

Rutgers 642:613 - Fall 2003

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Chapter 4, Hodgkin-Huxley, etc

<http://www.math.rutgers.edu/~sontag/613.html>

Excitability

neurons, muscle cells, others, use potentials as *signals*

excitable cells: if an applied current exceeds a *threshold*
then there is a large excursion “*action potential*”

respond fully or not at all: “analog/digital conversion”

digital information is more robust to noise

Hodgkin-Huxley (+Katz) 1952 (Nobel 1963 for HH)

first (still?) most successful quantitative model in physiology

worked with giant axon of squid - voltage clamp technique

gave rise to huge mathematical industry

especially FitzHugh-Nagumo simplified models

<http://www.math.rutgers.edu/courses/338/hodhuxPrg/html/hh-applet.html>

and, when interconnecting, in 2-d: excitable media:

waves appear because of delay and refractory behavior

Hodgkin-Huxley Model

$V = V_i - V_e$, I outward current, recall $C \frac{dV}{dt} = -I_{\text{total}}$
ignoring pumps and non-gated channels (fast time scale)
important currents: K , Na ; lump rest as L (“leakage”)
assume linear I-V curves, so

$$C \frac{dV}{dt} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_L(V - V_L)$$

(“ $+I_{\text{applied}}$ ” if external current applied, but we’ll assume a “delta function” resulting in perturbation in $V(0)$)

assume Nernst V_S ’s *constant*: changes \ll tot concentrations

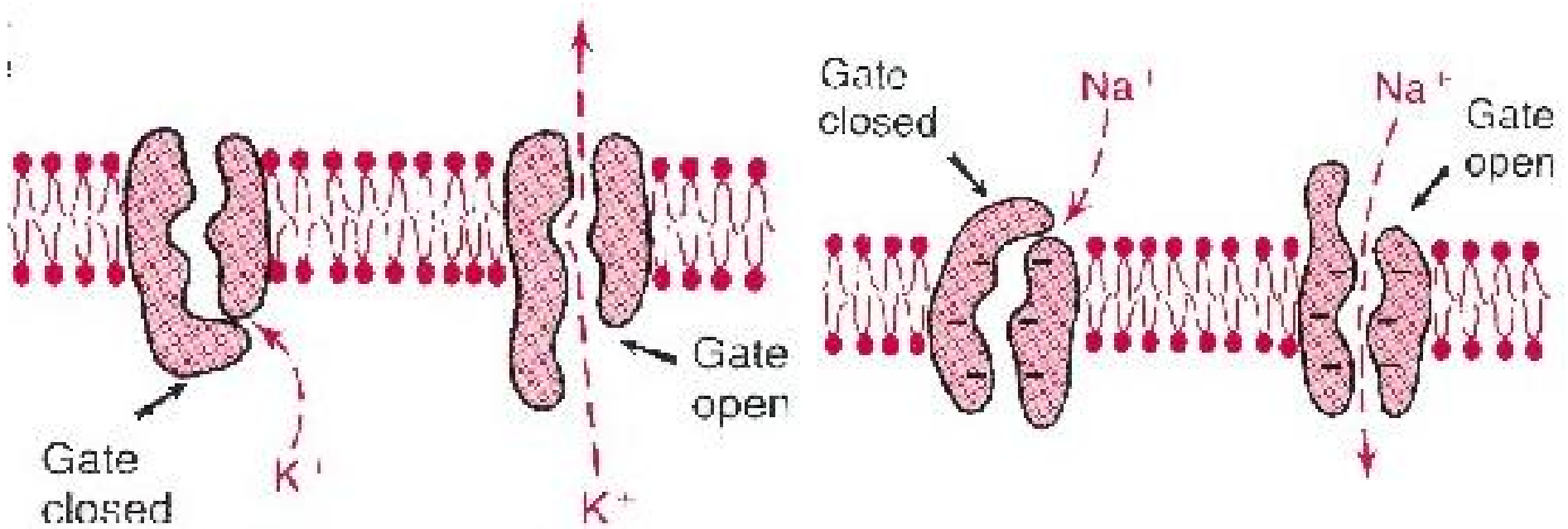
if also all conductances g_S ’s constant: where

$$\lim_{t \rightarrow \infty} V(t) = V_{\text{eq}} := \frac{g_{Na}V_{Na} + g_KV_K + g_LV_L}{g_{Na}V_{Na} + g_KV_K + g_L} \text{ resting potential}$$

with fast time constant ≈ 1 msec

and indeed this happens for *small* $V(0)$ (recall applet)
but not true for large $V(0)$: conjecture: $g_S = g_S(V)$

voltage-gated channels



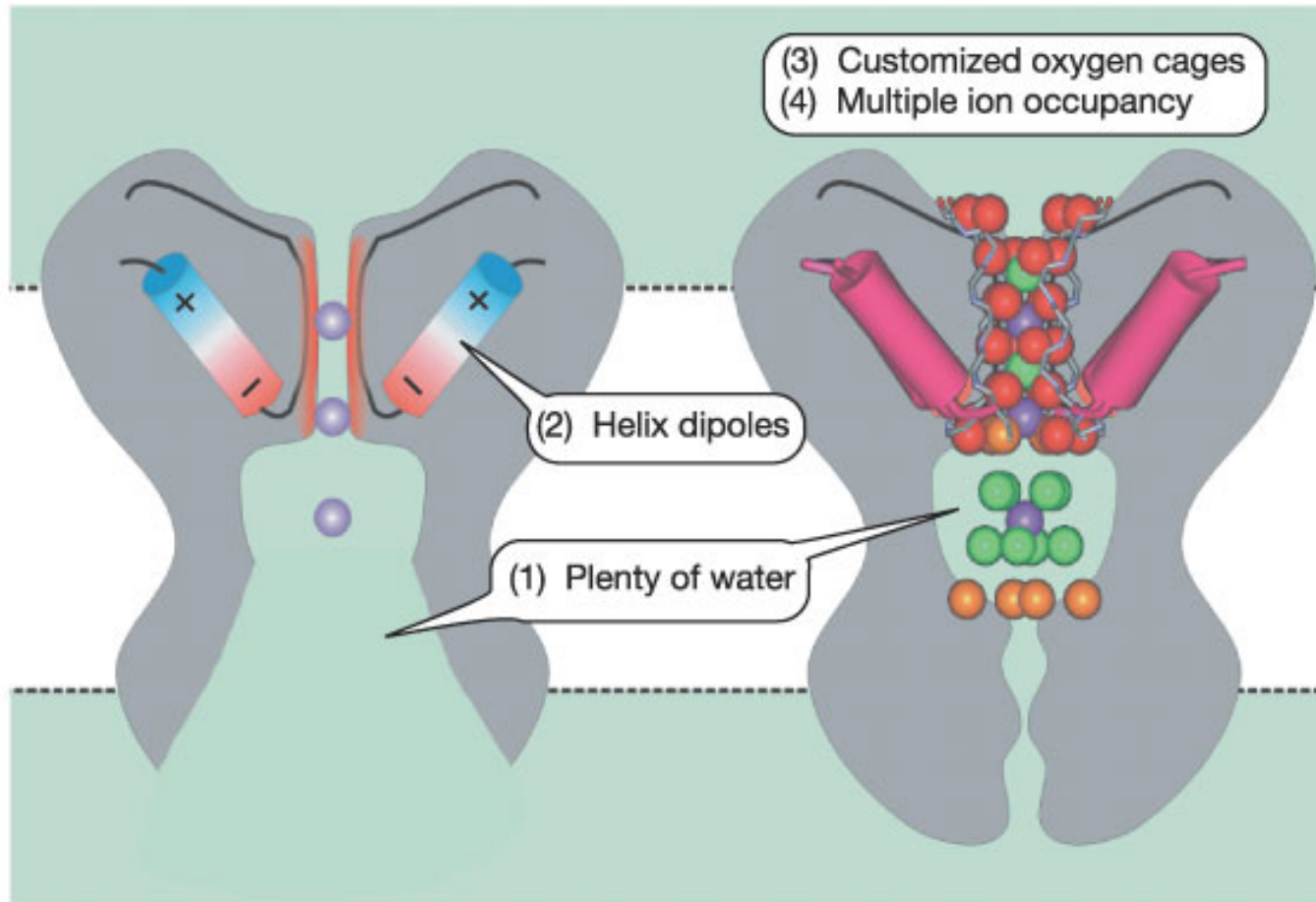
change in membrane potential towards depolarization
triggers opening of ion gates

e.g. if $g_{Na} \gg g_K$ and $\gg g_L$ then we have
 $C\dot{V} \approx -g_{Na}(V - V_{Na})$ so $V \rightarrow V_{Na} \gg V_{eq}$

turns out that Na-gated channels have two types of gates:
activation and inactivation (but K channels only activation)

K^+ voltage-gated channel

from Nature 419, 35-42 (05 September 2002), “The voltage-gated potassium channels and their relatives” by Gary Yellen



purple sphere: K^+ ion

green spheres: water molecules of hydration

red spheres: backbone oxygens of selectivity filter

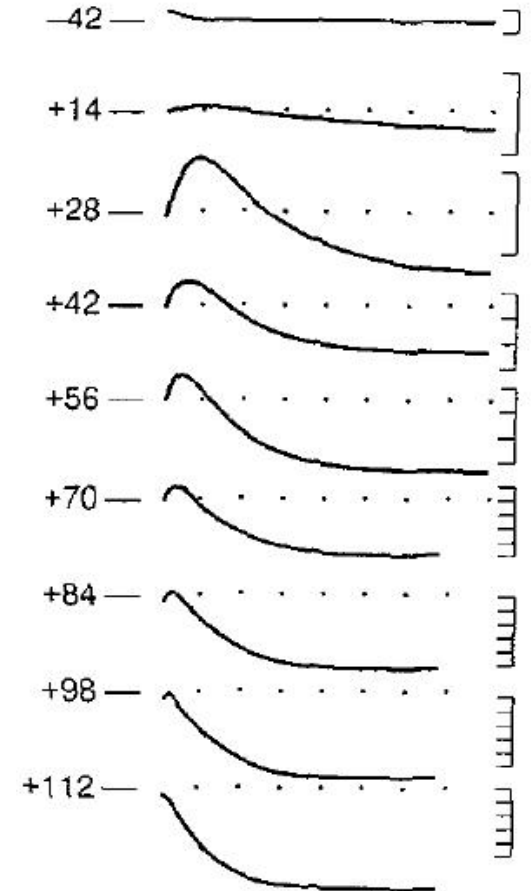
orange spheres indicate side chain oxygen atoms

Voltage-clamp experiments

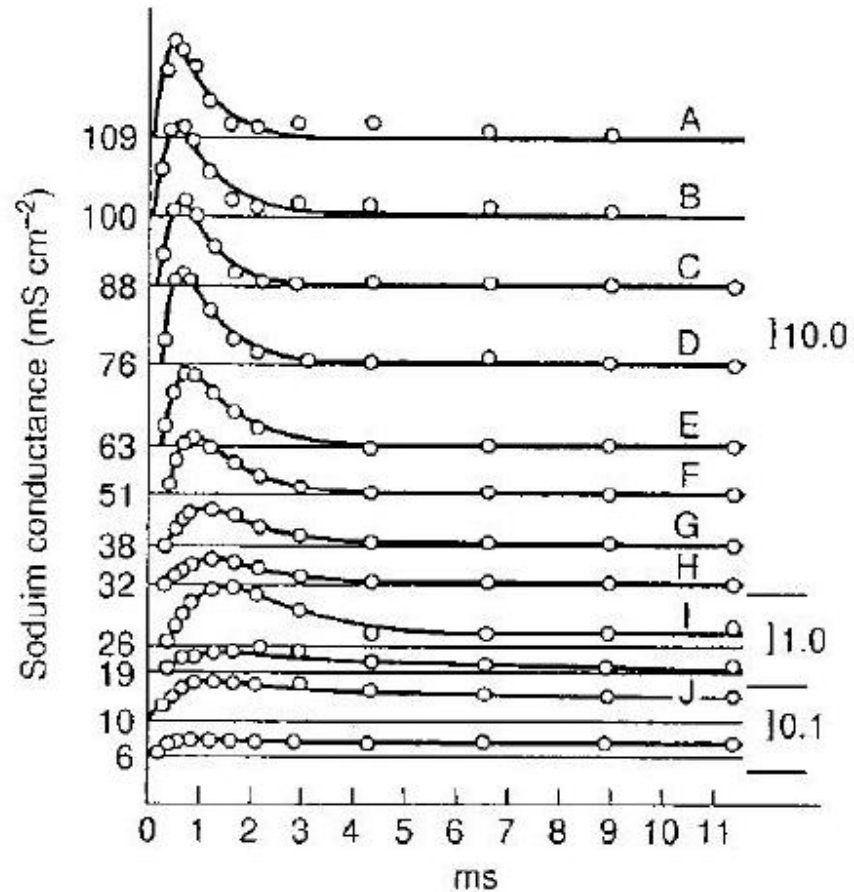
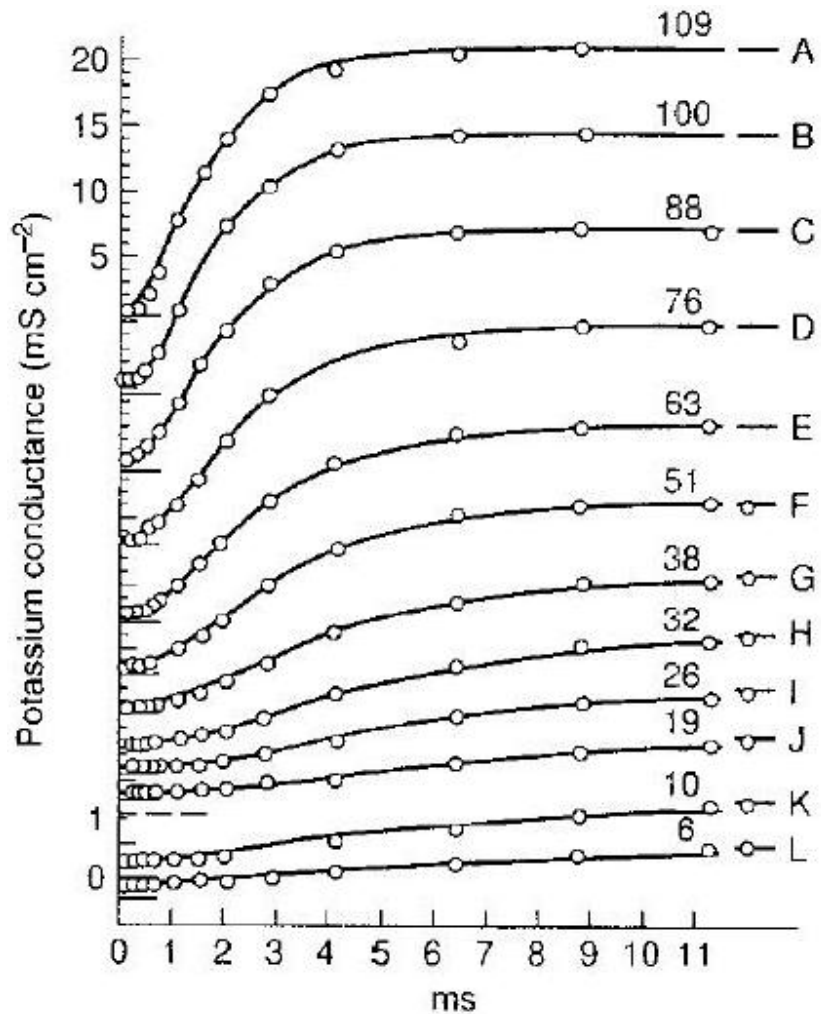
H&H experimental technique: force fixed voltage difference across membrane (thread conductor into axon, eliminating spatial voltage gradient \Rightarrow only current across membrane)

now measure current that must be supplied in order to keep this voltage constant - must match the membrane current

figure shows how current changes ($I(t)$) when V changed from resting ($\approx -70\text{mV}$) to a larger value; time scale 1ms; horiz $0.5\text{mA}/\text{cm}^2$; from original HH



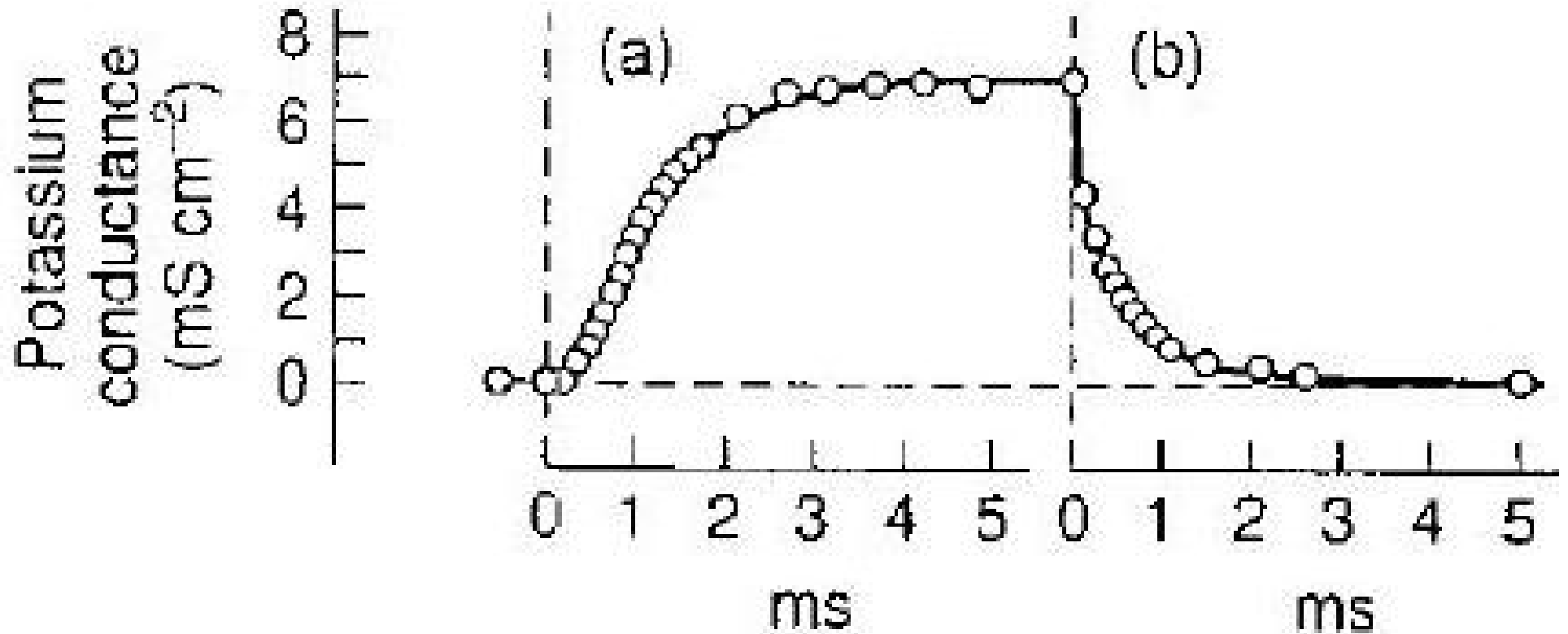
plot current against voltage, thus finding conductance...
 but complication: don't want total: **need g_S for each channel separately** – see book for details on how it was done



experimental $g_K(V)(t)$, $g_{Na}(V)(t)$, for different clamped V 's
 and with solid curves as per model to be given

another data point to help modeling

they also plotted $g_K(V)(t)$ for a $V = V(t)$ consisting of a step-up and then a step-down:



model for g_K

from now on, let $v := V - V_{eq}$

how to model $g_K(v)(t)$ and $g_{Na}(v)(t)$?

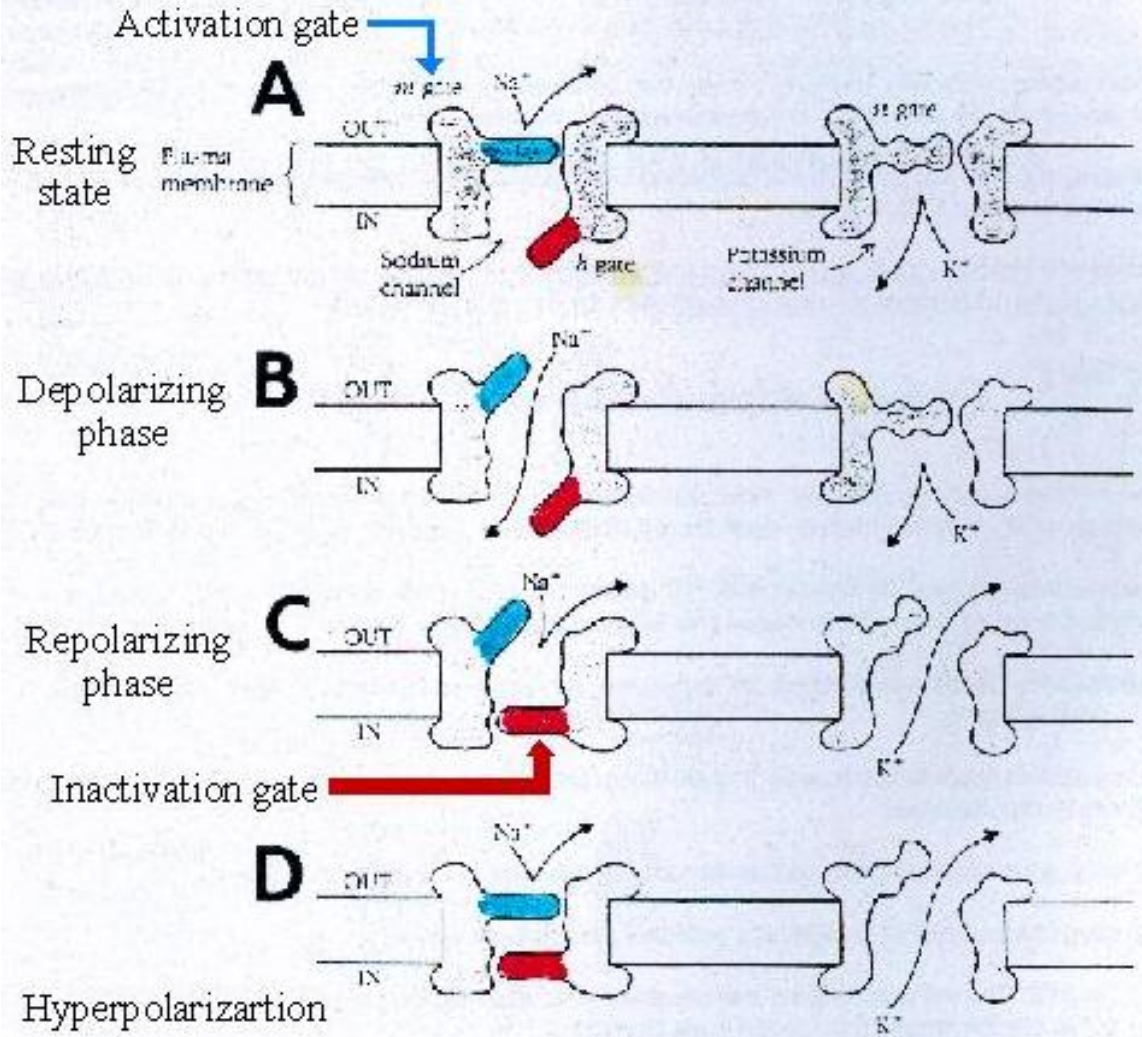
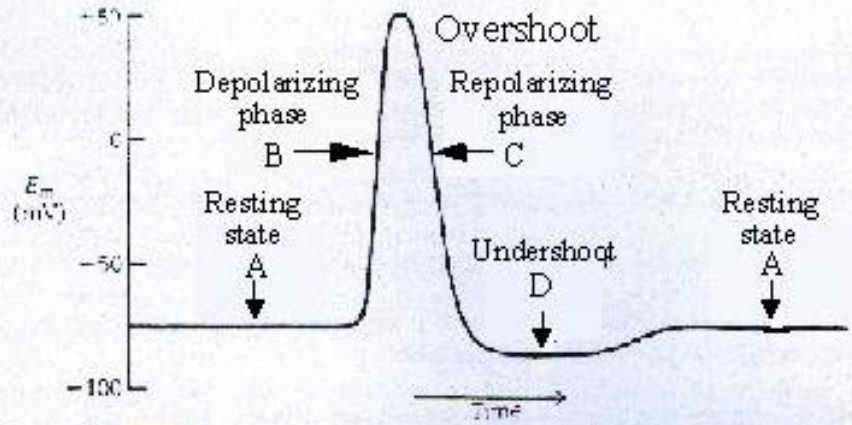
for any fixed v , they look \approx exponential approach to a value, so one would guess $\dot{g} = \alpha(\gamma_v - g)$, i.e. $g(t) \rightarrow \gamma_v$ as $t \rightarrow \infty$, where $\alpha > 0$ determines speed of convergence

but this \Rightarrow slope $\neq 0$ at $t = 0$, contrary to observations of zero slope and subsequent inflection point before saturating

this suggests a *power* g^k of such a g
for K, picked $k = 4$

Na more complicated: experiments suggest *two* channels, one that opens first and one that closes

for these, start with linear ode's; then use $k = 1$ and $k = 3$



Equations:

$$C\dot{v} = -g_K(t)(v - v_K) - g_{Na}(t)(v - v_{Na}) - \bar{g}_L(v - v_L)$$

$$\tau_m(v)\dot{m} = m_\infty(v) - m$$

$$\tau_n(v)\dot{n} = n_\infty(v) - n$$

$$\tau_h(v)\dot{h} = h_\infty(v) - h$$

$$g_K(t) = \bar{g}_K n(t)^4$$

$$g_{Na}(t) = \bar{g}_{Na} m(t)^3 h(t)$$

where functions of v as follows: write

$$\frac{1}{\tau_m(v)} (m_\infty(v) - m) = \alpha_m(v)(1 - m) - \beta_m(v)m$$

and same for n, h ; then:

$$\alpha_m = 0.1 \frac{25-v}{\exp\left(\frac{25-v}{10}\right) - 1}, \beta_m = 4 \exp\left(\frac{-v}{18}\right), \alpha_h = 0.07 \exp\left(\frac{-v}{20}\right)$$

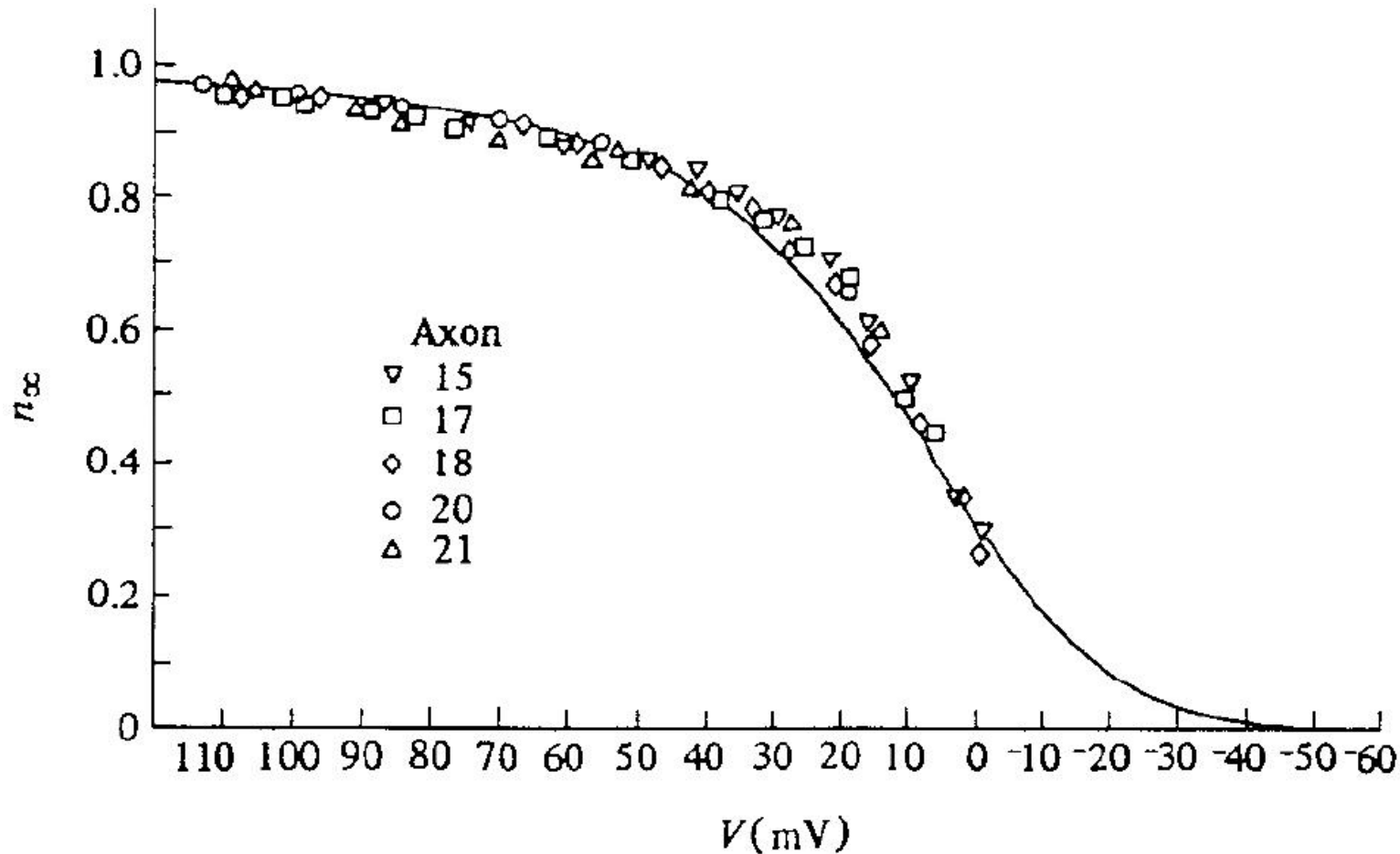
$$\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) + 1}, \alpha_n = 0.01 \frac{10-v}{\exp\left(\frac{10-v}{10}\right) - 1}, \beta_n = 0.125 \exp\left(\frac{-v}{80}\right)$$

$$\bar{g}_K = 36, \bar{g}_{Na} = 120, \bar{g}_L = 0.3$$

$$v_{Na} = 115, v_K = -12, v_L = 10.6$$

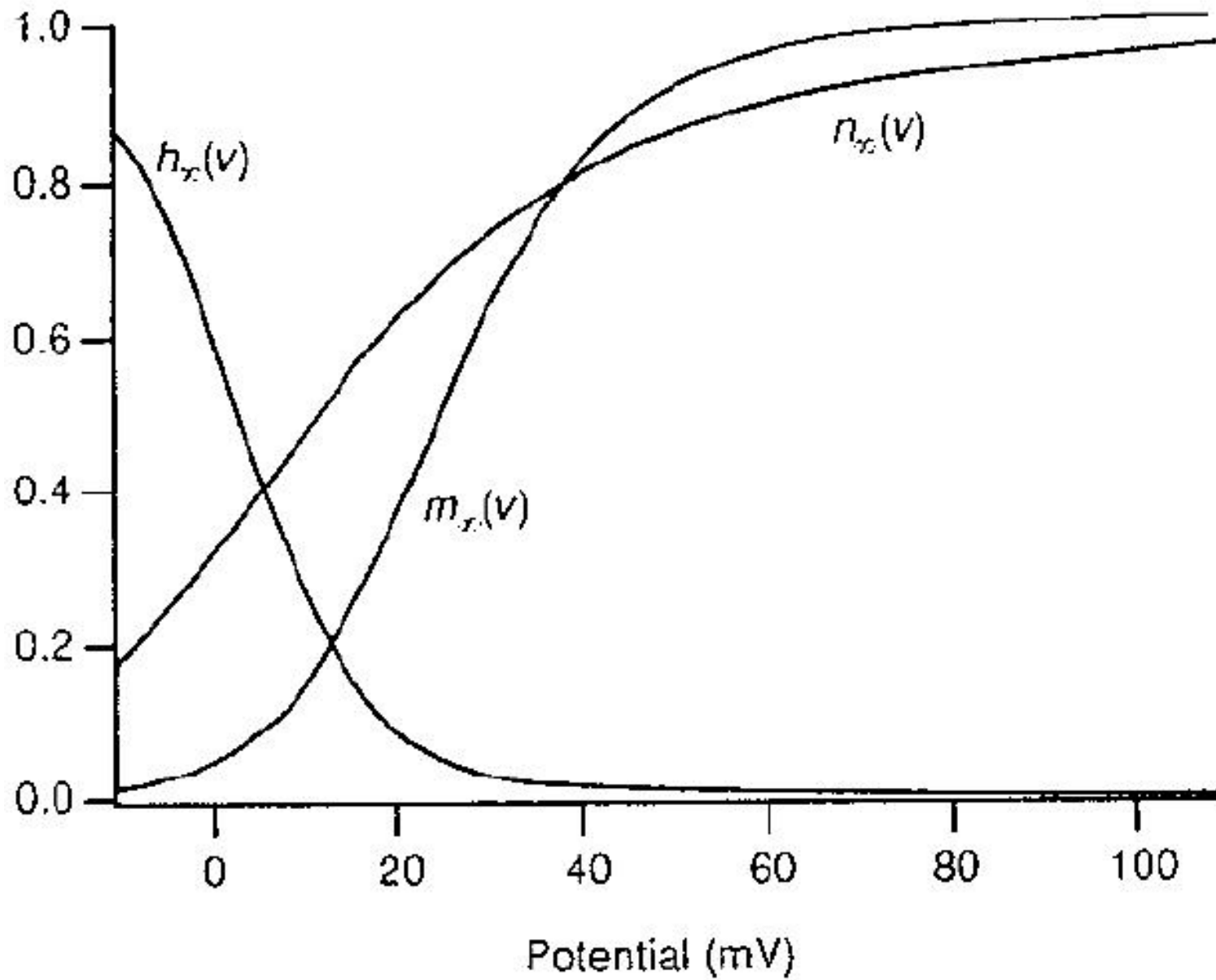
how did they come up with the numbers?

for any fixed v_0 , $n(t) = n_\infty(v_0) \exp(-t/\tau_n(v_0))$,
so find $n_\infty(v_0)$ and $\tau(v_0)$ by fit to experimental data
next plot $n_\infty(v)$ vs v & fit by a “simple” function

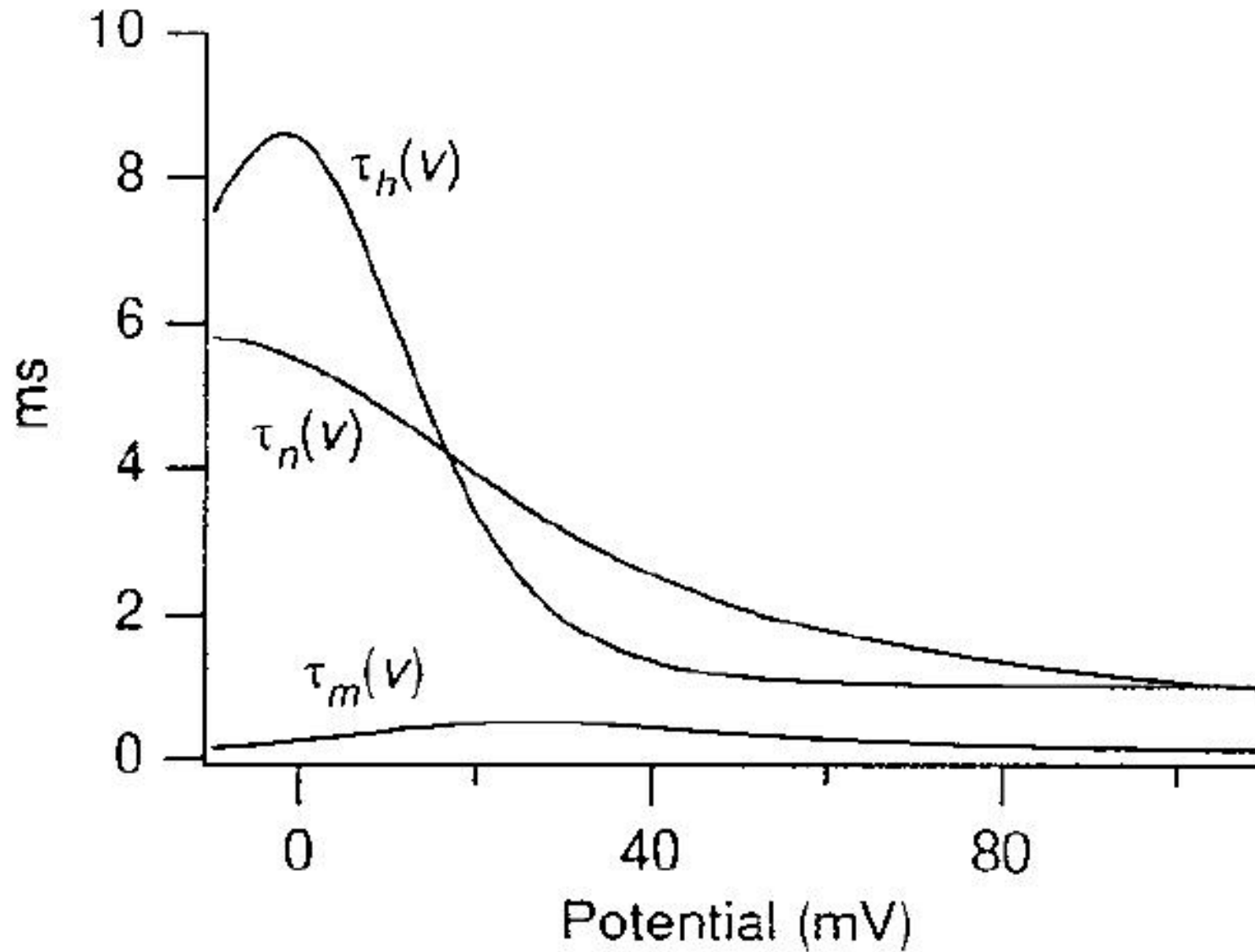


similarly for m, h (assuming one acts before other, so can separate effects of each)

conductances



time constants



extremely important: $\tau_m \ll \tau_n$ and $\ll \tau_h$

intuitive analysis of model

$$C\dot{v} = \underbrace{-g_K(t)(v - v_K)}_{<0} \underbrace{-g_{Na}(t)(v - v_{Na}) - \bar{g}_L(v - v_L)}_{>0}$$

provided $v < \min\{v_L, v_{Na}\}$ (since $v_{Na} > 0$, $v_L > 0$, $v_K < 0$)

if perturbation $v_0 = v(0^+) \approx 0$:

since (see plots) $m_\infty(0) \approx 0$ (and \bar{g}_L , Δv 's not large enough),

$$g_K(t) \approx \bar{g}_K n_\infty(0)^4 \gg \bar{g}_{Na} m_\infty(0)^3 h_\infty(0) \approx g_{Na}(t),$$

we have that $\dot{v} < 0$, so $v(t)$ stays $< v_0$, and $v(t) \rightarrow 0$

but if $v_0 \gg 1$, so $m_\infty(v_0)$ is large enough,

then, since $m(t) \approx m_\infty(v_0)$, $n(t) \approx n_\infty(0)$, $h(t) \approx h_\infty(0)$
($m(t)$ reacts fast to new v because $\tau_m \approx 0$, but n, h slow):

$$g_K(t) \approx \bar{g}_K n_\infty(0)^4 \ll \bar{g}_{Na} m_\infty(v_0)^3 h_\infty(0) \approx g_{Na}(t)$$

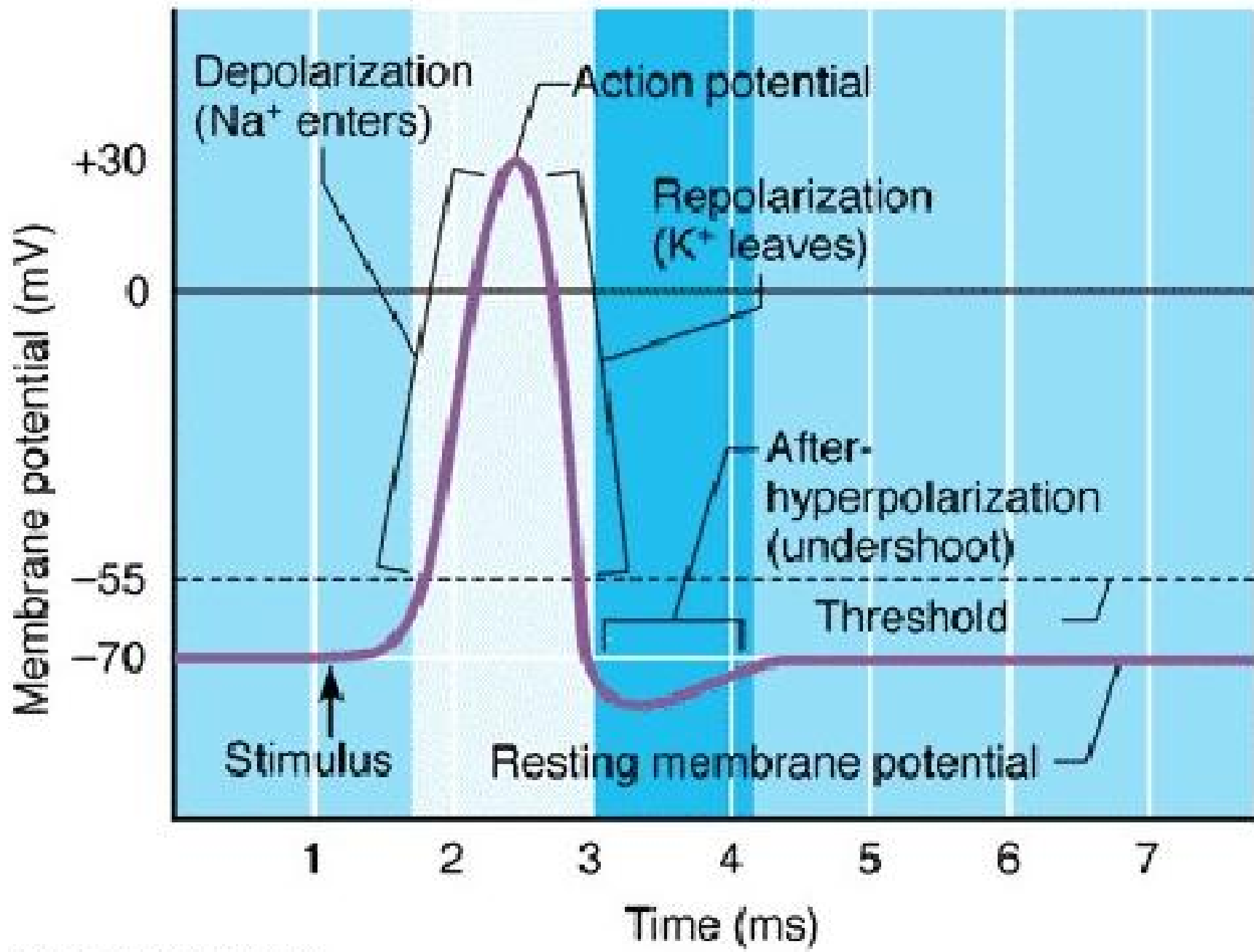
$\dot{v} > 0$, so stay $> v_0$, \rightsquigarrow positive feedback effect $v(t) \nearrow$

but, as $v \gg 1$, eventually (τ_h, τ_n large): $h \searrow$, $n \nearrow$:

inactivation of Na gate and *activation* of K gate

\therefore first term dominates, so $v(t) \rightarrow 0$ (resting potential)

Absolute refractory period Relative refractory period



refractory period

once that $h(t) \approx 0$, even if \exists perturbation so that $v \nearrow$
slow τ_h means that the Na term still does not dominate

h needs enough time to catch up with $v \approx 0$ so as to \nearrow

so even a superthreshold impulse will not cause
a new action potential during that period

but after sufficient time, provided that v was small for a
while (perhaps not zero, but enough to make m increase to
a reasonable value), a new action potential can take place

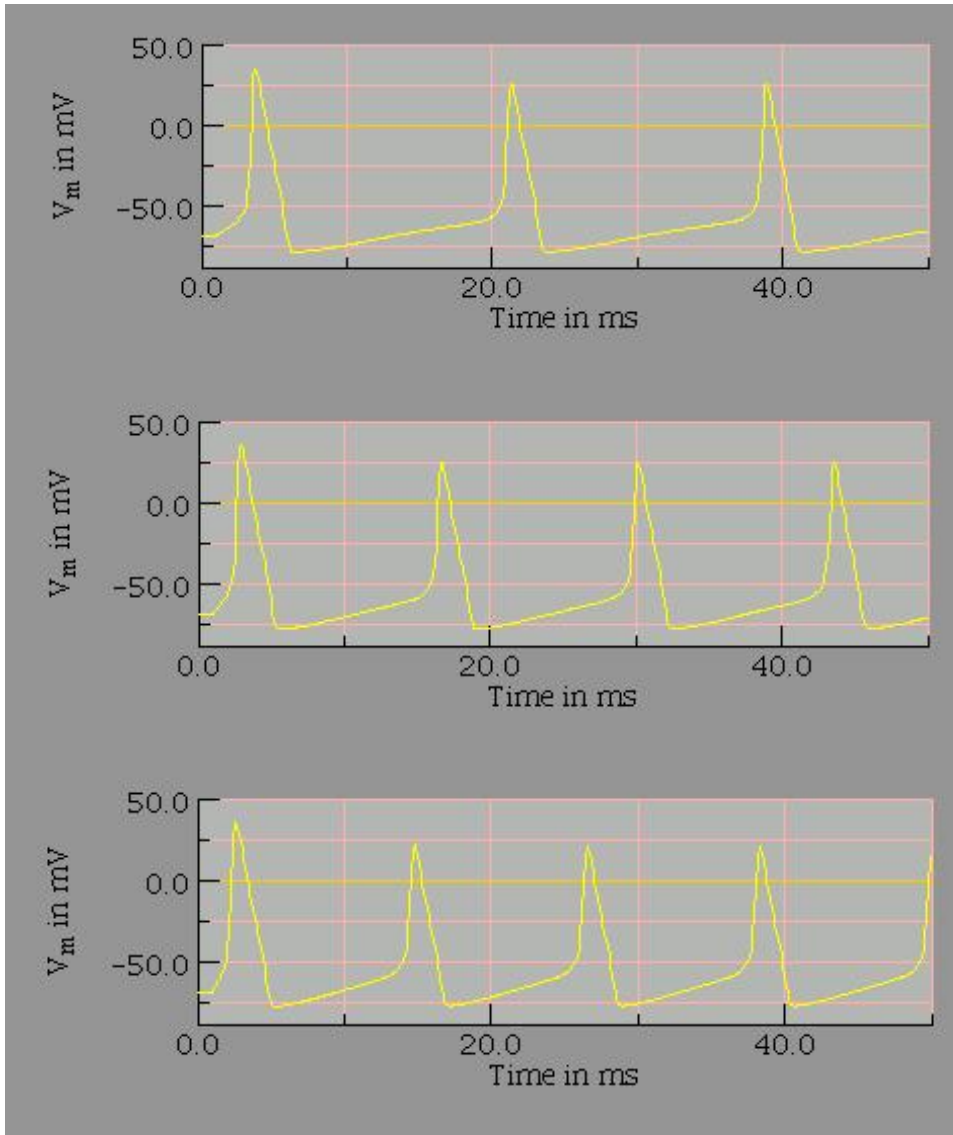
in this manner, a constant applied current may produce a
firing train

frequency encoding of amplitude

higher applied voltage means fire earlier amplitude:

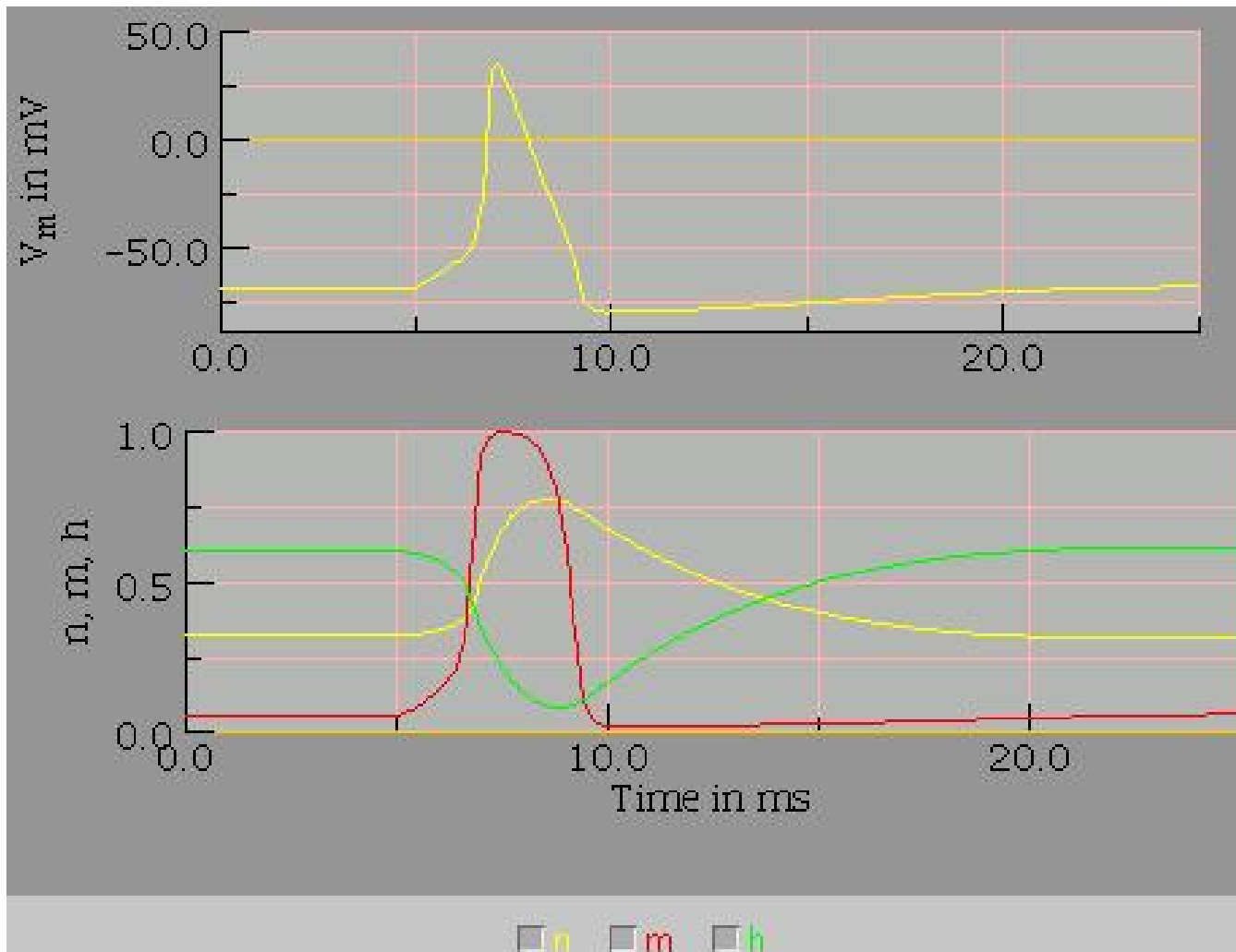
applet with duration=50

and current: 0.05 (3 spikes), 0.1 (4), 0.15 (5)



simulation with applet

stimulus at $t = 5$ (to see better), duration 1, current=0.1



m tracks v , and also moves faster in response to stimulus

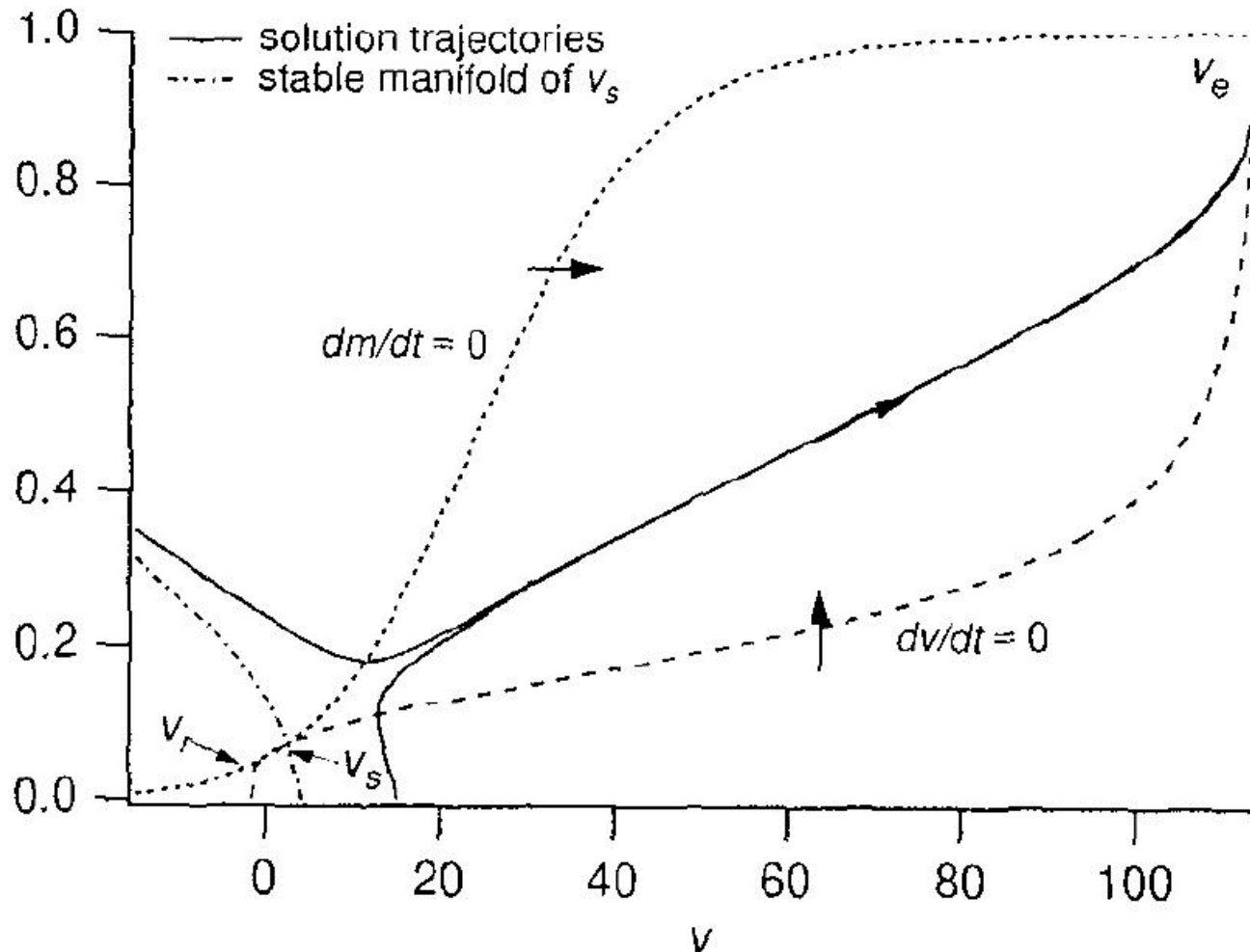
FitzHugh: fast time scale

look at what happens in *small time intervals*

so (since $\tau_m \ll \tau_n$ and $\ll \tau_h$), assume $n(t) \equiv n_0$, $h \equiv h_0$:

$$C\dot{v} = -\bar{g}_K n_0^4 (v - v_K) - \bar{g}_{Na} m^3 h_0 (v - v_{Na}) - \bar{g}_L (v - v_L)$$

$$\tau_m(v)\dot{m} = m_\infty(v) - m$$



three equilibria:

v_r : “resting”

v_s : saddle

v_e : “excited”

dashed $\dot{v} = 0$

dash-dot $\dot{m} = 0$

solid 2 solutions

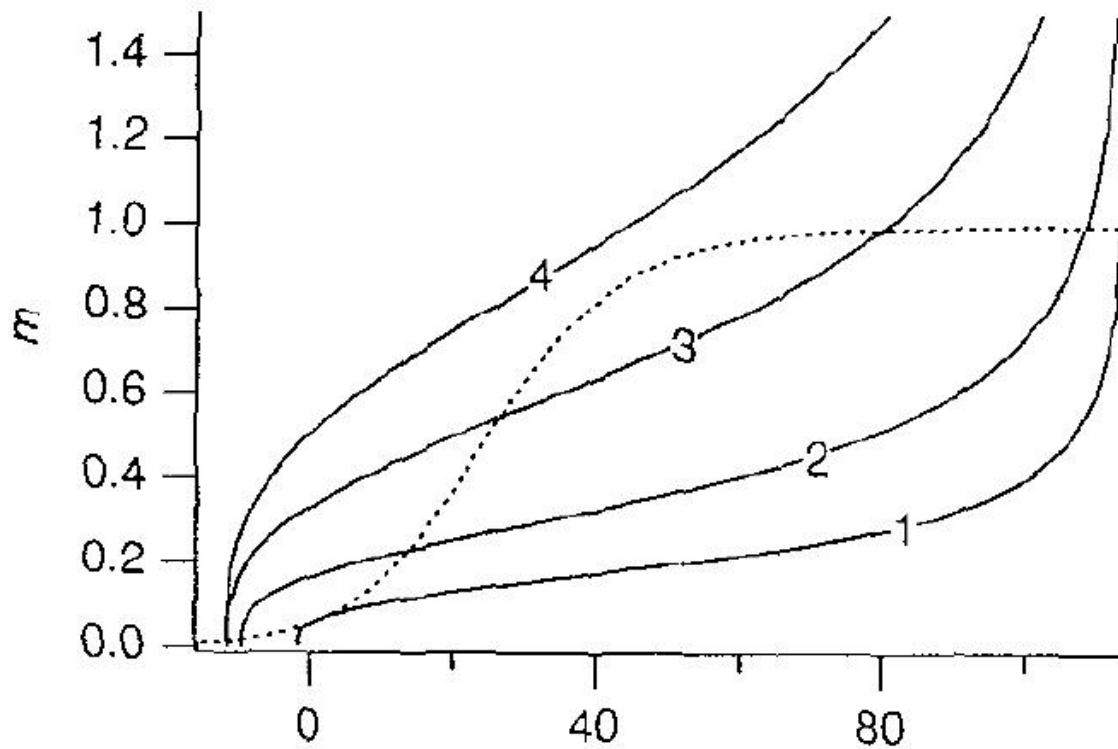
start “right” side of separatrix: $\xrightarrow{t \rightarrow \infty}$ far away “excited” state

but h, n not really constant...

suppose that v reached v_e fast

plot of h, n shows that $h_\infty(v_e) < h_\infty(v_r), n_\infty(v_e) > n_\infty(v_r)$

so $h \searrow, n \nearrow$, and m -nullcline moves e.g. $1 \rightarrow 2 \rightarrow 3 \rightarrow 4$:



think of “stepping to next value”: then system in fast scale equilibrates, but started from v_e , which (x -axis) moves \leftarrow – continues until saddle-node bifurcation, when only v_r left. jump to v_r ; then h, n go back to original: $4 \rightarrow 3 \rightarrow 2 \rightarrow 1$ and x coordinate (v) moves slowly back to 0

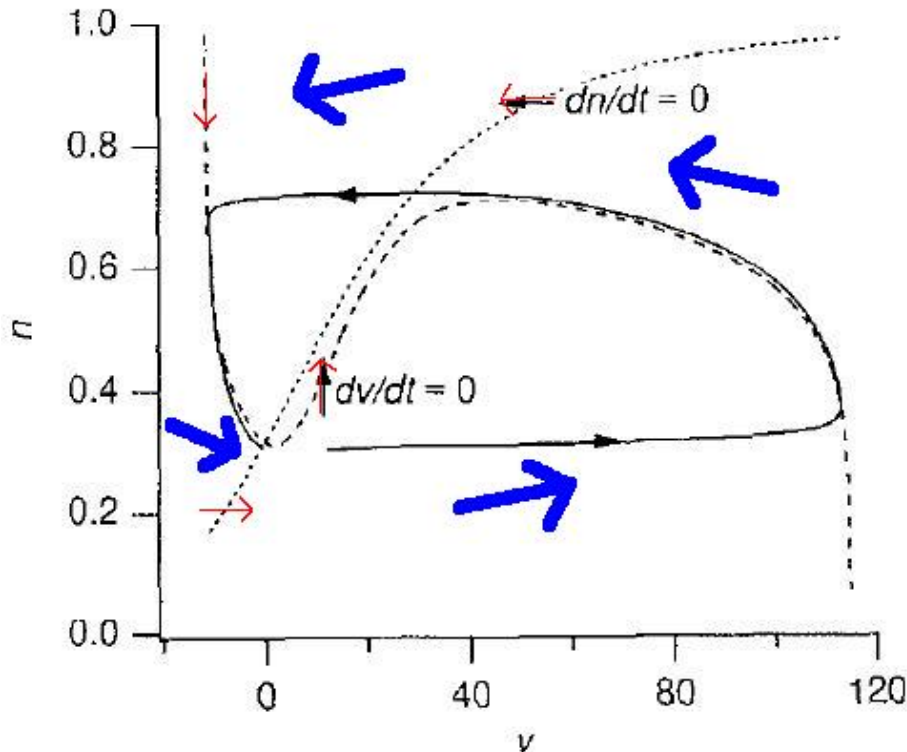
an alternative view - longer time scale

FitzHugh: $h(t) + n(t) \approx 0.8$ constant during action potential
 (see approx symmetry of h, n in simulations) \rightsquigarrow eliminate h

also: $\tau_m \ll 1$ so $m(t) \equiv m_\infty(v)$ (instantaneous tracking)

$$C\dot{v} = -\bar{g}_K n^4 (v - v_K) - \bar{g}_{Na} m_\infty(v)^3 (0.08 - n)(v - v_{Na}) - \bar{g}_L (v - v_L)$$

$$\tau_n(v) \dot{n} = n_\infty(v) - n$$



dots $\dot{n}=0$, dashes $\dot{v}=0$

fast on horizontal $n=\text{constant}$
 n “parameter” for v eqn

fixed n : $v \rightarrow$ equil, fast

“step” n : $v \rightarrow$ another equil

until at upper side: moving \nwarrow while under $\dot{n} = 0$

but at one point, horizontal dynamics is so that only equilibrium is on other side - go there fast ($v \rightarrow 0$ at end)

simplified version

captures all characteristics, but far simpler ($\varepsilon = 1/\tau_n$):

$$\begin{aligned}\dot{v} &= f(x, v) \\ \dot{n} &= \varepsilon g(x, y)\end{aligned}$$

let $x(t) = v(t/\varepsilon)$ and $y(t) = n(t/\varepsilon)$, so:

$$\begin{aligned}\varepsilon \dot{x} &= f(x, y) \\ \dot{y} &= g(x, y)\end{aligned}$$

(same system, same nullclines, etc, just faster)

may view ε as singular perturbation parameter

system of this special form enough for our purposes:

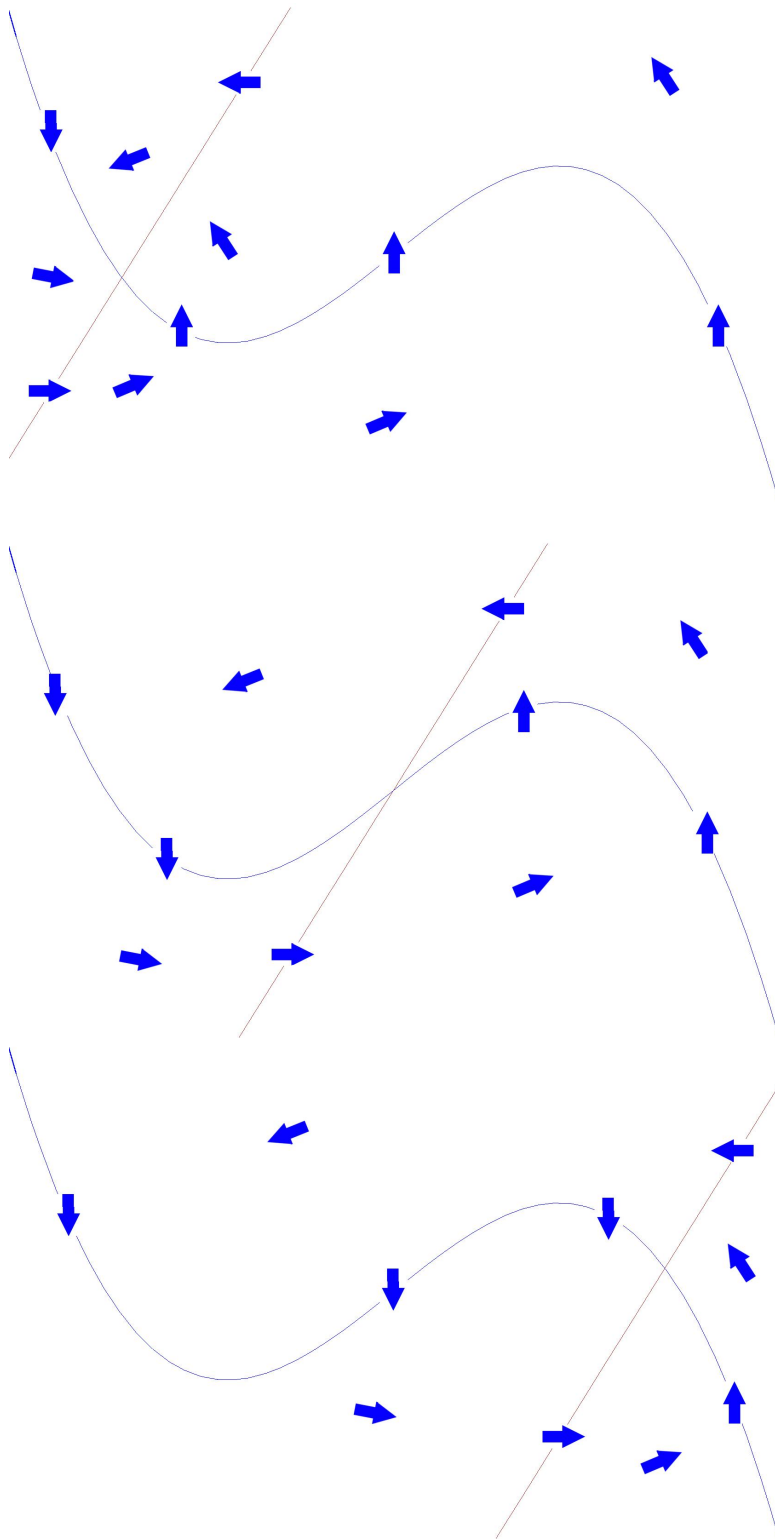
$$\begin{aligned}\varepsilon \dot{x} &= f(x) - y + I && \text{graph of } f \text{ of "cubic" shape} \\ \dot{y} &= x - y\end{aligned}$$

increasing I (constant, think as applied current):

go from stable but not excitable, to stable excitable,

to limit cycles appearing through a Hopf bifurcation,

and then back through Hopf to excitable and just stable



$$\begin{aligned}\varepsilon \dot{x} &= f(x) - y + I \\ \dot{y} &= x - y\end{aligned}$$

Jacobian at steady state:

$$\begin{pmatrix} \frac{1}{\varepsilon} f' & \frac{1}{\varepsilon} \\ 1 & -1 \end{pmatrix} \text{ so } \det = \frac{1}{\varepsilon} (1 - f') > 0$$

(assume $f' < 1$ always)

and $\text{tr} = \frac{1}{\varepsilon} f' - 1$ so ($0 < \varepsilon \ll 1$):

first picture stable

then going through Hopf

(at $f' \approx 0$, first “elbow” of cubic, =
local min of $y = f(x)$)

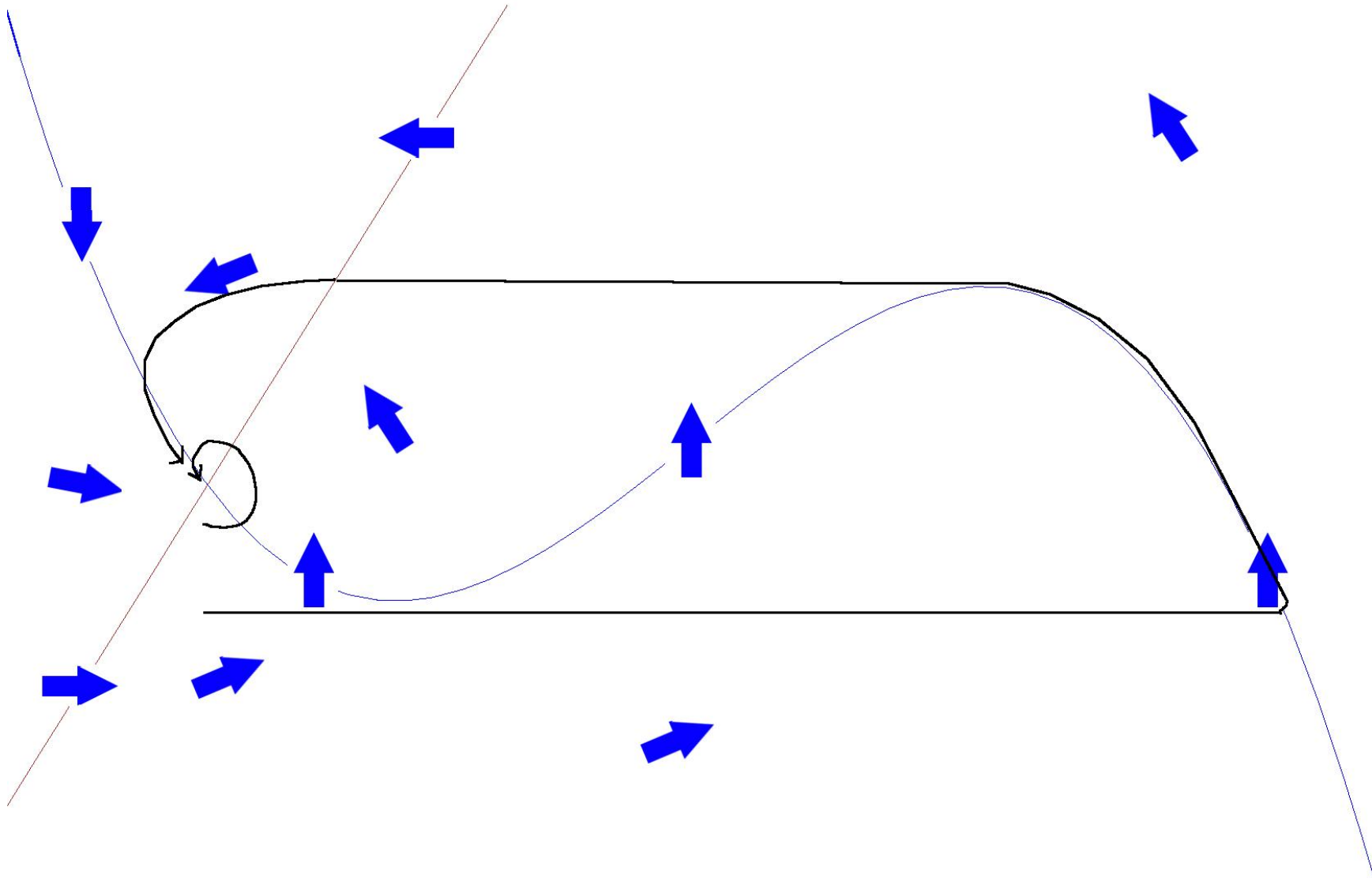
into unstable spiral

and finally back to stable

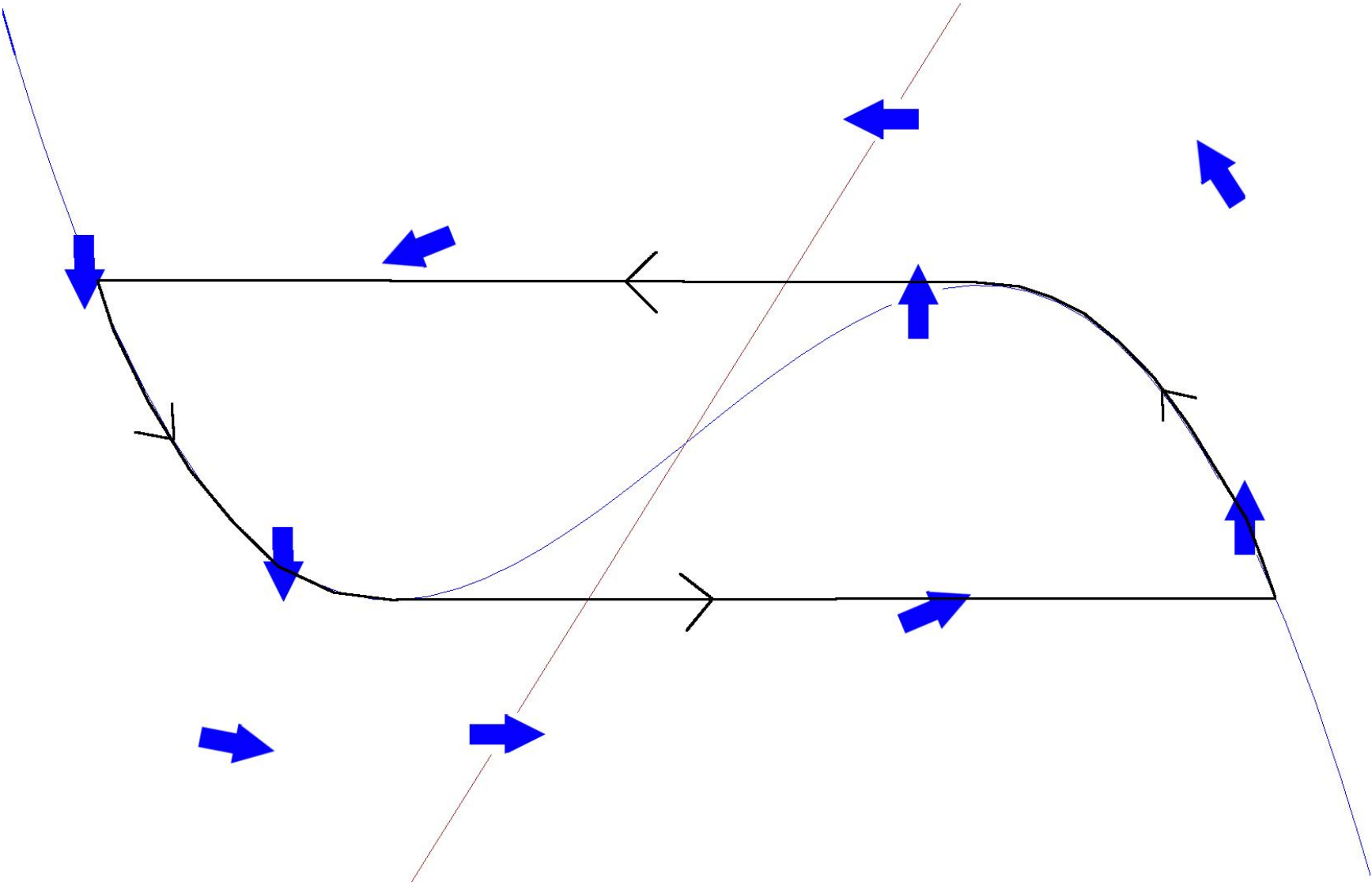
through another Hopf

excitable behavior

small perturbation: return to stable; but if large enough, go fast to stable point and then follow stable manifold



limit cycle



estimate of times

for excitable case, trip up on right branch: assume is graph of $x = V_+(y)$ (branch of cube root, for example)

then $\frac{dy}{dt} \approx G_+(y) = V_+(y) - y$ (since following curve)

so $\int \frac{dy}{G_+(y)} = \int dt$ implies

$$\Delta T = \int_{y_0}^{y_1} \frac{dy}{G(y)}$$

where y_0, y_1 are upper and lower points

for periodic orbit case: similar: just add also the trip back down on the leftmost branch; ignore (assuming $\varepsilon \approx 0$) the horizontal trips, \Rightarrow period is:

$$\Delta T = \int_{y_0}^{y_1} \left(\frac{1}{G_+(y)} - \frac{1}{G_-(y)} \right) dy$$

see book for many models of other excitable neuron types!