Diffusion

The conservation law for a compound with concentration c:
rate change of c = local production + accumulation due to transport.
Model:

$$\frac{d}{dt}\int_\Omega c\,dV = \int_\Omega p\,dV - \int_{\partial\Omega} \mathbf{J}\cdot\mathbf{n}\,dA$$

Here p represents the production and $\mathbf{J}$ is the flux of c.
The divergence theorem:

$$\int_{\partial\Omega} \mathbf{J}\cdot\mathbf{n}\,dA = \int_\Omega \nabla\cdot\mathbf{J}\,dV$$

The law is valid for every volume, thus:

$$\frac{\partial c}{\partial t} = p - \nabla\cdot\mathbf{J}$$

Models for p and $\mathbf{J}$ are needed to compute c.

Fick's Law

$$\mathbf{J} = -D\nabla c$$

The diffusion coefficient D depends upon the solute and the temperature of the embedding fluid:

$$D = \frac{kT}{f}$$

T is the temperature measured on Kelvin, f is a frictional constant and k is the Boltzmann's constant.
The conservation law with this assumption is a reaction-diffusion equation:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) + p$$

1D Diffusion through a pore in the membrane

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial^2 x}$$

Fixed intra and extra cellular concentration:

$$c(0,t) = [C]_i \quad c(L,t) = [C]_e$$

At steady state:

$$\frac{\partial c}{\partial t} = 0 \implies D\frac{\partial^2 c}{\partial^2 x} = 0 \implies \frac{\partial c}{\partial x} = a \implies c(x) = ax + b$$

Taking the boundary condition into consideration yields:

$$c(x) = [C]_i + ([C]_e - [C]_i)\frac{x}{L}$$

and a constant flux: $J = -D\frac{\partial c}{\partial x} = \frac{D}{L}([C]_i - [C]_e)$

Flow through a semi-preamble membrane

Consider two solutions:

- A: Contains 100mM Cl^- ions and 100mM Na^+ ions
- B: Contains 10mM Cl^- ions and 10mM Na^+ ions

Both are neutral. If they are only separated by a membrane permeable to Cl^- but not Na^+, this will happen:

- Cl^- will diffuse from A to B due the concentration gradient
- $[Cl^-]_A$ will drop and $[Cl^-]_B$ will increase
- $[Na^+]_A$ and $[Na^+]_B$ will remain fixed (no flow)
- A and B will no longer be neutral
- $[Na^+]_A > [Cl^-]_A \Rightarrow A > 0, [Cl^-]_B > [Na^+]_B \Rightarrow B < 0.$
- Cl^- will be attracted to A and repelled from B

The Nernst Equilibrium Potential

We now have two forces driving Cl^- across the membrane:

- Flow from A to B due to the concentration gradient
- Flow from B to A due to the charge gradient

At some point an equilibrium is reached were the net flow is zero. The transmembrane potential at that point is called the Nernst Equilibrium Potential.

An expression for this potential will now be derived

Plank's equation

Models the ion-flux caused by an electrical field:

$$J = -m\frac{z}{|z|}c\nabla\phi$$

with
m - mobility of the ions in the liquid
$z/|z|$ - sign of the charge of the ion
c - the concentration of the ion
$\nabla\phi$ - the electrical field

Fick's law:

$$J = -D\nabla c$$

Relationship between m and D:

$$m = D\frac{|z|F}{RT}$$

here R is the gas constant and F is Faraday's constant.
Combined effect of concentration gradient and an electric field:

$$J = -D(\nabla c + \frac{zF}{RT}c\nabla\phi)$$

Nernst Equilibrium Potential

Consider equilibrium in 1D flow:

$$\frac{dc}{dx} + \frac{zF}{RT} c \frac{d\phi}{dx} = 0$$

$$\frac{1}{c}\frac{dc}{dx} + \frac{zF}{RT}\frac{d\phi}{dx} = 0$$

Integrating from inside (x=0) to outside (x=L) yields:

$$\ln(c)|_{c(0)}^{c(L)} = -\frac{zF}{RT}(\phi(L) - \phi(0))$$

We define the transmembrane potential to be $v = \phi_i - \phi_e$ The value of the transmembrane potential at zero flux is then

$$v_{\text{eq}} = \frac{RT}{zF} \ln(\frac{c_e}{c_i}) \qquad (1)$$

Equation (1) is referred to as the Nernst Equilibrium Potential.

Accumulation around the membrane

The membrane has properties similar to a capacitor

- Consists of two conducting medias (intra- and extra cellular space)
- These are separated by an insulating material (the membrane)

The potential over a capacitor is proportional to the separated charge (q):

$$v = q/c$$

The factor c is called the capacitance of the capacitor.

The cell membrane modeled as a leaky capacit

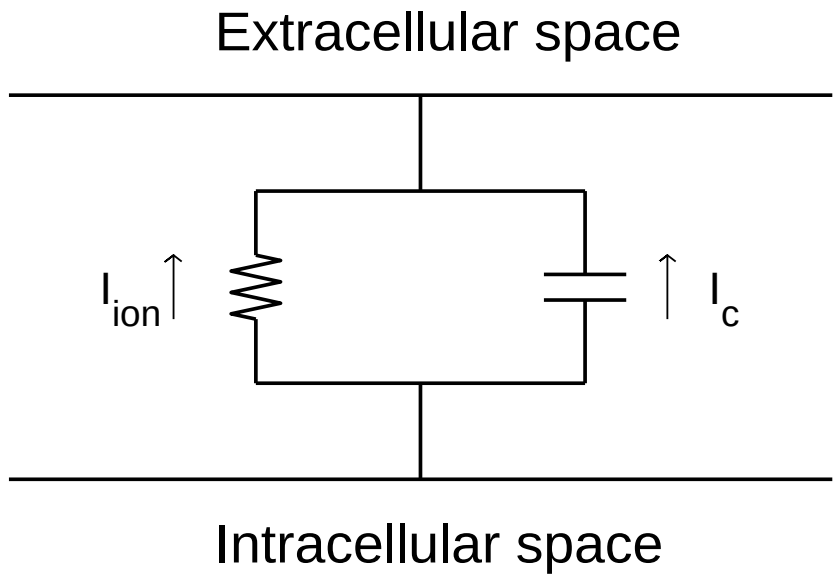
As any real capacitor the membrane conducts some current. The flux of ions (I_{ion}) will cause a change in q and thus v.

Consider the change over a time interval Δt. It follows that $\frac{\Delta v}{\Delta t} = \frac{1}{c}\frac{\Delta q}{\Delta t}$ and in the limit we get:

$$\frac{dv}{dt} = \frac{1}{c}\frac{dq}{dt}$$

The term $\frac{dq}{dt}$ is called the capacitive current and is denoted I_c.

Electrical circuit model of the cell membrane



The membrane behaves like resistor and capacitor in parallel:

$$I_t = I_{\text{ion}} + I_c$$

If the loop is closed then $I_t = 0$. In that case all the ions passing the membrane accumulate and change the membrane potential accordingly.

Ionic currents

For passive ionic channels the flow through it must obey the equilibrium potential, i.e. be zero when $v = v_{\text{eq}}$.
An number of models exists, two common are:
Linear:

$$I(v) = g(v - v_{\text{eq}})$$

Here g is the conductance of the channel.

Goldman-Hodgkin-Katz:

$$I(v) = gv\frac{c_i - c_e e^{\frac{-zvF}{RT}}}{1 - e^{\frac{-zvF}{RT}}}$$

Derived from Nernst-Planck equation with assuming a constant (non-zero) field strength.

Nernst-Plack equation:

$$J = -D(\nabla c + \frac{zF}{RT} c \nabla \phi)$$

Consider 1D flow through a channel and assume $\nabla\phi$ is constant in space and that c and ϕ are in steady-state.

$$\frac{d\phi}{dx} = \frac{\Delta\phi}{\Delta x} = \frac{\phi(L) - \phi(0)}{L - 0} = \frac{\phi_e - \phi_i}{L} = -v/L$$

The equation is reduced to an ODE:

$$J/D = -\frac{dc}{dx} - \frac{zF}{RT} c(-v/L) = -\frac{dc}{dx} + kc$$

where $k = \frac{zFv}{RTL}$

The equation

$$J/D = -\frac{dc}{dx} + kc$$

is solved by

$$e^{-kx}c = c_i + \frac{J}{D}\frac{1}{k}(e^{-kx} - 1)$$

We determine J by using $c(L) = c_e$:

$$J = Dk\frac{c_i - c(L)e^{-kL}}{1 - e^{-kL}} = D\frac{zFv}{RTL}\frac{c_i - c_e e^{\frac{-zvF}{RT}}}{1 - e^{\frac{-zvF}{RT}}}$$

J has dimension moles per area per time, an expression for current is given by

$$I = zFJ = \frac{D}{L}\frac{z^2F^2}{RT}v\frac{c_i - c_e e^{\frac{-zvF}{RT}}}{1 - e^{\frac{-zvF}{RT}}}$$

This is the Goldman-Hodgkin-Katz current equation.

Channel gating

The conductance of a channel varies with time and with transmembrane potential. Model for current per membrane area:

$$I(V,t) = g(V,t)\phi(V) \tag{2}$$

Current through a single open channel is $\phi(V)$ and the amount of open channels per membrane area is $g(V,t)$.

Two different measuring techniques help to distinguish the factors in (2).

- Instantaneous: The transmembrane potential is quickly forced from one state to another and the current is measured right after the switch.
- Steady-State: The current measurements are performed the current has reached a steady state.

If the conductances changes slowly the instantaneous measurements reflects changes in $\phi(V)$ only. The steady-state measurement will also include effects of channel kinetics.

Two State K^+-channel

Assumes that the channel can exist in two states, closed(C) and open(O):

$$C \underset{\beta(v)}{\overset{\alpha(v)}{\rightleftarrows}} O$$

Applying law of mass action:

$$\frac{d[0]}{dt} = \alpha(v)[C] - \beta(v)[O]$$

Dividing by the total amount of channels ([C]+[O]) yields

$$\frac{dg}{dt} = \alpha(v)(1-g) - \beta(v)g$$

where g is the portion of open channel ([O]/([C]+[O])).

Multiple sub-units

For some channels it is more appropriate to model the gate as series of several sub-gates. Example with two gates:

$$\begin{array}{ccc} S_{00} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & S_{10} \\ \alpha \downarrow\uparrow \beta & & \alpha \downarrow\uparrow \beta \\ S_{01} & \underset{\beta}{\overset{\alpha}{\rightleftarrows}} & S_{11} \end{array}$$

Using law of mass action we get a system of four equation. Will try to reduce this number to one!

Combine the states S_{01} and S_{10} into $S_1 = S_{01} + S_{10}$:

$$\begin{aligned} \frac{S_{01}}{dt} &= \alpha S_{00} + \beta S_{11} - (\alpha + \beta) S_{01} \\ + \quad \frac{S_{10}}{dt} &= \alpha S_{00} + \beta S_{11} - (\alpha + \beta) S_{10} \\ \hline = \quad \frac{S_1}{dt} &= 2\alpha S_{00} + 2\beta S_{11} - (\alpha + \beta) S_1 \end{aligned}$$

Define $S_0 = S_{00}$ and $S_2 = S_{11}$, we can then write:

$$\mathsf{S}_0 \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} \mathsf{S}_1 \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} \mathsf{S}_2$$

Only two independent variables since $S_0 + S_1 + S_2 = S_T$, constant. Define $x_i = S_i/S_T$. Claim:

$$x_2 = n^2, \text{ with } \frac{dn}{dt} = \alpha(1-n) - \beta n$$

Sodium

Behavior of the Sodium conductance can not be described by a chain of identical gates.

Two subunits of type m and one of type h.

$$\begin{array}{ccccc} S_{00} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} & S_{10} & \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} & S_{20} \\ \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta & & \gamma \downarrow\uparrow \delta \\ S_{01} & \underset{\beta}{\overset{2\alpha}{\rightleftarrows}} & S_{11} & \underset{2\beta}{\overset{\alpha}{\rightleftarrows}} & S_{21} \end{array}$$

Here S_{ij} denotes i open m gates and j open h gates. Arguments similar to the one used above leads to these equations for m and h:

$$\frac{dm}{dt} = \alpha(1-m) - \beta m, \quad \frac{dh}{dt} = \gamma(1-h) - \delta h$$

Excitable Cells

Unlike other cells, excitable cells can be triggered to set off an action potential.

During the action potential the transmembrane potential departs from its resting potential, reaches a peak potential and returns to the resting potential after some time.

Nerve cells and cardiac cells uses the action potential as a signal to neighboring cells.

The trigger must be of a certain size, if below the threshold the cell will not “fire”.

The Hodgkin-Huxley Model

Developed to study the action potential of the squid nerve cells.

Assumed three different current I_{Na}, I_{K} and I_{L}
Assumed also linear current-voltage relationship:

$$-C_m \frac{dv}{dt} = I_{\text{ion}} = g_{\text{Na}}(v - v_{\text{Na}}) + g_{\text{K}}(v - v_{\text{K}}) + g_{\text{L}}(v - v_{\text{L}})$$

Can collect the current terms due to linearity:

$$C_m \frac{dv}{dt} = -g_{\text{eff}}(v - v_{\text{eq}})$$

where

$$g_{\text{eff}} = g_{\text{Na}} + g_{\text{K}} + g_{\text{L}}$$

and

$$v_{\text{eq}} = \frac{g_{\text{Na}} v_{\text{Na}} + g_{\text{K}} v_{\text{K}} + g_{\text{L}} v_{\text{L}}}{g_{\text{eff}}}$$

v_{eq} is a weighted average of the individual equilibrium potentials. The weighing factors are time and voltage dependent.

A steady applied current I_{app} moves the membrane potential to different equilibrium.

$$C_m \frac{dv}{dt} = -g_{\text{eff}}(v - v_{\text{eq}}) + I_{\text{app}} = 0$$

Implies

$$v = v_{\text{eq}} + \frac{1}{C_m \, g_{\text{eff}}} I_{\text{app}}$$

The applied current will be compensated by an ionic current going the opposite way, thus the net current will be zero.

For a sufficiently large I_{app}, v will pass the threshold potential and an action potential is triggered. The conductivities will vary greatly.

Voltage Clamp measurements

The transmembrane potential is forced by an applied current to a fixed value.

Since $I_{\text{ion}} = -I_{\text{app}}$ for a fixed v, we can measure I_{ion} as a function of time for a given level of v.

Since v is fixed the observed variations must be due to temporal variation in the conductivities.

Total membrane current for different steps

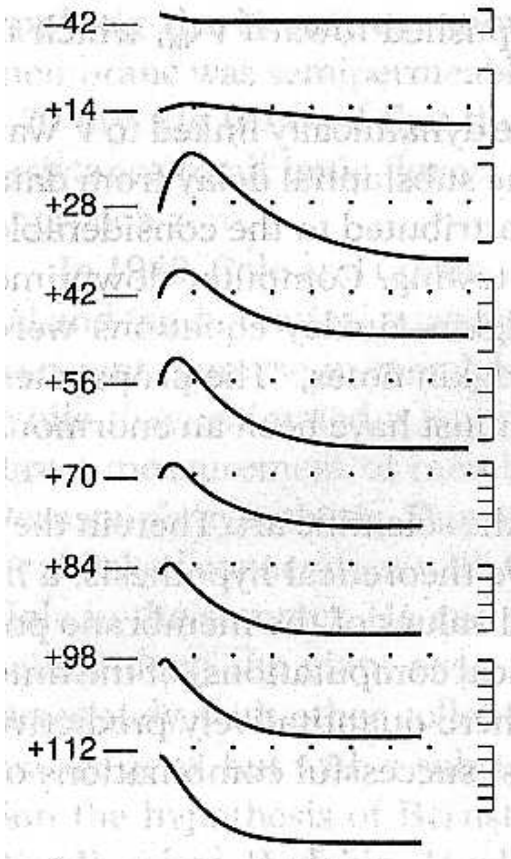


Figure 4.2 Experimental results describing the total membrane current in response to a step depolarization. The numbers on the left give the final value of the membrane potential, in mV. The interval between dots on the horizontal scale is 1 ms, while one division on the vertical scale represents 0.5 mA/cm^2. (Hodgkin and Huxley, 1952a, Fig. 2a.)

From measurements to models

Initially, Hodgkin and Huxley assumed $I_{\text{ion}} = I_{\text{Na}} + I_{\text{K}}$. Two kind of experiments conducted:

- 1: Normal concentrations
- 2: $[\text{Na}]_e$ replaced by cohline $\Rightarrow$ affects I_{Na} but not I_{K}.

Assumed further:

- Initially $I_{\text{K}} = 0$
- $I^1_{\text{Na}}/I^2_{\text{Na}}$ = K, constant
- $I^1_{\text{K}} = I^2_{\text{K}}$

Once I^1_{ion} and I^2_{ion} is recorded we can determine K from the first and the second assumptions.

Expressions for the currents in terms of measurable quantities can now be obtained:

$$I^1_{\text{Na}} = \frac{K}{K-1}(I^1_{\text{ion}} - I^2_{\text{ion}})$$

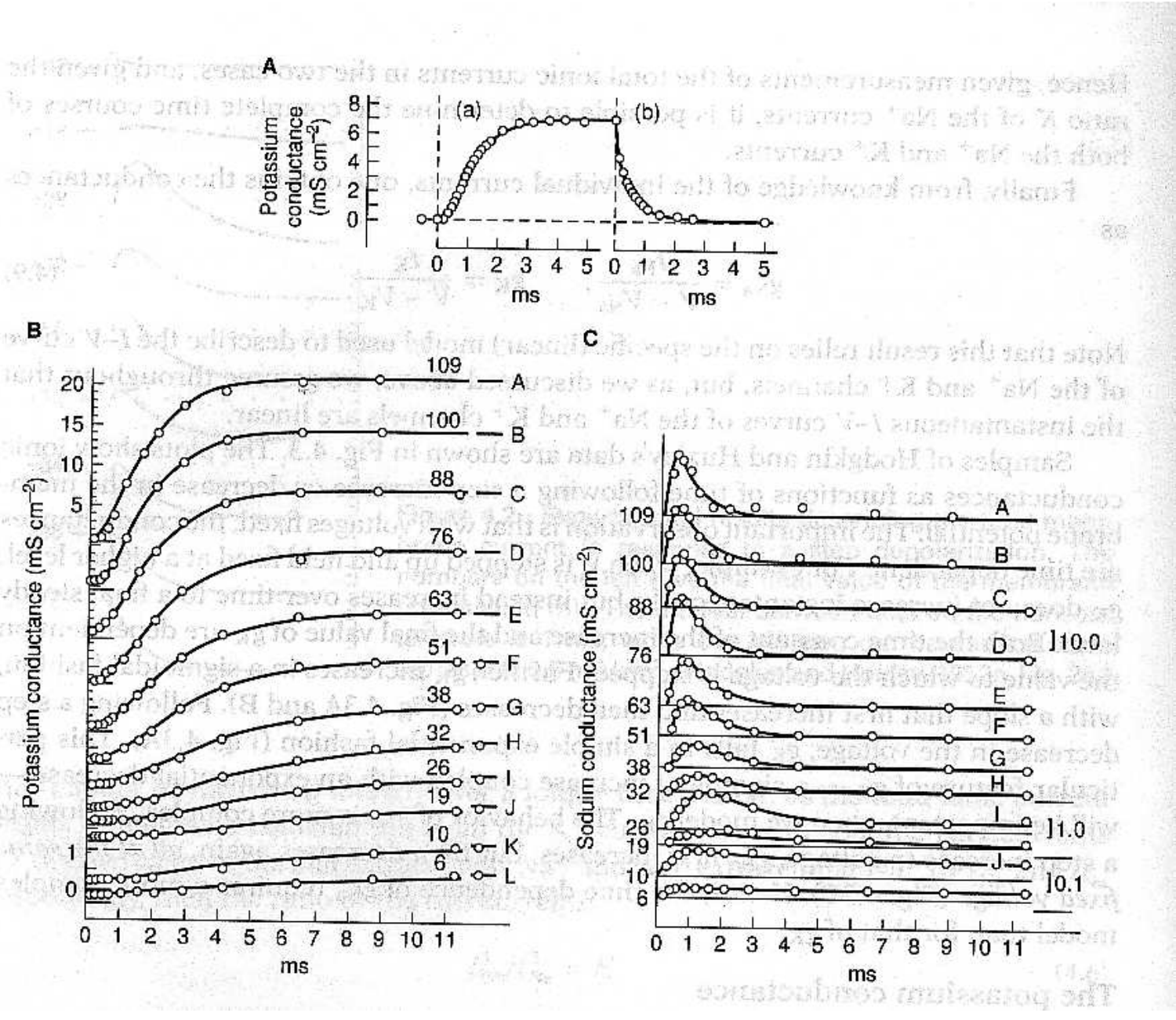
$$I_{\text{K}} = \frac{1}{1-K}(I^1_{\text{ion}} - K I^2_{\text{ion}})$$

Assuming linear current-voltage relationships we get expressions for the conductivities:

$$g_{\text{Na}} = \frac{I_{\text{Na}}}{V - V_{\text{Na}}}, \quad g_{\text{K}} = \frac{I_{\text{K}}}{V - V_{\text{K}}}$$

For each pair of voltage clamp experiment (with a given voltage step), we now have a time course for g_{Na} and g_{K}.

Potassium and Sodium conductance



Model for the Potassium conductance

Assumed $\frac{dg_{\mathrm{K}}}{dt} = f(v,t)$.

Ended up with introducing a second variable:

$$g_{\mathrm{K}} = \overline{g}_{\mathrm{K}} n^4, \text{ with } \frac{dn}{dt} = \alpha(v)(n-1) - \beta(v)n$$

and $\overline{g}$ is the maximum conductance. Forth power was chosen to get the correct shape of the solution.

The solution of

$$\tau_n \frac{dn}{dt} = n_\infty - n$$

with constant coefficients is

$$n(t) = n_\infty + (n(0) - n_\infty)e^{-t/\tau_n}$$

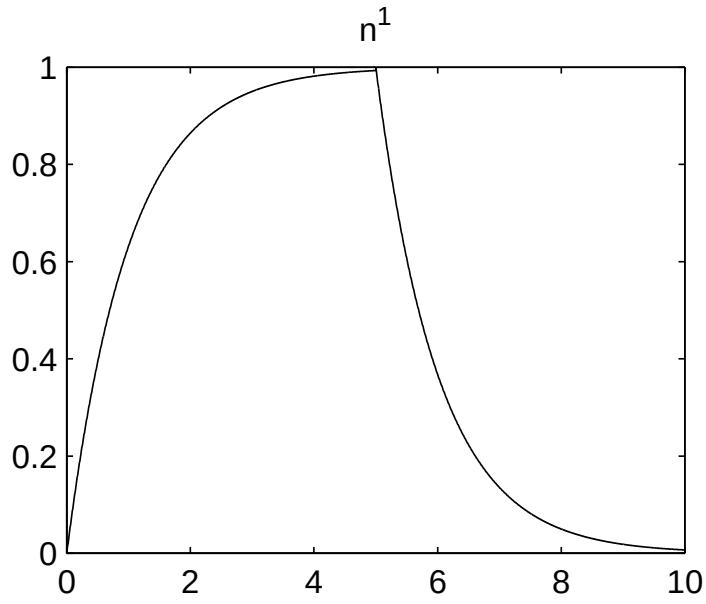
If we assume that $n_\infty(0) = 0$ a step from from 0 to v yields:

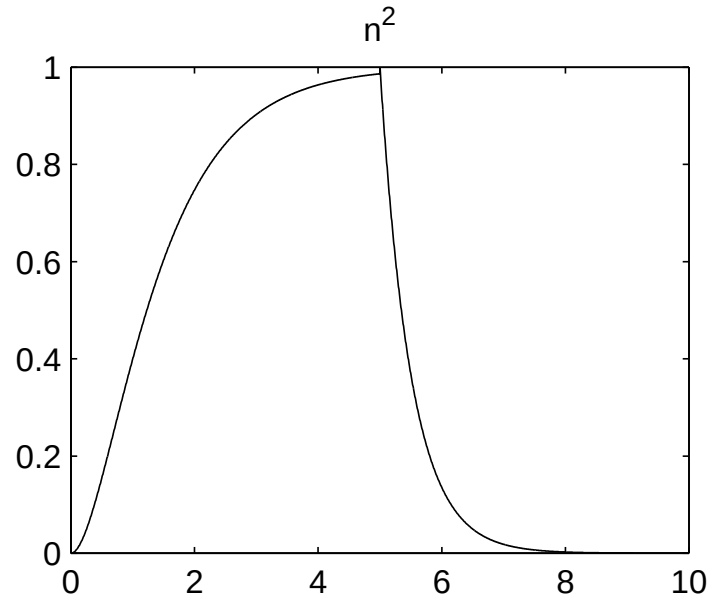
$$\begin{aligned} n(t) &= n_\infty(v) + (n_\infty(0) - n_\infty(v))e^{-t/\tau_n(v)} \\ &= n_\infty(v)(1 - e^{-t/\tau_n(v)}) \end{aligned}$$

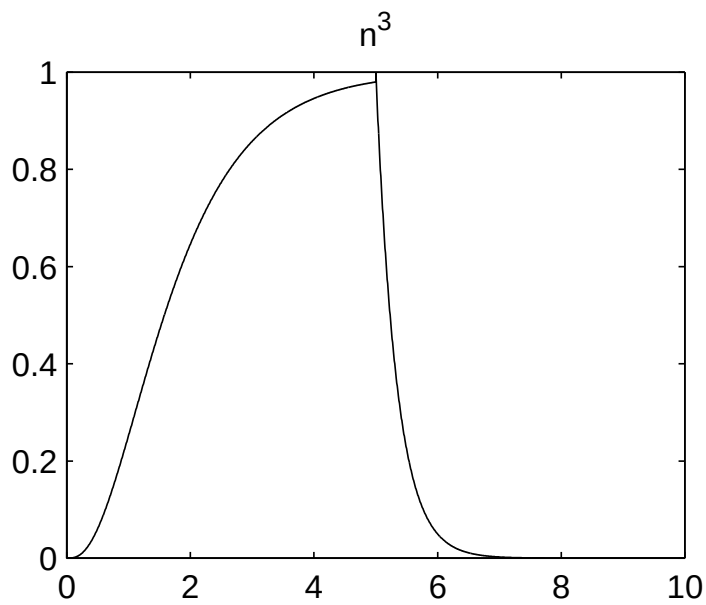
A step in the other direction gives:

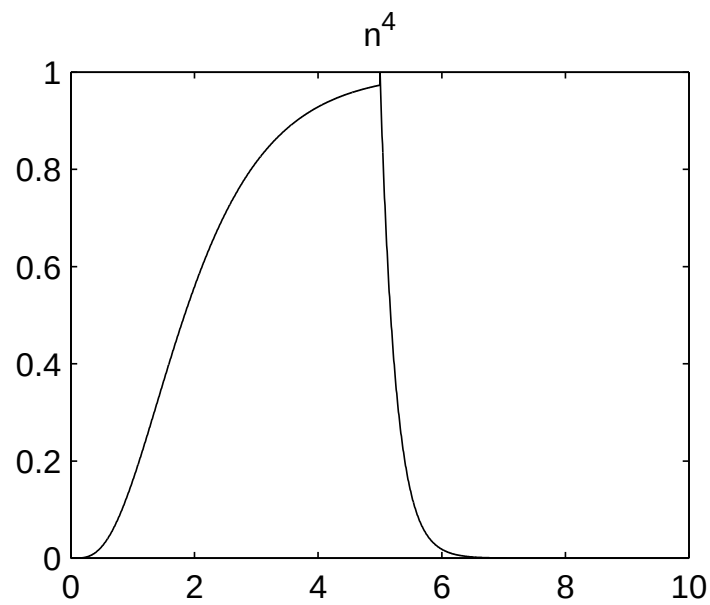
$$\begin{aligned} n(t) &= n_\infty(0) + (n_\infty(v) - n_\infty(0))e^{-t/\tau_n(v)} \\ &= n_\infty(v)e^{-t/\tau_n(v)} \end{aligned}$$

Gating variable raised to different powers









Sodium conductance model

H&H realized that two different types of channels were at work. Ended up with

$$\frac{dg_{\text{Na}}}{dt} = \overline{g}_{\text{Na}} m^3 h$$

Values for m_τ, m_∞, h_τ and h_∞ obtained by fitting the solution to plots of g_{Na}.

The Hodgkin-Huxley Model

Introduces a third current, not time dependent:

$$C_m \frac{dv}{dt} = -\overline{g}_{\mathsf{K}} n^4 (v - v_{\mathsf{K}}) - \overline{g}_{\mathsf{Na}} m^3 h (v - v_{\mathsf{Na}}) - \overline{g}_{\mathsf{L}} (v - v_{\mathsf{L}})$$

with

$$\frac{dg}{dt} = \alpha_g(v)(1 - g) - \beta_g(v) g, \quad g = m, h, n$$

Model based on voltage clamp measurement. How will it behave under normal conditions?

The model will predict the action potential.

Qualitative analysis

Would like to reduce the number of state variables to simplify analysis.

One way is to treat the slowest variables as constants. Of the three gating variables m has the fastest dynamics. (Controls the activation of the Na-current).

Reduced model:

$$C_m \frac{dv}{dt} = -\overline{g}_{\mathsf{K}} n_0^4 (v - v_{\mathsf{K}}) - \overline{g}_{\mathsf{Na}} m^3 h_0 (v - v_{\mathsf{Na}}) - \overline{g}_{\mathsf{L}} (v - v_{\mathsf{L}})$$

Equilibria in the reduced HH-model

The nullclines $\frac{dv}{dt} = 0$ and $\frac{dm}{dt} = 0$ form curves in the (v, m)-plane. Their intersections are the equilibria.

Initially three steady states v_r, v_s and v_e. v_r and v_e are stable and v_s unstable.

As n_0 and h_0 changes, the $\frac{dv}{dt} = 0$ line will shift. v_e will decrease, coincide with v_s and disappear.

v_r will become the only stable equilibrium.

Phase plot for the fast sub-system

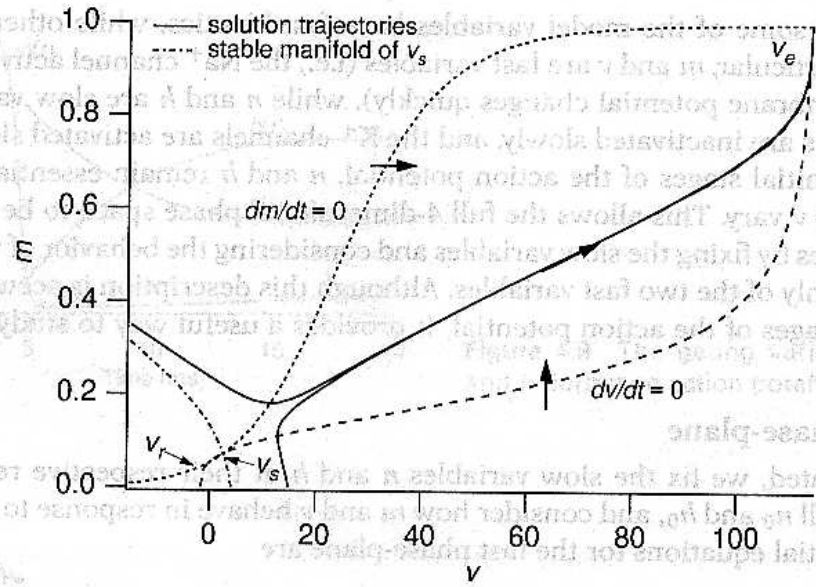


Figure 4.10 The Hodgkin–Huxley fast phase-plane, showing the nullclines $dv/dt = 0$ and $dm/dt = 0$ (with $h_0 = 0.596$, $n_0 = 0.3176$), two sample trajectories and the stable manifold of the saddle point v_s.

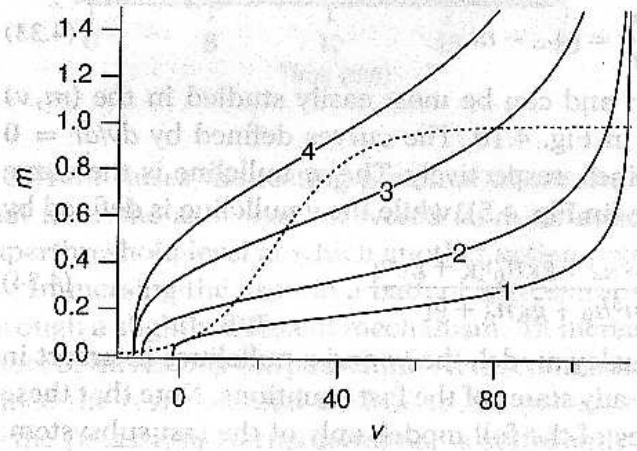


Figure 4.11 The Hodgkin–Huxley fast phase-plane as a function of the slow variables, showing the m nullcline (dashed) and the movement of the v nullcline (solid) and the disappearance of the steady states. For these curves, parameter values are (1) $h_0 = 0.596$, $n_0 = 0.3176$; (2) $h_0 = 0.4$, $n_0 = 0.5$; (3) $h_0 = 0.2$, $n_0 = 0.7$; and (4) $h_0 = 0.1$, $n_0 = 0.8$.

Alternative reduction:

- m is very fast, almost in equilibrium: $m = m_\infty(v)$
- $h + n$ almost constant: $h = 0.8 - n$

We then have

$$C_m \frac{dv}{dt} = -\overline{g}_{\mathsf{K}} n^4 (v - v_{\mathsf{K}}) - \overline{g}_{\mathsf{Na}} m_\infty^3(v) \overbrace{(0.8 - n)}^{h} (v - v_{\mathsf{Na}}) - \overline{g}_{\mathsf{L}} (v - v_{\mathsf{L}})$$

Equilibria found by looking at the crossing of the nullclines $\frac{dv}{dt} = 0$ and $\frac{dn}{dt} = 0$ in the (v, n)-plane.

Phase plot for the fast-slow reduced system

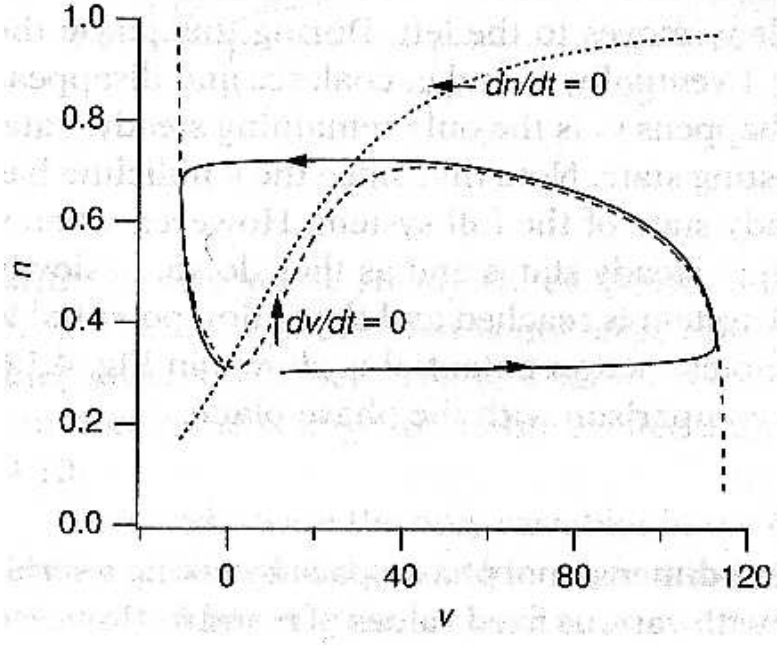
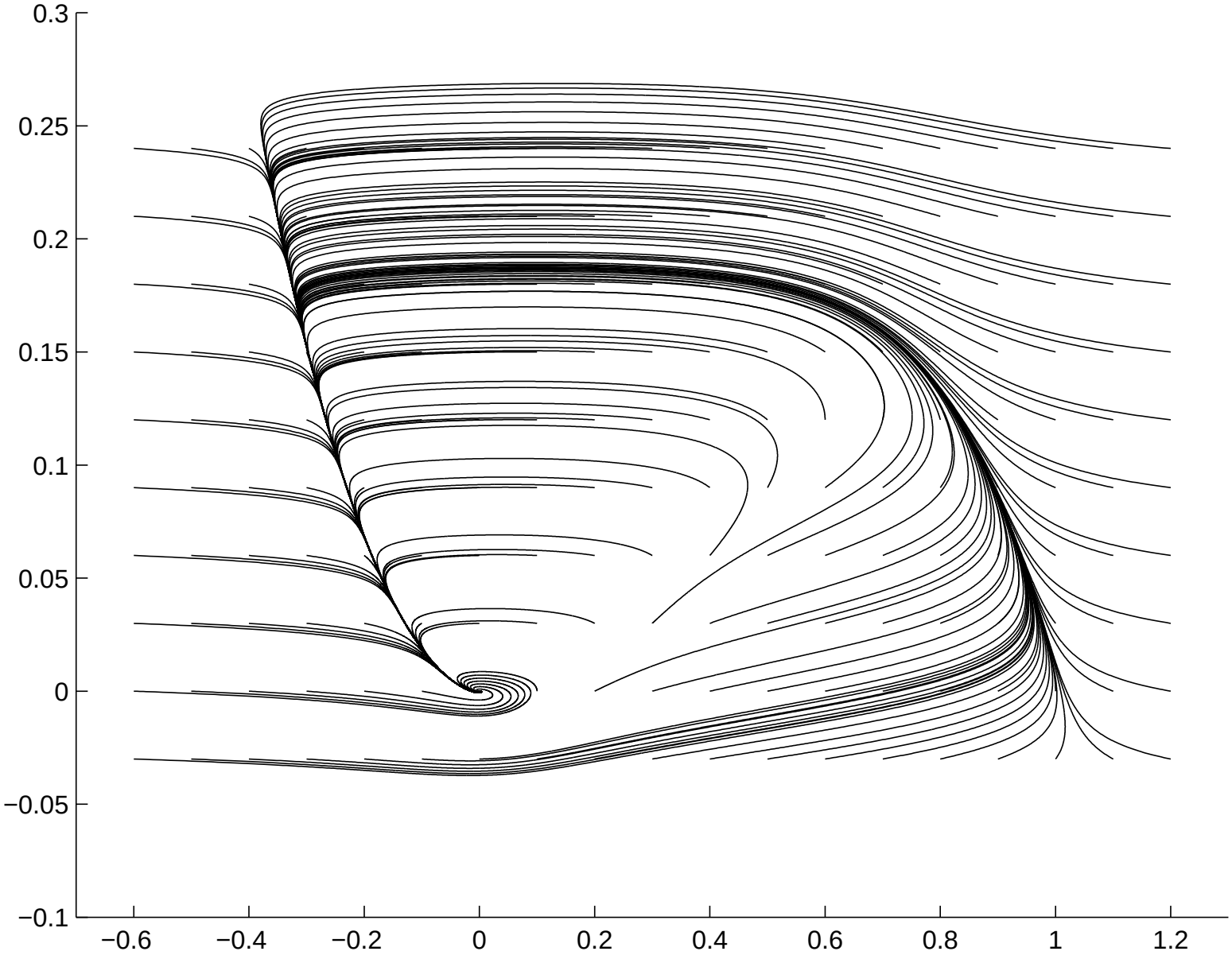


Figure 4.13 Fast–slow phase-plane of the Hodgkin–Huxley model.

Properties of the phase plot

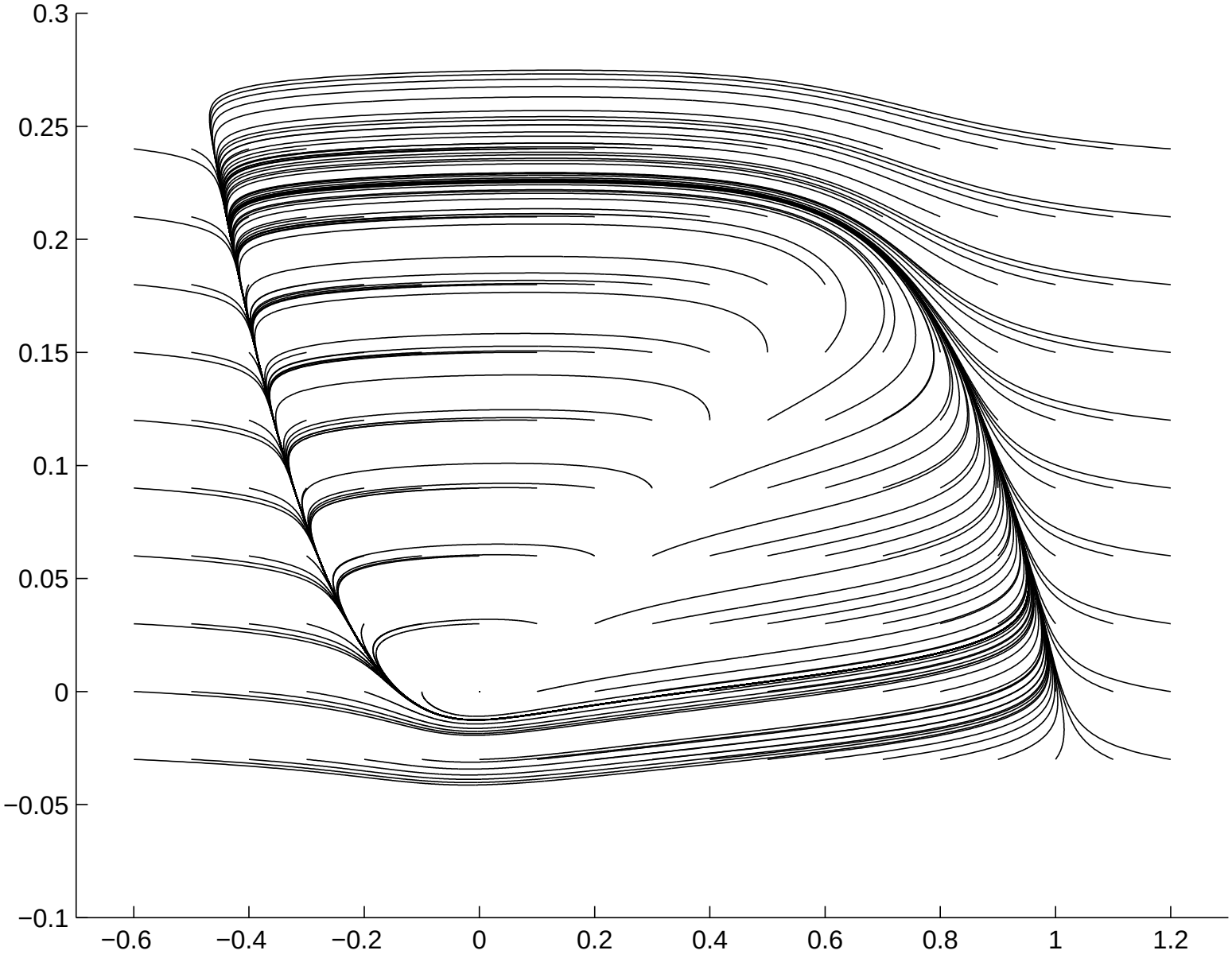
- $\frac{dv}{dt} = 0$ cubic form, with two stable and one unstable branch
- $\frac{dn}{dt} = 0$ sigmoid form
- One crossing with default parameters
- Trajectories horizontal due faster dynamic of v
- Starting points to the left of the unstable branch converges to equilibrium without crossing the unstable branch
- Starting points to the right of the unstable branch crosses this branch, reaches the rightmost branch, follows this branch and the trajectory continues to rise until $\frac{dn}{dt} = 0$ is crossed. The trajectory finally reaches the leftmost branch and follows it to the equilibrium points.

Simulations with different initial conditions



Modified model

The point (0,0) is no longer a stable equilibrium.



The FitzHugh-Nagumo model

Purpose:
Keep the qualitative behavior of the Hodgkin-Huxley system, but in a simplified form. Derivation based on a an electrical circuit model.

On dimensionless form:

$$\begin{aligned} \epsilon \frac{dv}{dt} &= f(v) - w - w_0 \\ \frac{dw}{dt} &= v - \gamma w - v_0 \end{aligned}$$

The variable w is called the recovery variable.

Typically f is chosen to be "cubic", i.e. with three zeros, $f(0) = f(\alpha) = f(1)$ and $0 < \alpha < 1$. Some choices:

$$f(v) = Av(v - \alpha)(1 - v)$$

$$f(v) = \begin{cases} -v, & v < \alpha \\ 1 - v, & v > \alpha \end{cases}$$

$$f(v) = \begin{cases} -v, & v < \alpha/2 \\ v - \alpha, & \alpha/2 < v < (1 + \alpha)/2 \\ 1 - v, & v > (1 + \alpha)/2 \end{cases}$$