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


and, when interconnecting, in 2-d: excitable media:
waves appear because of delay and refractory behavior

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
\[
CV \approx -g_{Na}(V - V_{Na}) \text{ so } V \rightarrow V_{Na} \gg V_{eq}
\]

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

http://jimswan.com/237/channels/channel_graphics.htm
**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

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

Voltage-clamp experiments
H&H experimental technique: force fixed voltage difference across membrane (thread conductor into axon, eliminating spatial voltage gradient ⇒ 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 \((\approx -70mV)\) to a larger value; time scale 1ms; horiz 0.5mA/cm²; from original HH

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:

experimental \( g_K(V)(t) \), \( g_{Na}(V)(t) \), for different clamped \( V \)’s and with solid curves as per model to be given
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 $g = \alpha(\gamma_v - g)$, i.e. $g(t) \to \gamma_v$ as $t \to \infty$, where $\alpha > 0$ determines speed of convergence

but this $\Rightarrow$ slope $\neq 0$ at $t = 0$, contrary to observations of zero slope and subsequent infection 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:

\[
C\frac{dv}{dt} = -g_K(t)(v-v_K) - g_{Na}(t)(v-v_{Na}) - g_L(v-v_L)
\]
\[
\tau_m(v)\frac{dm}{dt} = m_\infty(v) - m
\]
\[
\tau_n(v)\frac{dn}{dt} = n_\infty(v) - n
\]
\[
\tau_h(v)\frac{dh}{dt} = h_\infty(v) - h
\]
\[
g_K(t) = g_{K0}n(t)^4
\]
\[
g_{Na}(t) = g_{Na0}m(t)^3h(t)
\]

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:

\[
\alpha_m = 0.1\frac{25-v}{\exp\left(\frac{25-v}{10}\right)-1}, \beta_m = 4 \exp\left(-\frac{v}{18}\right), \alpha_h = 0.07 \exp\left(-\frac{v}{20}\right)
\]
\[
\beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right)+1}, \alpha_n = 0.01\frac{10-v}{\exp\left(\frac{10-v}{10}\right)-1}, \beta_n = 0.125 \exp\left(-\frac{v}{80}\right)
\]
\[
g_K = 36, g_{Na} = 120, g_L = 0.3
\]
\[
v_{Na} = 115, v_K = -12, v_L = 10.6
\]

how did they come up with the numbers?

for any fixed $v_0$, $n(t) = n_\infty(v_0) \exp\left(-t/\tau_n(v_0)\right)$, 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

intuitive analysis of model

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

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 \( \bar{g}_L, \Delta v's \) not large enough),

\[ g_K(t) \approx \bar{g}_Kn_\infty(0)^4 \gg \bar{g}_{Na}m_\infty(0)^3h_\infty(0) \approx g_{Na}(t), \]

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

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):

\[ g_K(t) \approx \bar{g}_Kn_\infty(0)^4 \ll \bar{g}_{Na}m_\infty(v_0)^3h_\infty(0) \approx g_{Na}(t) \]

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

but, as \( v \gg 1 \), eventually (\( \tau_h, \tau_n \) large): \( h \searrow n \nearrow \):

\( inactivation \) of \( Na \) gate and \( activation \) of \( K \) gate

\( \therefore first \) term dominates, so \( v(t) \to 0 \) (resting potential)
refractory period

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

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

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

FitzHugh: fast time scale

look at what happens in small time intervals

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

$C\dot{v} = -g_K n_0^4 (v - v_K) - g_N a m^3 h_0 (v - v_{Na}) - g_L (v - v_L)$

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

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: $\lim_{t \to \infty} \rightarrow$ far away “excited” state

$m$ tracks $v$, and also moves faster in response to stimulus
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 $h \nearrow, n \searrow$, 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

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

\[
\begin{align*}
\dot{v} &= f(x, v) \\
\dot{n} &= \varepsilon g(x, y)
\end{align*}
\]

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

\[
\begin{align*}
\varepsilon \dot{x} &= f(x, y) \\
\dot{y} &= g(x, y)
\end{align*}
\]

(same system, same nullclines, etc, just faster)
may view $\varepsilon$ as singular perturbation parameter
system of this special form enough for our purposes:

\[
\begin{align*}
\varepsilon \dot{x} &= f(x) - y + I \\
\dot{y} &= x - y
\end{align*}
\]

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

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

\[
\begin{align*}
C \dot{v} &= -\tilde{g}_K n^4 (v - v_K) - \tilde{g}_Na \omega_\infty(v)^3 (0.08 - n) (v - v_Na) - \tilde{g}_L (v - v_L) \\
\tau_n(v) \dot{n} &= n_\infty(v) - n
\end{align*}
\]
dots $\dot{n} = 0$, dashes $\dot{v} = 0$

fast on horizontal $n$=constant $n$ “parameter” for $v$ eqn

fixed $n$: $v \rightarrow$ equil, fast

“step” $n$: $v \rightarrow$ another equil
until at upper side: moving $\nearrow$ 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)

Jacobian at steady state:

\[
\begin{pmatrix}
\frac{1}{\varepsilon} f' & \frac{1}{\varepsilon} \\
0 & -1
\end{pmatrix}
\]
so det $= \frac{1}{\varepsilon} (1 - f') > 0$
(assume $f' < 1$ always)
and 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

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!