6. Neuronal Signalling, Hodgkin-Huxley, excitable kinetics

(J.D. Murray, Volume 1, Chapter 7, Section 7.5).

6.1 Neuronal Signalling

Neurons (nerve cells) send signals to each other using electrical currents.

Neurons have *axons* - long cylindrical tubes which extend from the neuron - and electrical currents travel along the outer membrane of the axon, and move from one neuron to another via synapses.

The current along the axon, $I(t)$, is made up of the sum of the currents from the movement of different chemical ions and the rate of change of charge, Q, which is related to the voltage, V by $V = \frac{Q}{C}$, where C is the capacitance.

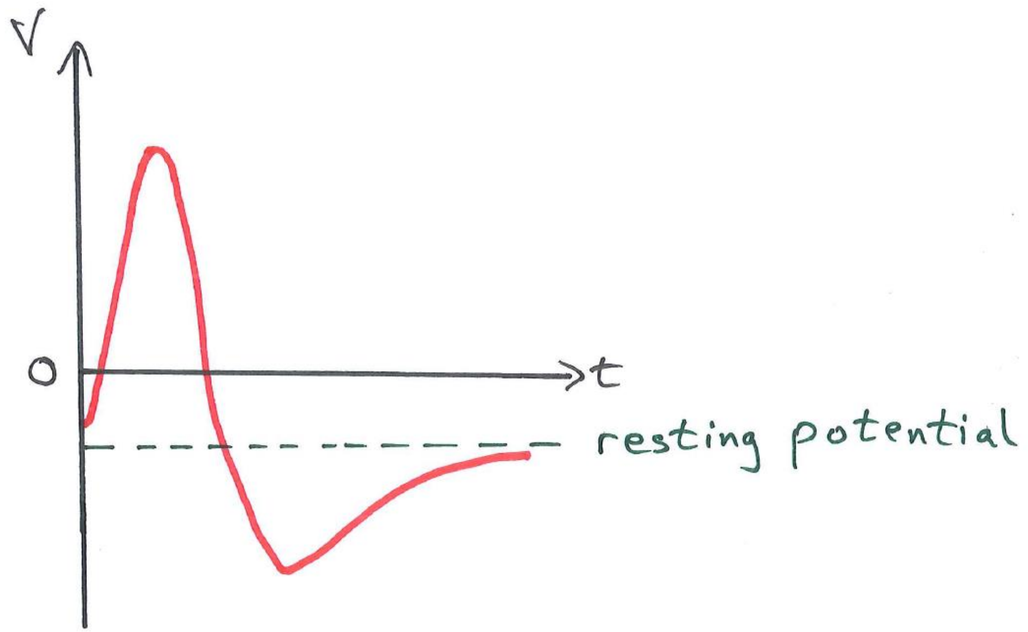
Hence, for the so-called "space-clamped" system (no spatial movement), we have

$$I(t) = C\frac{dV}{dt} + I_i(t), \qquad (6.1)$$

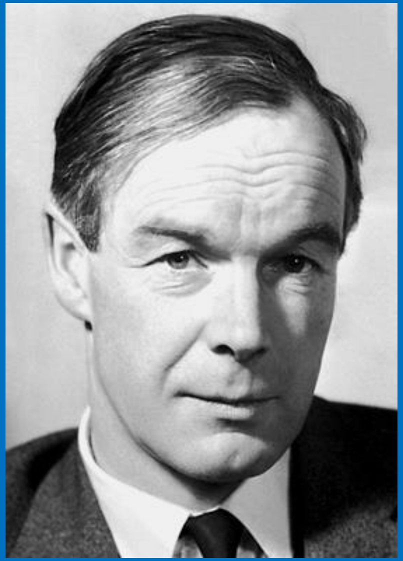
where $I_i(t)$ is the contribution from the different chemical ions.

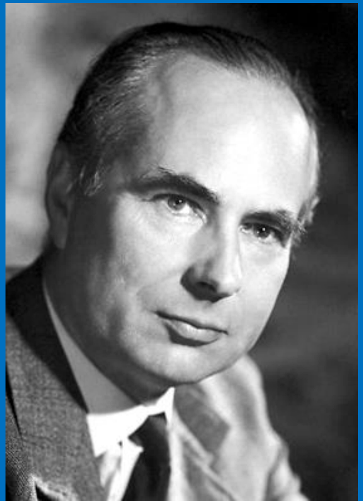
6.2 Hodgkin-Huxley (1952)

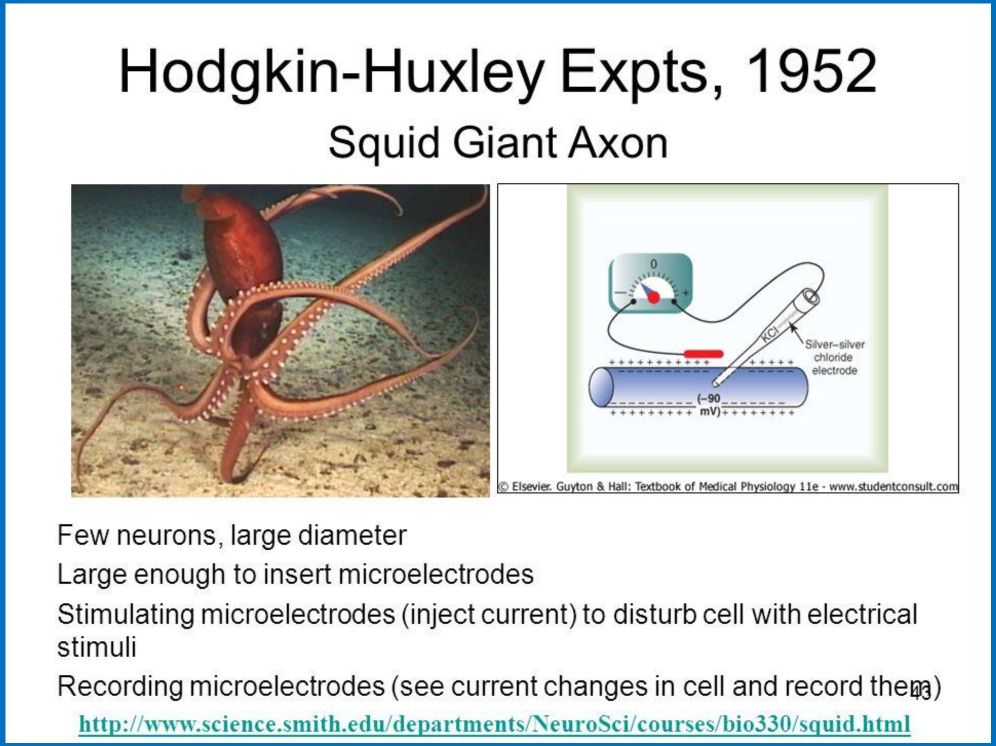
In 1952, Hodgkin and Huxley (HH) studied the squid giant axon to investigate how it "fired" - that is, sent a spike, or pulse, signal - the so-called *action potential*. Their work won them a Nobel Prize.

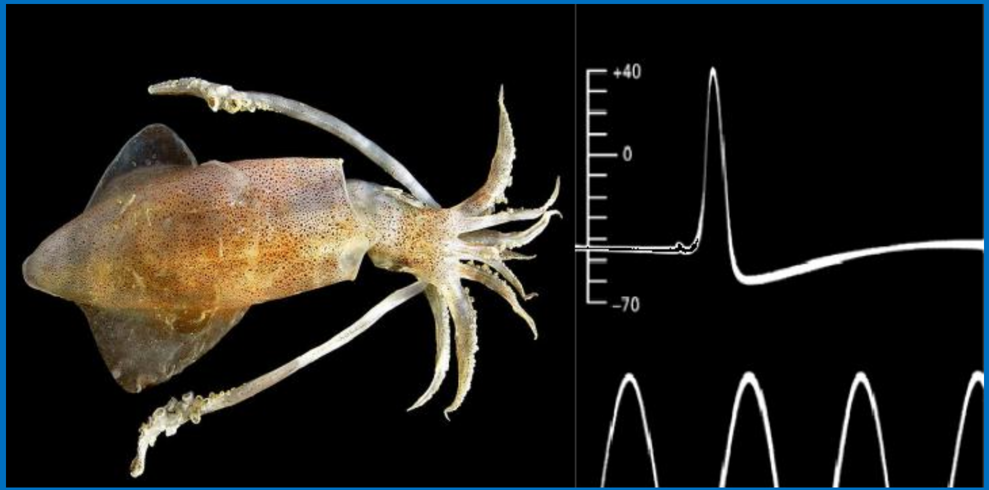


Alan Hodgkin and Andrew Huxley 1952 (Nobel Prize 1963): Squid Giant Axon









$$I(t) = C\frac{dV}{dt} + I_i(t), \qquad (6.1)$$

The key chemicals in the system are potassium (K) and sodium (Na), so $I_i(t) = I_{Na} + I_K + I_L$, where I_{Na}, I_K are currents due to Na and K, respectively, while I_L is the so-called "leakage" current due to other chemicals.

Now these chemical signals arise due to differences in the potential, V, and the equilibrium potentials for the chemicals, V_{Na}, V_K, V_L. They proposed that

$$\begin{aligned} I_{Na} &= g_{Na}m^3h(V - V_{Na}) \\ I_K &= g_K n^4(V - V_K) \\ I_L &= g_L(V - V_L), \end{aligned}$$

where g_{Na}, g_K and g_L are constants (*conductances*) and m, n and h are related to the state of various ion channels (open or closed) and so lie in the interval $[0, 1]$.

So, now all we have to do is substitute these into Equation (6.1) and this gives us an ODE for V.

BUT!!!!!

$$
\begin{aligned}
I_{Na} &= g_{Na} m^3 h (V - V_{Na}) \\
I_K &= g_K n^4 (V - V_K) \\
I_L &= g_L (V - V_L),
\end{aligned}
$$

However, the m, n and h are, themselves variables! They depend on the voltage and satisfy the following set of ODEs:

$$
\begin{aligned}
\frac{dm}{dt} &= \alpha_m(V)(1-m) - \beta_m(V)m \\
\frac{dn}{dt} &= \alpha_n(V)(1-n) - \beta_n(V)n \\
\frac{dh}{dt} &= \alpha_h(V)(1-h) - \beta_h(V)h,
\end{aligned}
\tag{6.2}
$$

where the $\alpha' s$ and $\beta' s$ are given functions of V (found by fitting data).

So, the full system is Equation (6.1) coupled with Equations (6.2) - a 4th order system.

HH solved these numerically and showed that they gave rise to the behaviour that was observed experimentally - that is, action potential.

Summary

- Introduced the idea of electrical signalling and, in particular, the *action potential*.

Now we do:

- Fitzhugh-Nagumo model
- Excitability

6.3 Fitzhugh-Nagumo Model

It turns out that there are many different timescales in the HH model so we can separate the timescales and reduce it to a 2 variable system. However, this is quite complicated algebraically.

Fitzhugh and Nagumo captured the essence of the problem with the following model (a sort of "model of a model"):

$$\begin{aligned} \frac{dv}{dt} &= f(v) - w + I_a \\ \frac{dw}{dt} &= b^* v - \gamma^* w, \end{aligned}$$

where $f(v) = v(a - v)(v - 1)$.

Here $a \in (0, 1)$, and b^* and γ^* are positive constants.

Here, v represents voltage (V), w plays the role of the variables m, n and h, and I_a is the applied current.

Typically b^* and γ^* are small.

$$\frac{dv}{dt} = f(v) - w + I_a$$
$$\frac{dw}{dt} = b^* v - \gamma^* w,$$

w is the slow variable so we rescale to slow time

We rescale by setting $b^* = \epsilon b, \gamma^* = \epsilon\gamma$, where $0 < \epsilon << 1$ and b, γ are order 1. Setting $\tau = \epsilon t$ we obtain:

$$\epsilon\frac{dv}{d\tau} = f(v) - w + I_a$$
$$\frac{dw}{d\tau} = bv - \gamma w,$$

where v and w are now functions of τ (slight abuse of notation).

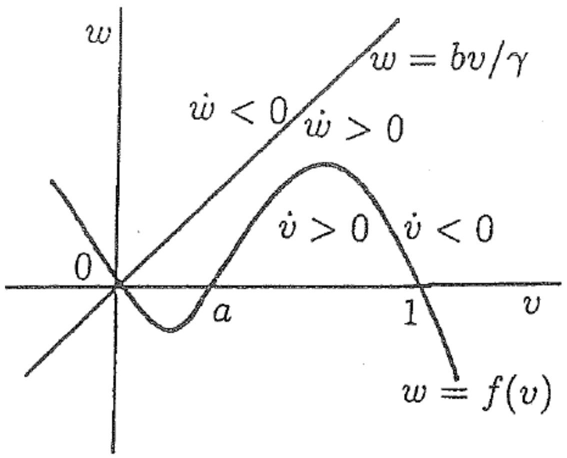
On this timescale, v is the fast variable

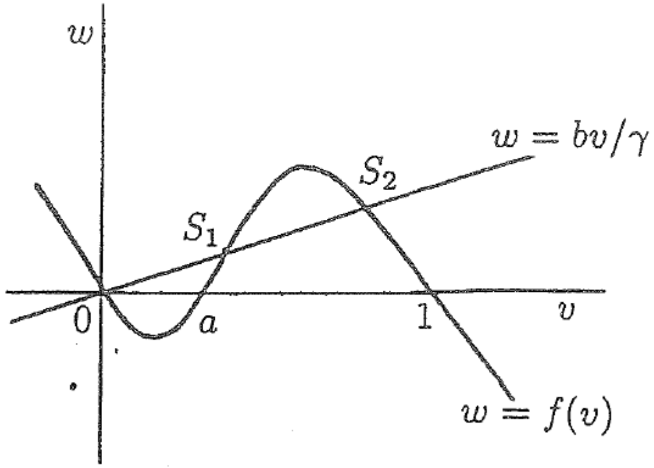
$$\epsilon \frac{dv}{d\tau} = f(v) - w + I_a$$
$$\frac{dw}{d\tau} = bv - \gamma w,$$

$$f(v) = v(a-v)(v-1)$$

6.3.1 Phase planes

Case $I_a = 0$





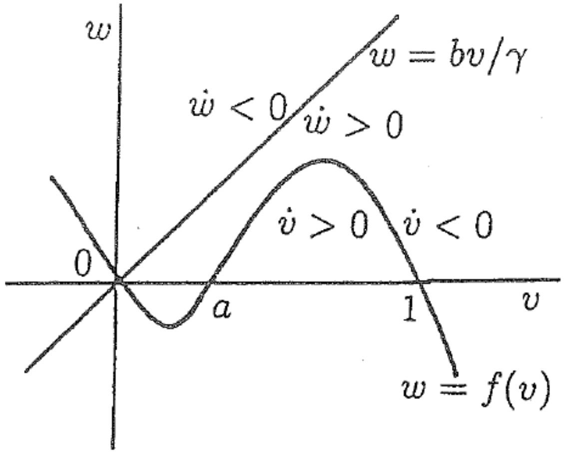
Then there are two (or one) other non-zero steady states (state)

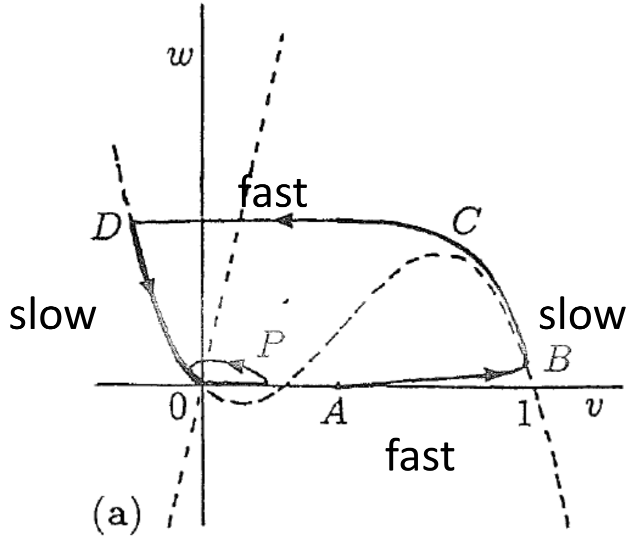
There is always the trivial steady state $(v, w) = (0, 0)$ and it is linearly stable (**Exercise - check**).

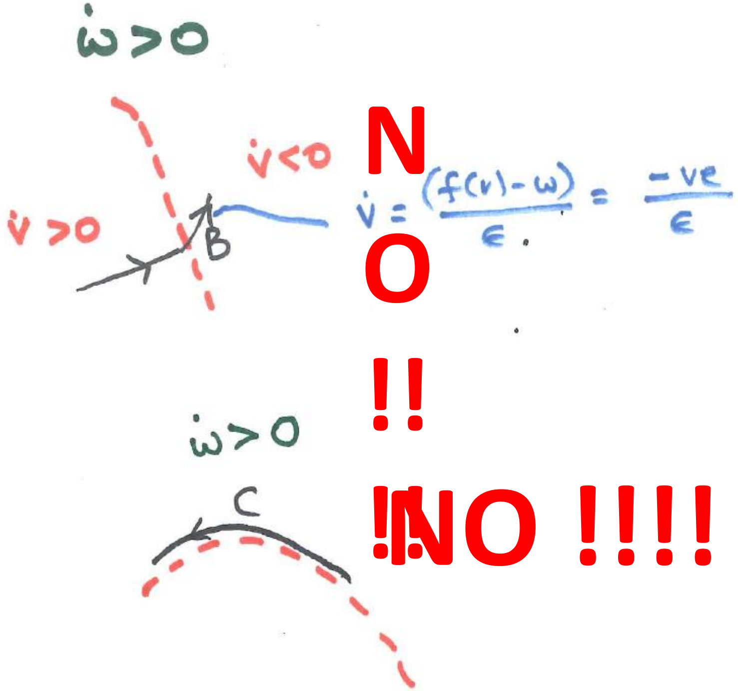
What if we perturb from the zero steady state?

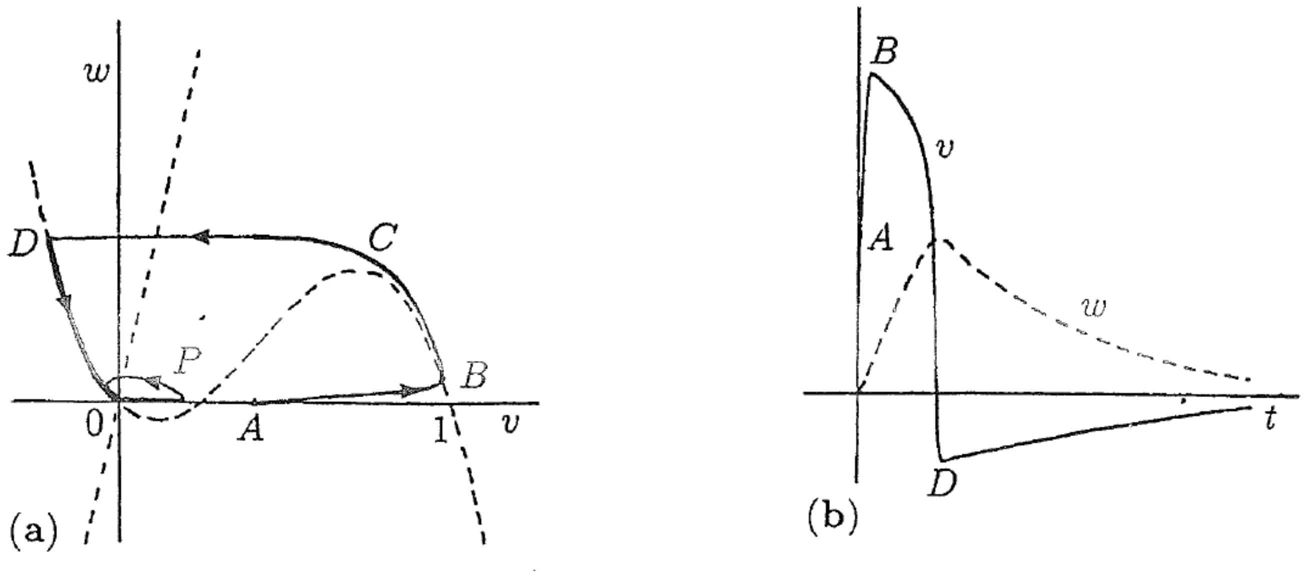
$$\epsilon \frac{dv}{d\tau} = f(v) - w + I_a$$
$$\frac{dw}{d\tau} = bv - \gamma w,$$

No non-zero steady states









$$\epsilon\frac{dv}{d\tau} = f(v) - w + I_a$$
$$\frac{dw}{d\tau} = bv - \gamma w,$$

What we see here is that if we perturb the system from the zero steady state a little bit, then it comes back.

However, if we perturb it beyond a **threshold** (that is, $v = a$) and if there is no non-zero steady state, then the system undergoes a *large excursion* before coming back to the zero steady state.

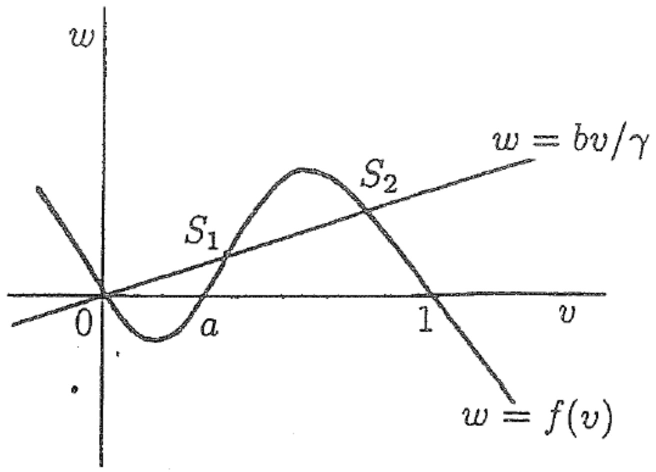
We say that the system is **excitable**.

We say that v is the fast variable and w is the slow variable.

$$\epsilon\frac{dv}{d\tau} = f(v) - w + I_a$$
$$\frac{dw}{d\tau} = bv - \gamma w,$$

Note that if two other non-zero steady states exist, then the system would evolve to the larger steady state.

For a perturbation beyond the threshold



Another example of an excitable system?

Summary

- Presented the Fitzhugh-Nagumo model
- Showed how it can produce an action potential
- Talked about toilets

Now we do:

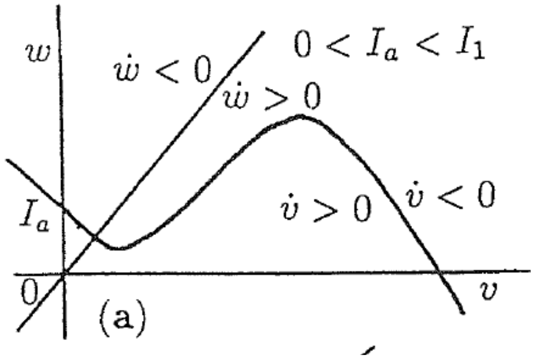
- Fitzhugh-Nagumo model
- Limit cycles

Case $I_a \neq 0$

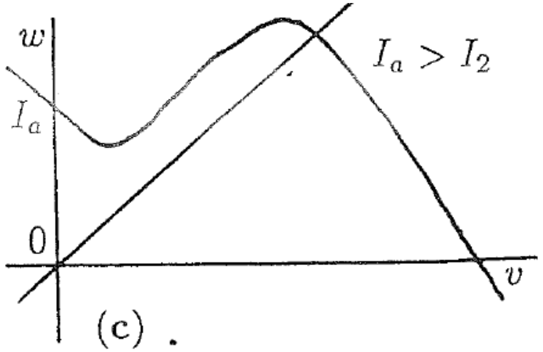
$$\epsilon \frac{dv}{d\tau} = f(v) - w + I_a$$
$$\frac{dw}{d\tau} = bv - \gamma w,$$

The v nullcline is now $w = f(v) + I_a$, so it intersects the v axis at I_a.

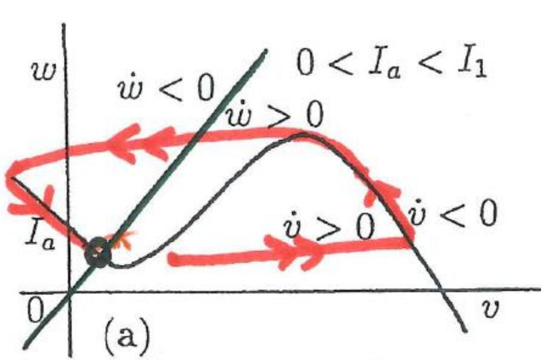
There are 3 subcases.



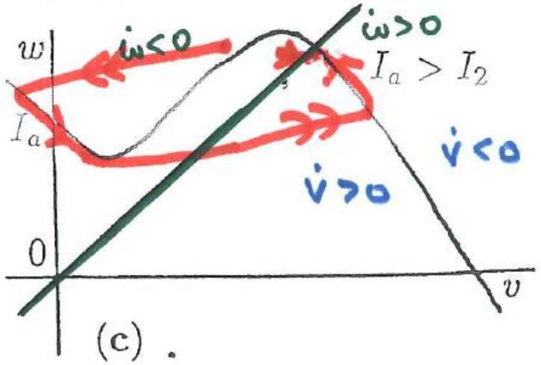
w
$\dot{w} < 0$
$0 < I_a < I_1$
$\dot{w} > 0$
I_a
$\dot{v} > 0$
$\dot{v} < 0$
0
v
(a)



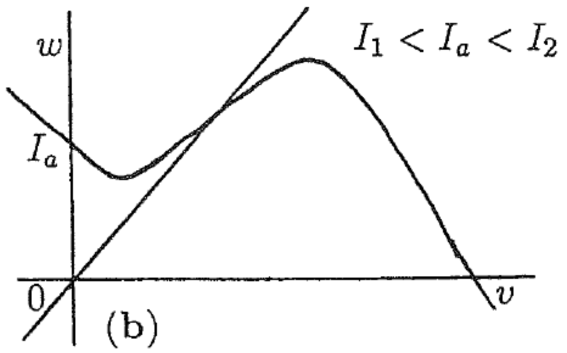
w
$I_a > I_2$
I_a
0
v
(c)

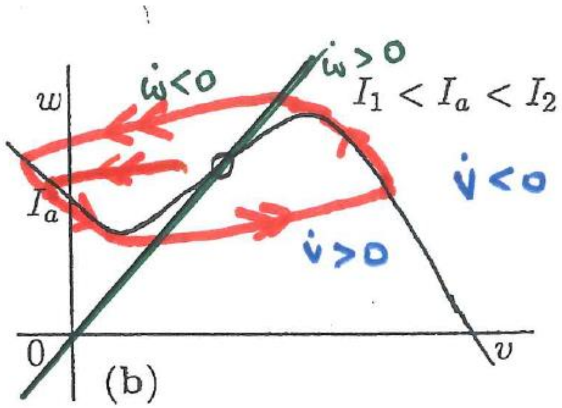


w
$\dot{w} < 0$
$0 < I_a < I_1$
$\dot{w} > 0$
I_a
$\dot{v} > 0$
$\dot{v} < 0$
0
v
(a)

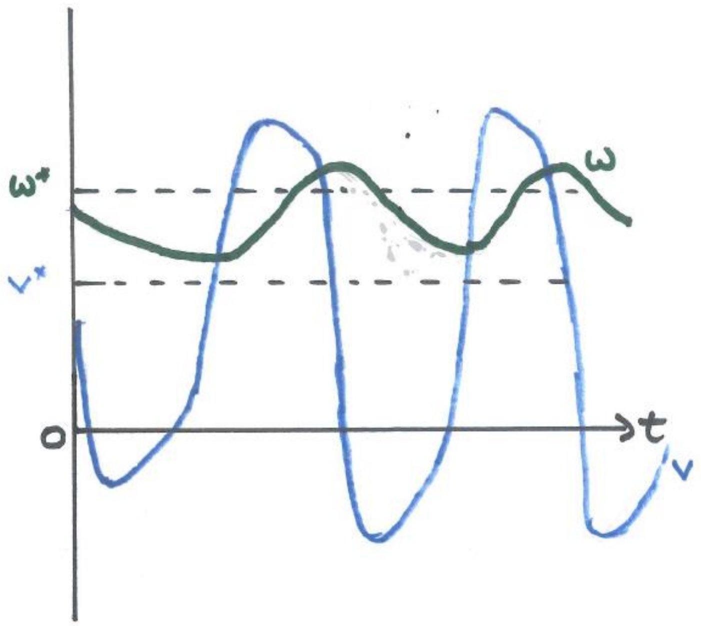


$\dot{w} < 0$
$\dot{w} > 0$
w
$I_a > I_2$
I_a
$\dot{v} < 0$
$\dot{v} > 0$
0
v
(c)





Limit cycle



Periodic firing

Summary

Showed that the Fitzhugh-Nagumo model can exhibit limit cycle behaviour – periodic firing