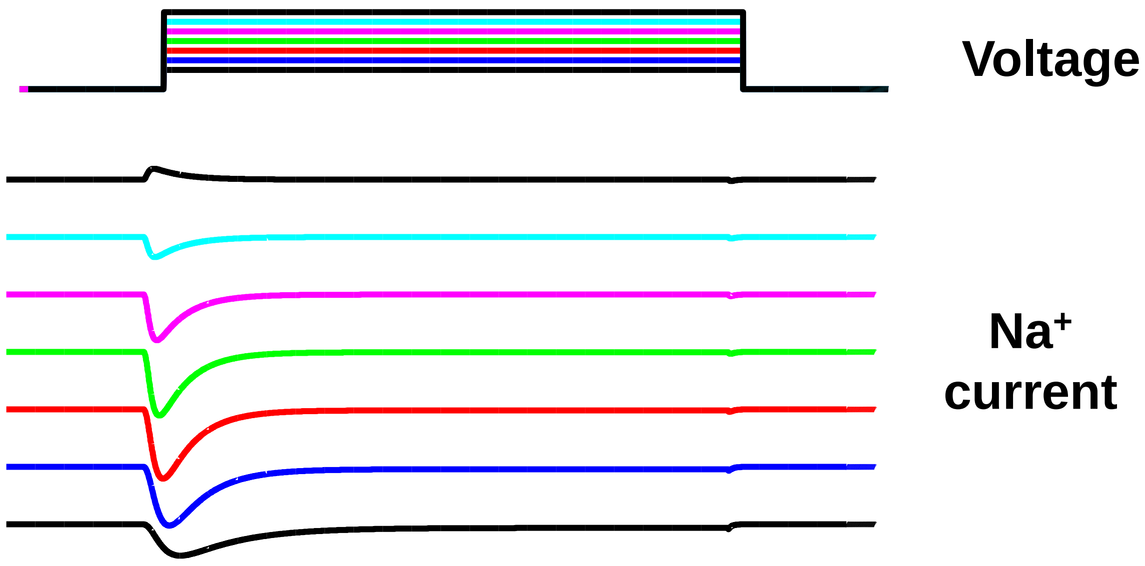
$$\alpha_n = 0.01(V_m + 50.0)/(1 - e^{(-(V_m+50.0)/10.0)})$$
$$\beta_n = 0.125\, e^{(-(V_m+60.0)/80.0)}$$

Why was voltage clamp transformative?

Voltage and conductance changing together



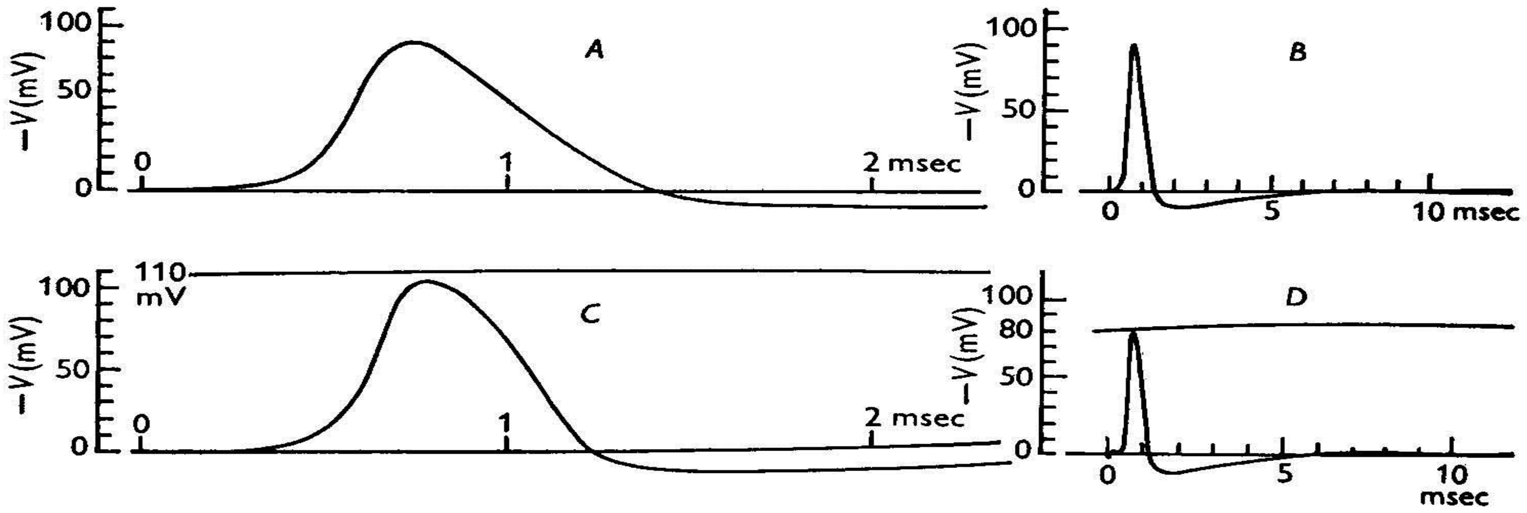
Voltage controlled. Conductance changes can be quantified.



Simulation of simplified experiment was critical for both model development and understanding

Behavior of Hodgkin-Huxley model

Important note: equations and parameters were derived from voltage-clamp data, action potential simulations were an independent test



Experiment

Simulation

In addition to producing realistic action potentials, the model:

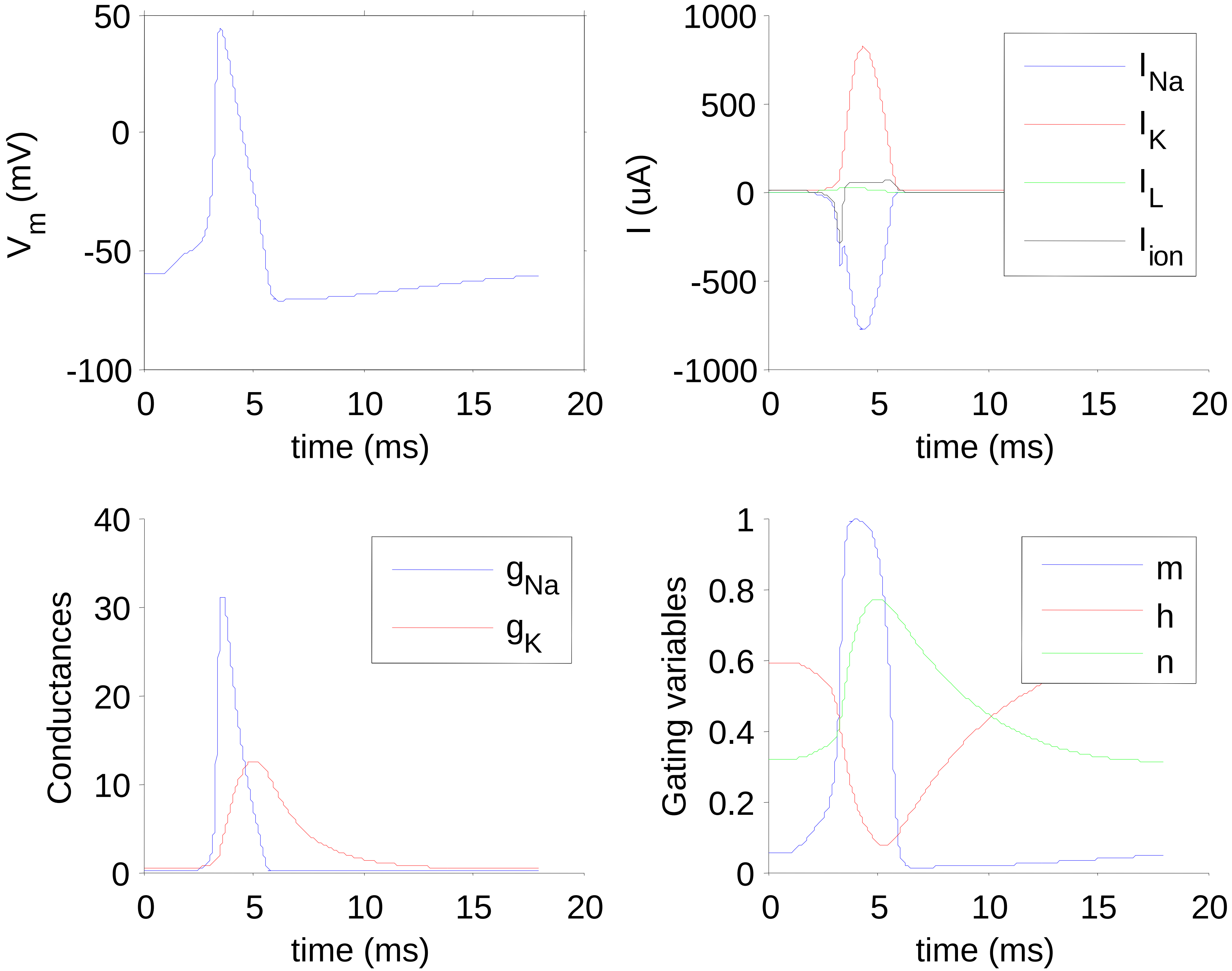
1) exhibits sub-threshold and supra-threshold responses

2) correctly reproduces refractoriness

3) reproduces “anode break” excitation

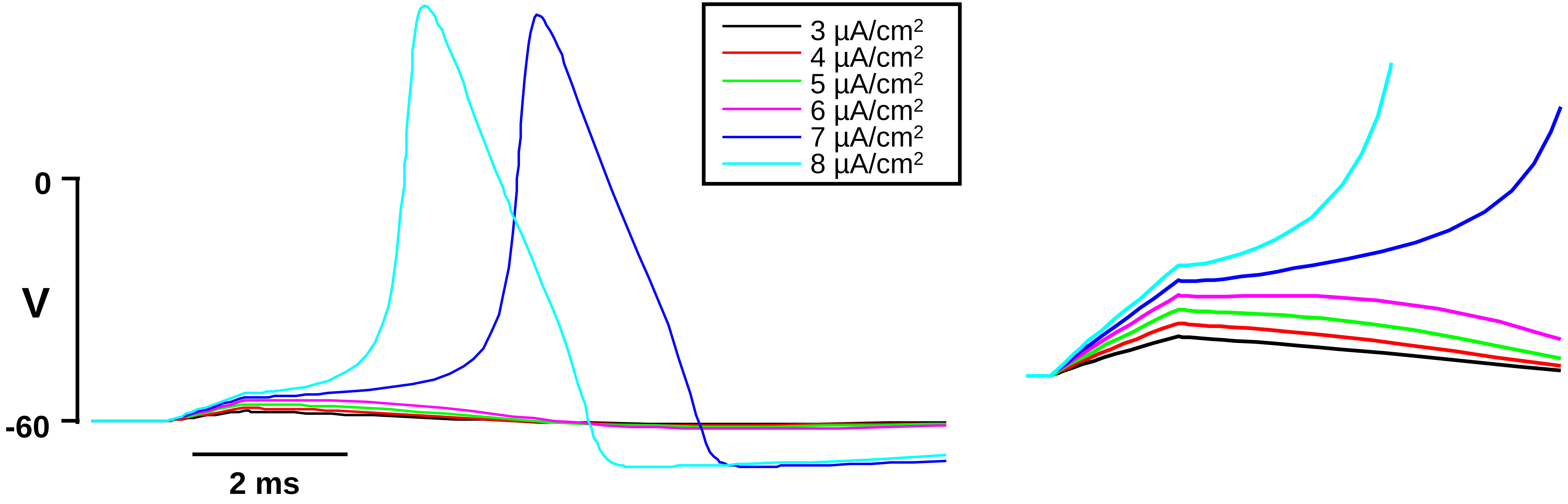
Behavior of Hodgkin-Huxley model

Response to brief injected current



Behavior of Hodgkin-Huxley model

The model exhibits sub-threshold and supra-threshold responses

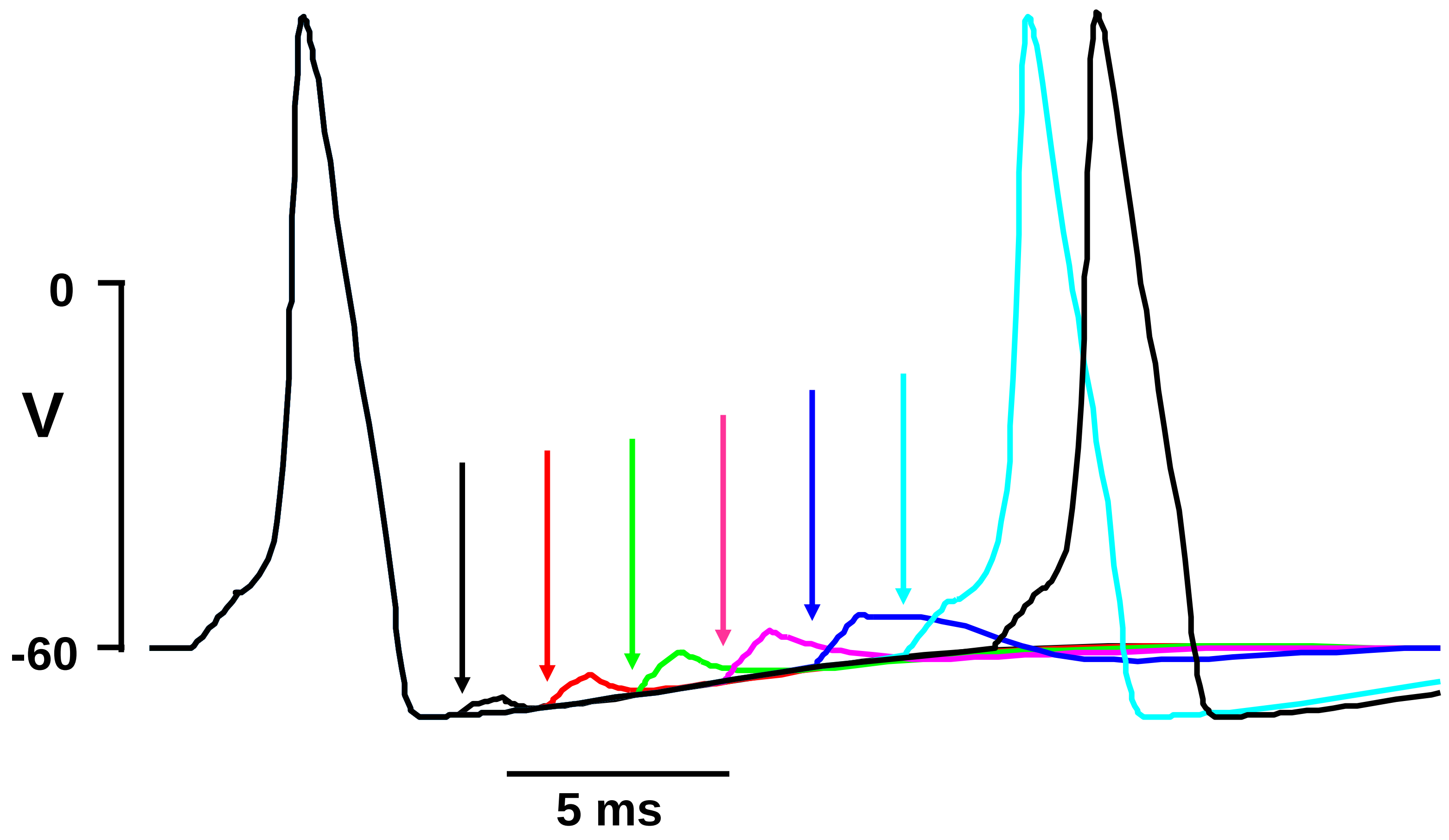


The threshold results from the positive feedback between V and I_{Na}
↑V leads to ↑I_{Na} leads to ↑V, etc.

In other words, bistability

Behavior of Hodgkin-Huxley model

The model correctly reproduces refractoriness

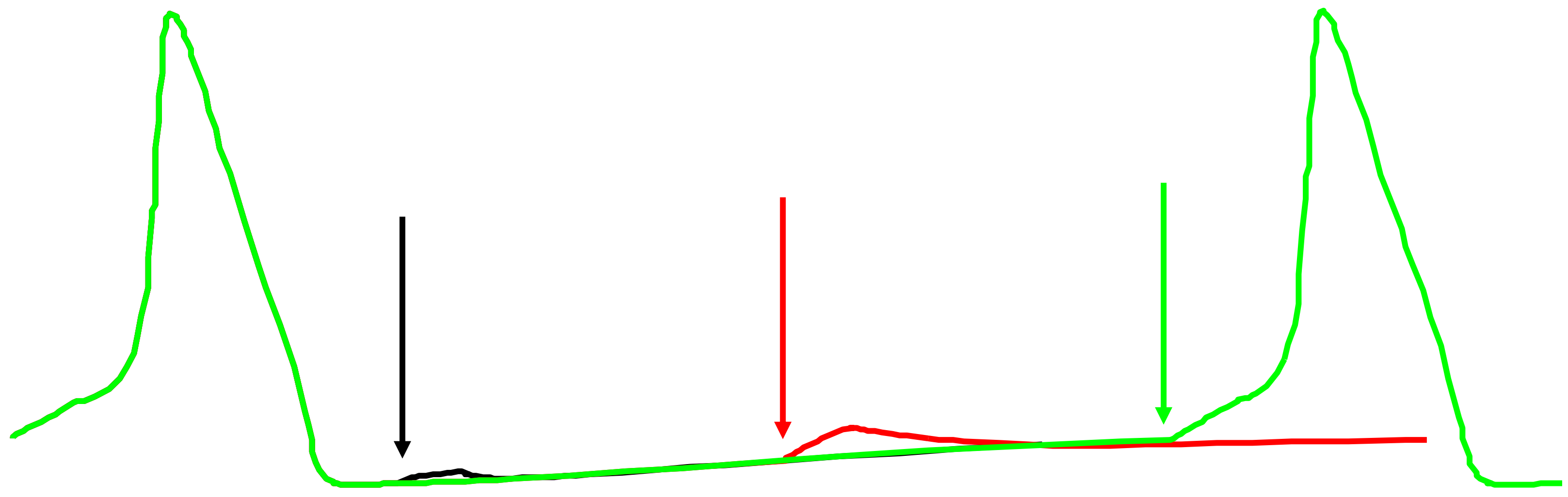


Stimuli given soon after an initial AP will fail to induce a second AP, until the refractory period is over.

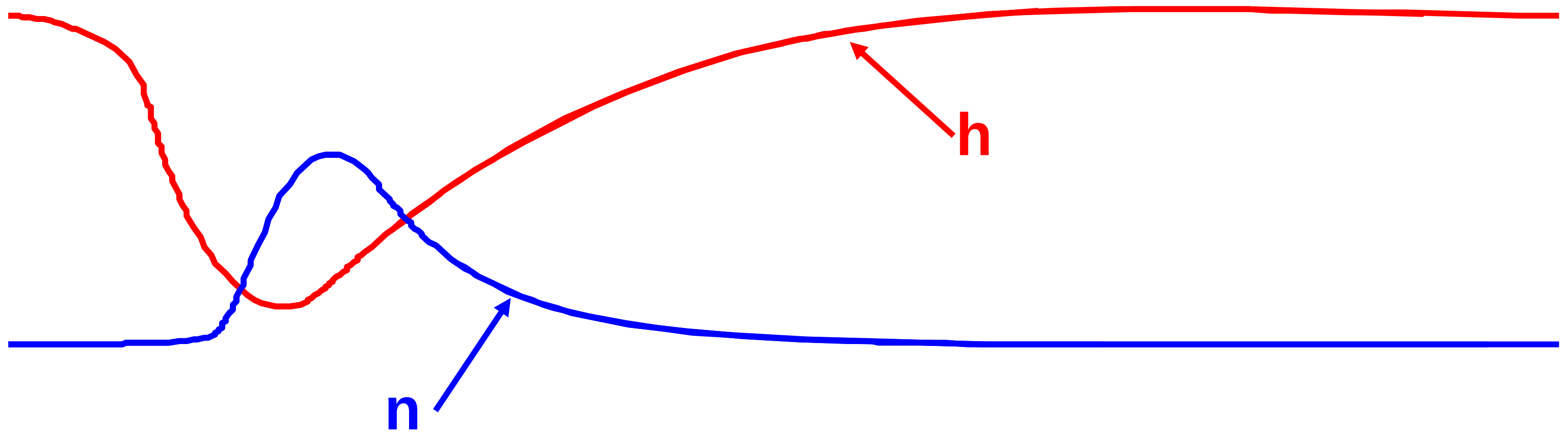
Behavior of Hodgkin-Huxley model

Mechanism of refractoriness

Increase in g_K as well as decrease in g_{Na}



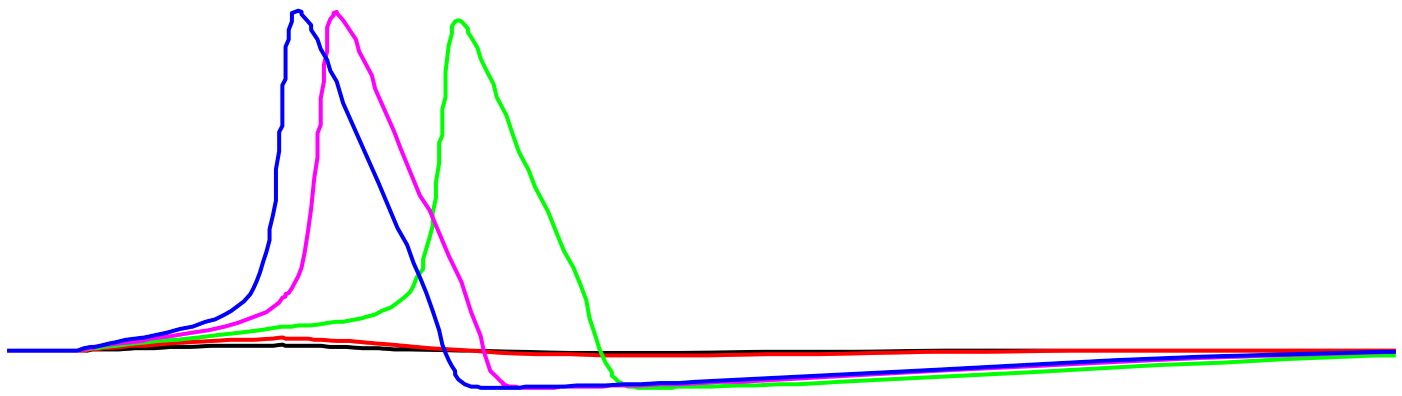
Remember: $g_K \sim n^4$, $g_{Na} \sim m^3h$



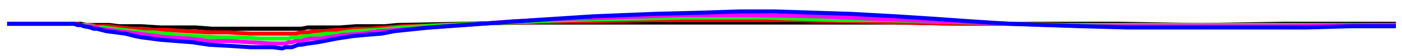
Behavior of Hodgkin-Huxley model

The model reproduced and explained "anode break" excitation.

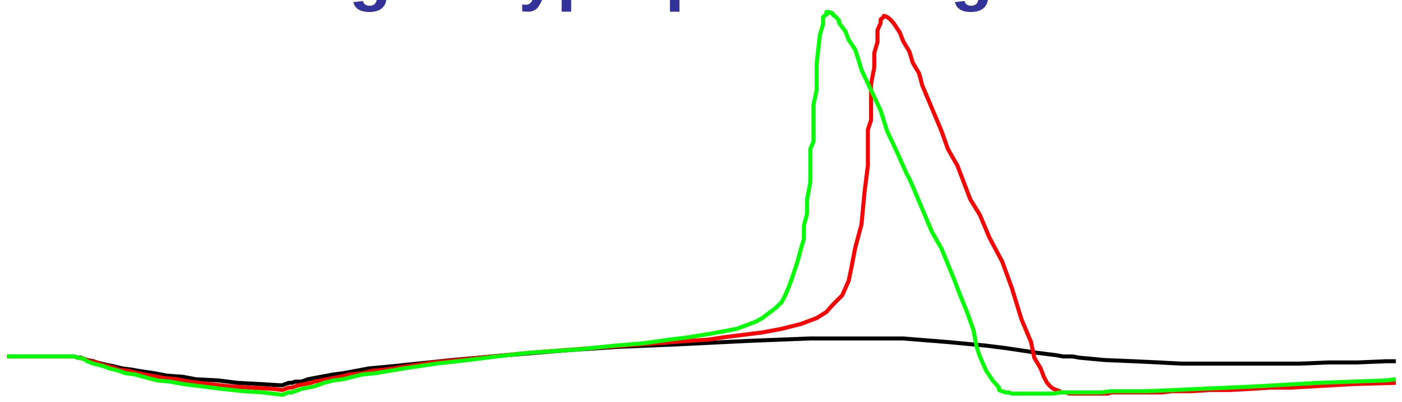
Depolarizing (cathodal) stimuli



Hyperpolarizing (anodal) stimuli



Stronger hyperpolarizing stimuli



Because this comes about after the stimulus, this is called "break" excitation

Summary

The Hodgkin-Huxley equations were derived entirely from voltage-clamp data. Simulations of action potentials represented an independent test of the model.

The model was able to reproduce several observed phenomena:

threshold behavior

refractoriness

anode break excitation

The simulations of these phenomena generated new predictions about the underlying biological mechanisms.