Hodgkin_Huxley_Model-NEUR472-21Apr20

April 1, 2021

1 The Hodgkin-Huxley Model

University of Otago NEUR472 2020, MGP

1.1 Intro

Hodgkin and Huxley (1952). Nobel prize 1963.

[74]:
```
using PyPlot
```

1.1 Single-Channel Current-Voltage Relationship Each channel is either open (conducting) or closed (non-conducting). Individual channel state transitions are very fast, in the order of 10s of microseconds. Individual channel conductances are in the order of 10pS.

Voltages are given here in mV referenced to resting membrane potential (RMP), following Hodgkin and Huxley. RMP in the squid giant axon (internal potential referenced to external ground) is -72mV.

[75]:
```
g_Na = 1.0e-11   # single sodium channel conductance ~10pS
E_Na = 115.0     # sodium reversal potential

g_K = 1.5e-11   # single potassium channel conductance ~15pS
E_K = -12.0     # potassium reversal potential

g_L = 2.0e-12   # single leak channel conductance ~2pS
E_L = 10.6     # leak reversal potential

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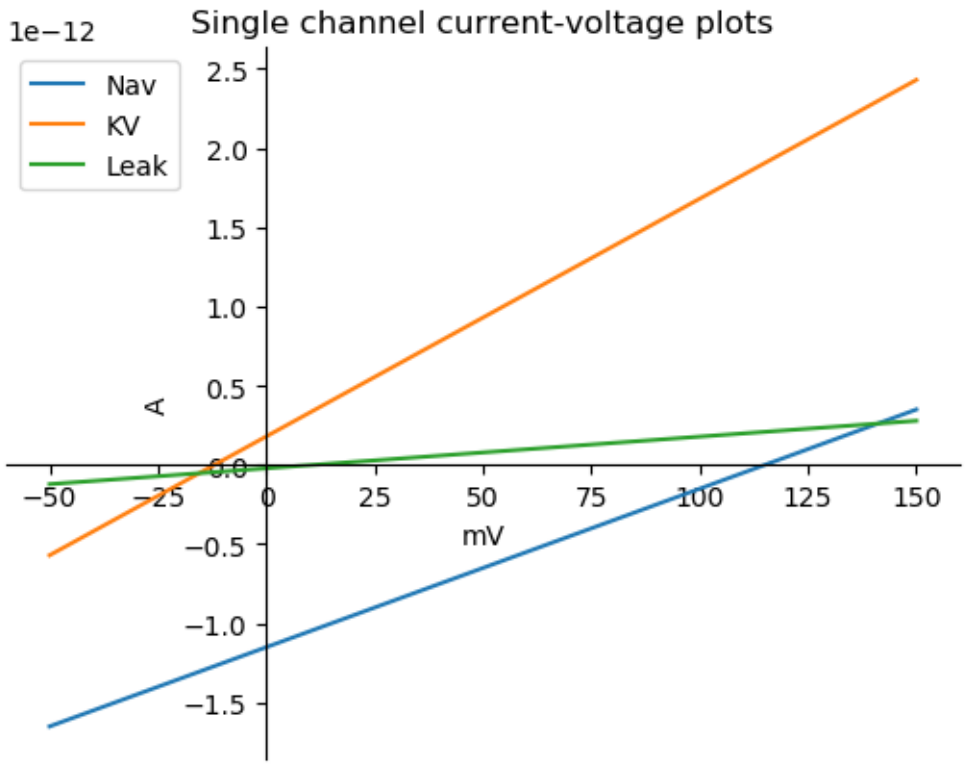


1.2 2 Channel Open-State Probabilities

Conductance in a patch, compartment or neuron due to voltage-gated channels depends on individual channel conductance times number of channels times the probability that a channel is open at a given voltage,

$$G_x(v) = N g_x P_0(v)$$

.

Single channel conductance and number of channels can be estimated by statistical analysis of conductance in a membrane patch (at fixed voltage the total current has a binomial distribution scaled by channel conductance x voltage). Models are usually parameterized by total conductance density (all channels open) g_x^* in (mS/cm^2) times membrane area A,

$$\bar{g}_x = A g^*$$

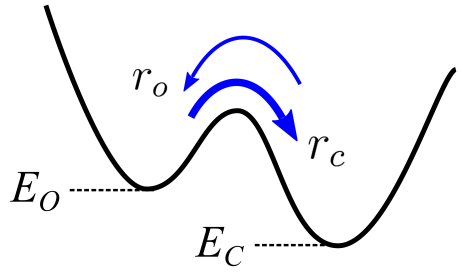
rather than channel count times channel conductance.

$$G_x(v) = \bar{g}_x P_0(v),$$

Current densities are in the order of $100\,mA.cm^{-2}$ (μA for a large cell)

Recall from class:

Boltzmann: $\frac{p_o}{p_c} = e^{-\Delta E/k_B T}$



$$\Delta E = E_O - E_C \approx k_B T/2$$

$$\frac{dP_o}{dt} = r_o P_c - r_c Po$$

$$\frac{dP_c}{dt} = r_c P_o - r_o Pc$$

Single-channel open-closed transitions are effectively instantaneous, but they occur probailistically when thermal noise pushes a channel from one state to the other over the energy barrier, and it takes a while (on the timescale of neural computation) to reach equilibrium. The transition rate is faster from the high- to the low-energy state. Equilibrium is reached when the proportion of channels in each state matches the ratio of rate constants for transitions to that state. This typically occurs with a time constant in the order of milliseconds.

1.2.1 2.1 Equilibrium Open-State Probability

In modelling vestibular hair cell MET channel gating we assumed that the open state probability is always equal to the equilibrium probability at a given voltage ($P_\infty(v)$), because (we assumed that) changes on a 1ms timescale are irrelevant to vestibular function. Substututing $P_C = 1 - P_O$ into Boltzmann's equation for the relative probability of being in one of two states at thermal equilibrium (above) gives a sigmoidal relationship between stimulus energy and open probability at equilibrium:

$$P_\infty(\Delta E) = \frac{1}{1 + e^{\Delta E/k_B T}}$$

1.2.2 2.2. Potassium channel kinetics

However, because action potentials are typically about 1ms across, the kinetics of channel opening are essential in modelling action potentials. Using $P_C = 1 - P_O$, we can write a single ODE for channel opening kinetics:

$$\frac{dP_o}{dt} = r_o(1 - P_o) - r_c P_o.$$

Hodgkin and Huxley discovered voltage-dependent sodium and potassium conductances in squid giant axons at Plymouth Marine Lab in 1939, but their work was interrupted by World War II and was not published until 1952. Advances in electronics and control theory during the war made voltage clamping possible, so that by 1950 they were able to quantify the relationship between trans-membrane voltages and conductances for sodium and potassium ions.

Ion channels were unknown at the time. Hodgkin and Huxley had initially assumed that ions must be transported across the membrane in lipid carriers. However, they noted that the empirically observed kinetics of conductance change could be explained by a Boltzmann-type thermodynamic model, and therefore hypothesised that unspecified "particles" in the membrane have conducting and non-conducting states with different energy levels.

Hodgkin and Huxley used "m" to represent sodium channel open state probability and "n" to represent potassium open state probability. They used α to represent opening rate constant and β to represent the closing rate constant. Thus their ODE for the open state probability of potassium conductance "particles" is:

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n.$$

This predicts an exponential-decay trajectory towards a new equilibrium probability, $P_\infty(v)$, following a step change in trans-membrane voltage (see assignment 1). But this model did not fit the voltage-clamp data. By laborious calculation using a mechanical calculator to solve ODES (there was one programmable electronic computer in Britain at the time, at Manchester University) they showed that membrane conductance is proportional to the 4th power of n. The current through voltage-gated potassium channels is given by

$$I_K = -\bar{g}_K n^4 (v - E_K),$$

where $\bar{g}_K$ is the total conductance if all channels are open. Hodgkin and Huxley deduced that "particles" must come in sets of four, and they must all independently jump into the conducting state in order for current to flow. Decades later it was discovered that voltage-gated channels are tetramers and that indeed all four voltage-sensing elements must be activated for current to flow through the channel.

1.2.3 2.3 Sodium Channel Kinetics

Voltage-gated sodium channels turn out to be slightly more complicated. Hodgkin and Huxley had to use two types of gating "particle" in order to fit their data. The model requires three particles of one type and one of the other type to be in the conducting state.

$$I_{Na} = -\bar{g}_{Na} m^3 h (v - E_{Na}).$$

The second type of particle was called "inactivating" because it works backwards, ie it tends to close when the membrane is depolarized rather than to open, as the other particles do.

We now know that voltage-gated sodium channels, like voltage-gated potassium channels, have four subunits with independently triggered voltage sensors, and a single, independent, inactivation gate that blocks the channel.

In that case you might expect that the exponent of m should be 4, not 3, in the Hodgkin-Huxley model. The short answer is that you can get realistic-looking simulated action potentials using an exponent of 4, but then it wouldn't be the Hodgkin-Huxley model, would it? The longer answer is that the reality is more complicated, and increasing the exponent of m from 3 to 4 in the Hodgkin-Huxley model doesn't make it usefully more accurate or realistic.

If we have a question whose answer might depend subtley on the precise timing and shape of action potentials, we will need to construct a more realistic model. The Hodgkin-Huxley model is a good foundation for learning how to do that. Biophysical models of neurons tend to be called "Hodgkin-Huxley models" even if they are not actually the Hodgkin-Huxley model.

1.2.4 2.4 Leak Channels

Hodgkin and Huxley also reported a leak current, due to a conductance that does not depend on voltage:

$$I_L = -\bar{g}_L(v - E_L).$$

1.3 3. The Hodgkin-Huxley Model

$$C\frac{dv}{dt} = -\bar{g}_{Na}m^3h(v - E_{Na}) - \bar{g}_K n^4(v - E_K) - \bar{g}_L(v - E_L)$$

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

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

$$\frac{dh}{dt} = \alpha_h(1 - h) - \beta_h h.$$

This is a nonlinear dynamical model in which membrane potential affects current flow which affects membrane potential. There is an equilibrium when the net current, i.e. the sum of all terms on the right, is zero. The voltage at equilibrium is called the *resting membrane potential*. Because the sodium equilibrium potential is above resting potential, voltage-gated sodium channels cause positive feedback - depolarization increases the depolarizing current.

The open state probability for each channel has an equilibrium when the right hand side adds to zero, e.g.

$$m_\infty(v) = \frac{\alpha_m}{\alpha_m + \beta_m},$$

and each approaches the equilibrium with time constant

$$\tau_m(v) = \frac{1}{\alpha_m + \beta_m}.$$

The ODEs for channel kinetics can be written in the form:

$$\tau_m(v)\frac{dm}{dt} = m_\infty(v) - m.$$

This (as you know) describes exponential decay towards $m_\infty(v)$ with time constant $\tau_m(v)$. The ODE allows us to model dynamic changes in conductance while the membrane potential is changing (including feedback between membrane potential and conductance).

1.3.1 3.1 Activation Curves

The activation [inactivation] curve for a channel is a plot of the equilibrium open-state probability, $P_\infty(v)$ for activation [inactivation] gates.

[76]:
```
α_n(v) = v == 10.0 ? 0.1 : 0.01*(10.0 - v)/(exp((10.0-v)/10)-1.0)
β_n(v) = 0.125*exp(-v/80.)

τ_n(v) = 1.0/(α_n(v) + β_n(v))
n_infinity(v) = α_n(v)*τ_n(v)

α_m(v) = v == 25.0 ?  1.0 : 0.1*(25.0 - v)/(exp((25.0-v)/10)-1.0)
β_m(v) = 4.0*exp(-v/18.)

τ_m(v) = 1.0/(α_m(v) + β_m(v))
m_infinity(v) = α_m(v)*τ_m(v)

α_h(v) = 0.07*exp(-v/20.)
β_h(v) = 1.0/(exp((30.0-v)/10)+1.0)

τ_h(v) = 1.0/(α_h(v) + β_h(v))
h_infinity(v) = α_h(v)*τ_h(v)

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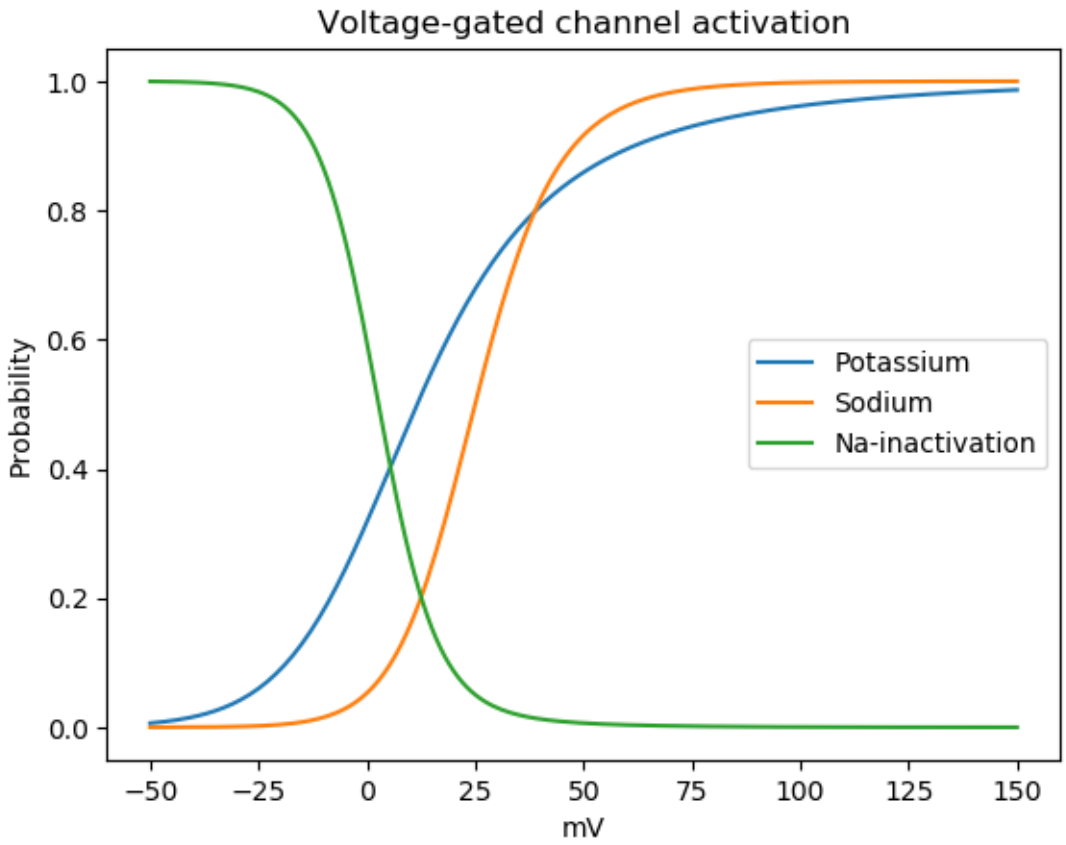

[77]:

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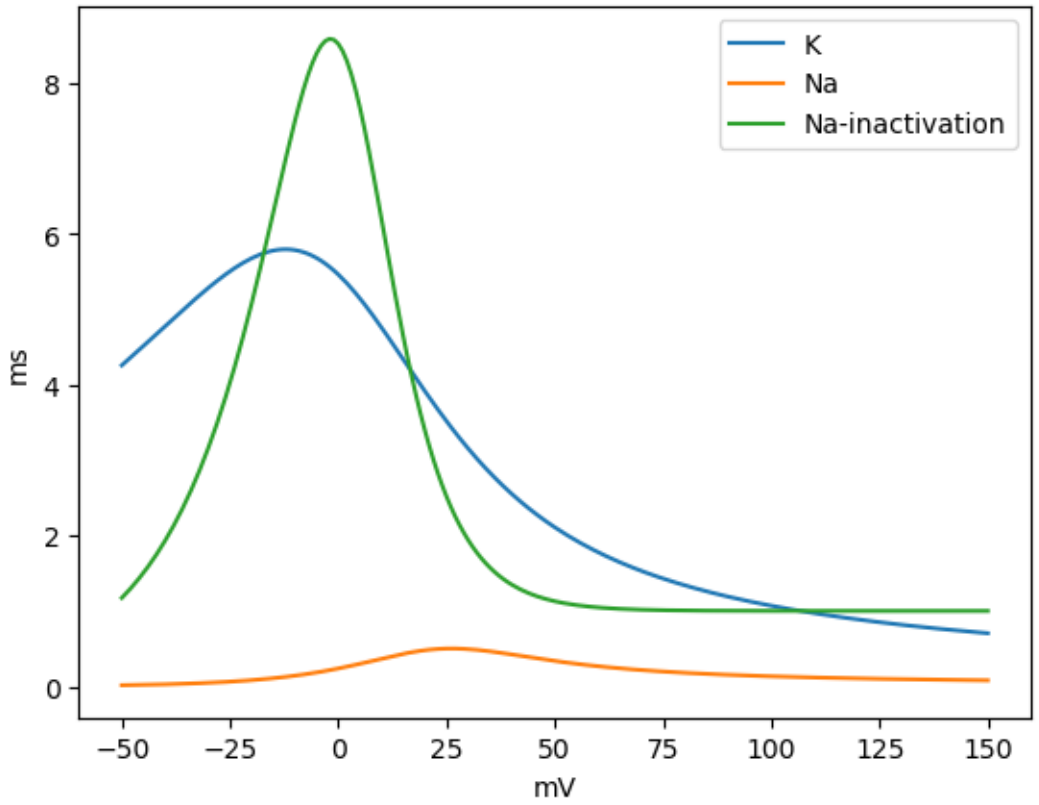

1.3.2 3.2 Current-Voltage Plots

[78]:
```
# membrane conductance consts in mS/cm^2
gstar_Na = 120.
gstar_K = 36.
gstar_L = 0.3


# cell diameter 500um (nb insanely big! This is squid giant neuron)
d = 50.0e-3  # in cm
A = π*d^2  # membrane area

# cell conductance in mS
gbar_Na = A*gstar_Na
gbar_K  = A*gstar_K
gbar_L  = A*gstar_L

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```

```
(nb plots show current as function of membrane potential at equilibrium; this␣
↪is the maximum conductance of the membrane times the equilibrum probability␣
↪that the channel is open at that potential).
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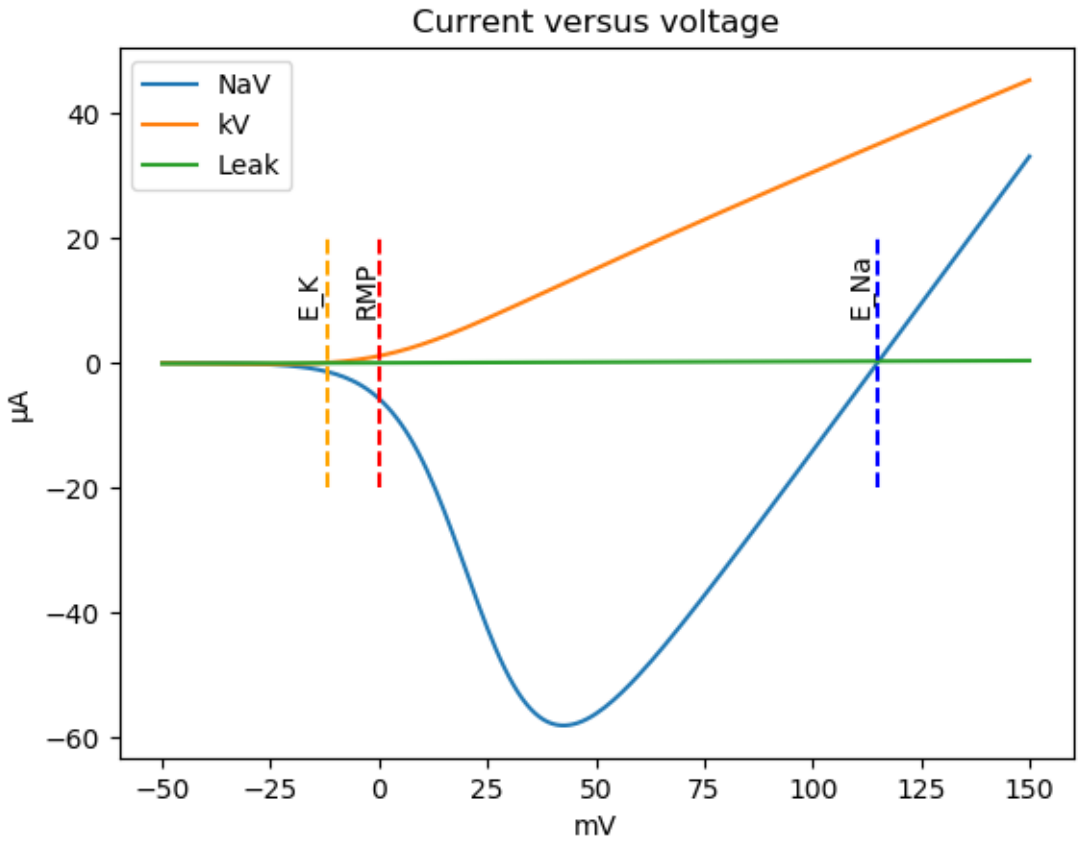

1.4 4 Numerical Solution of Hodgkin-Huxley Equations

The state variables of the Hodgkin-Huxley model are v, m, h and n.

The state vector is $x = [v, m, h, n]$ (Any order, as long as you keep track of which state variable correponds to which parameter in the model).

The *state update function* or *ode function* returns the derivative (rate of change) of state as a function of state and external input(s). (Always possible for any set of ODEs consistent with causality)

[79]:
```
# specific capacitance 1uF/cm^2
Cs = 1.0  # farads per cm^2
C = A*Cs

# state vector x = [v, m, h, n]
```

```
function hh_statederivative(x,I)

    # 'decode' the state vector for clarity
    v = x[1]
    m = x[2]
    h = x[3]
    n = x[4]

    # state derivative
    dx = zeros(length(x))

    dx[1] = *** DELETED ***
    dx[2] = *** DELETED ***
    dx[3] = *** DELETED ***
    dx[4] = *** DELETED ***

    return dx

end
;
```

This function can be used with the Julia DifferentialEquations.jl package (or equivalent in Python or MATLAB). We will not use a differential equation solver package. Instead we will directly code the Euler method, i.e. take small steps in the direction of the state derivative vector in each state, because it generalizes in a simple way for stochastic states and inputs (and the fancy differential equation solvers all fall back on that method in those cases anyway).

[80]:
```
# solve by (4d) Euler method

# time in ms
dt = 1.0e-2
T = 50.
t = 0.0:dt:T

# initial state vector
x0 = [0.0, 0.0, 0.0, 0.0]

# array to hold computed state
x = fill(0.0, length(t), length(x0))
x[1,:] = x0  # initial state in first row

I(t) = 0.1

# loop over time steps

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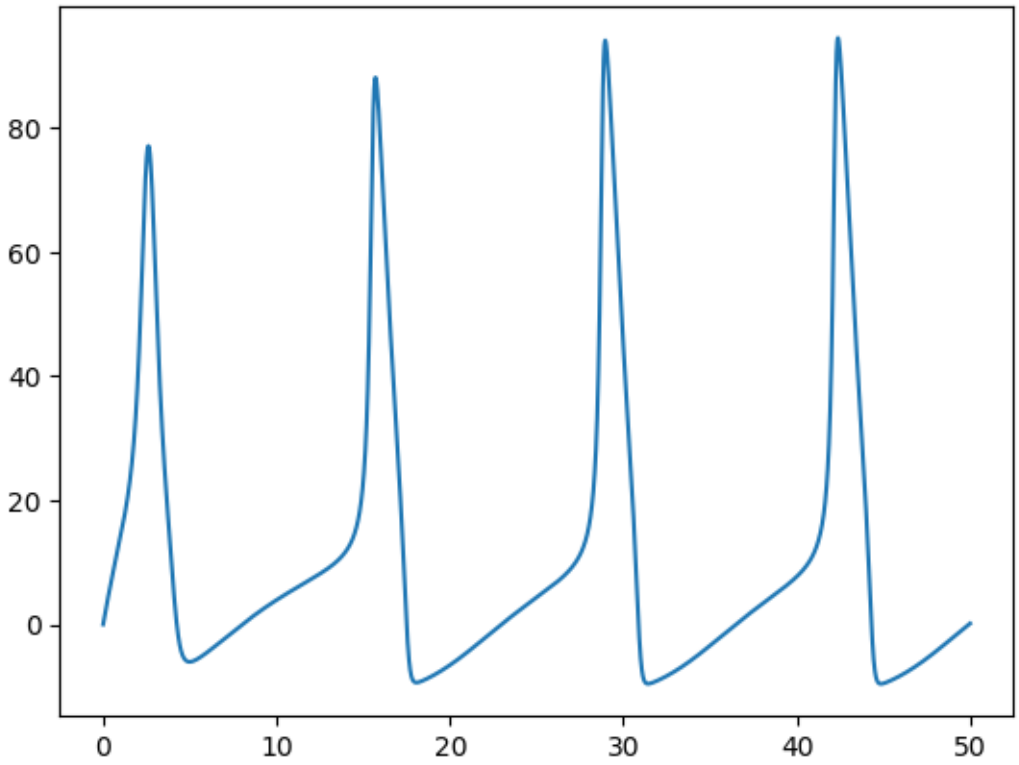
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