Let's look for a <u>travelling wave solution</u> so we can find a wave traveling down the axon

$v = v(\xi),\ w = w(\xi),\ \xi = ct - x,\ c > 0$ waves we'll draw at the end will go from right to left

$$\boxed{\begin{aligned} &① \quad \varepsilon c v' = f(v) - w + \varepsilon^2 v'' \\ &② \quad c w' = \gamma v - w \end{aligned}}$$

phase plane w/ v, w, v'

NB the primes are derivatives wrt ξ

with $v, w \to 0$ as $\xi \to \pm\infty$ (solitary waves in which the solution returns to the rest state at each end)

It is harder to do phase plane analysis now because the phase plane is three-dimensional rather than two: v, w, v'

However, $\varepsilon \ll 1$ so this allows us to make progress without having to consider the three-dimensional phase space.

There are <u>four different regions of behaviour</u>:

(i) To begin with, if we aren't on the curve $w = f(v)$ then we quickly move there because of

$$① \quad \underset{\text{fast motion}}{\varepsilon c v'} = \underbrace{f(v) - w}_{\neq 0} + \underset{\text{higher order correction}}{\varepsilon^2 v''}$$

Just like before (ignoring the higher order ε^2 term)

In this region, things happen over a fast ξ scale. This suggests rescaling $\boxed{\xi = \varepsilon J}$

$$① \Rightarrow c\frac{dv}{dJ} = f(v) - w + \frac{d^2 v}{dJ^2} \qquad ①'$$

and in this region, considering the other equation, $cw' = \gamma v - w$ (② from above)

$$\Rightarrow c\frac{\partial w}{\partial J} = \varepsilon(\gamma v - w)$$

$$\Rightarrow w = \text{constant.}$$

We choose coordinates such that the resting state corresponds to $(v, w) = (0, 0)$.
Thus $w = \text{const} = w_{\text{resting}} = 0$. This is not sayin that an const w must be zero but starting from rest, the slow variable w hasn't moved yet, so it equals its resting value (which is 0 in the shifted coords)

Now set $\frac{dv}{d\xi} = u$. Then we can write (1') $c\frac{dv}{d\xi} = f(v) - \cancel{w}_0 + \frac{d^2v}{d\xi^2} \Rightarrow cu = f(v) + u'$ where $'$ denotes derivative wrt ξ now

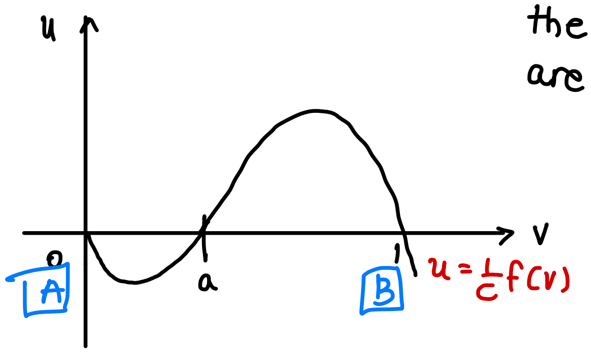
Then our phase plane system is $\begin{cases} v' = u \\ u' = cu - f(v) \end{cases}$ Phase plane system

stripped down eqns on pg 26 to phase plane in v, (v') which we called u (2D slice of 3D space)

$= v(v-a)(1-v), \quad 0<a<1$

Fixed points of this problem are $u=0$, $\underbrace{v=0,a,1}$

the 3 equilibria are the zeros of $f(v)$ with $u=0$

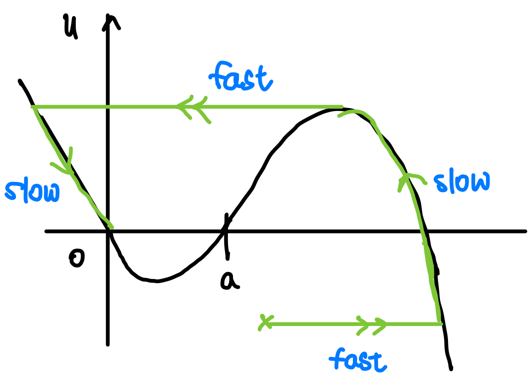


can see this through linearisation

Linear stability analysis shows that $\underline{v=0,1 \text{ are saddles}}$ and $\underline{v=a \text{ is an unstable node}}$

So we are interested in the trajectory in the phase plane that goes from $v=0$ to $v=1$ fixed points (to replicate the action potential we had in the space-clamped case where we had the fast behaviour jumping out of the nullcline.)

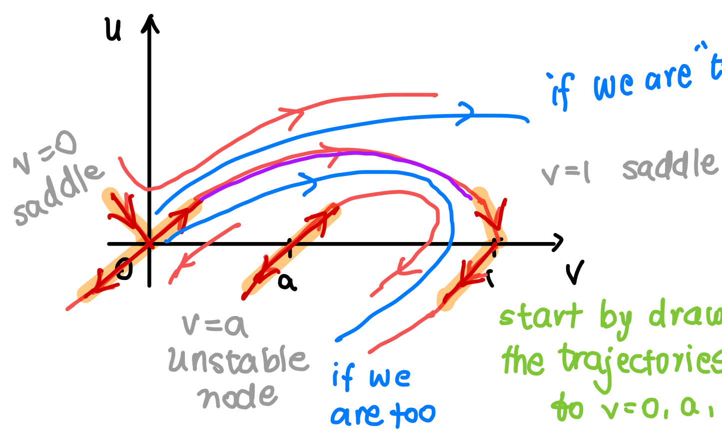
Similar to what we had before



There is only one value of c that achieves this now:

$$\frac{du}{dv} = \frac{u'}{v'} = \frac{cu - f(v)}{u} = c - \frac{f(v)}{u} = c \quad \text{at } v=0, \text{ so gradient of trajectory is } c$$

because $f(v=0)=0$



if we are "too high" we will "fly off"

we are after the purple one that takes us from $v=0$ to $v=1$

if we are too low we'll also fly off

start by drawing the trajectories close to $v=0, a, 1$ given their known nature & fill in the trajectories after

Like a shooting problem. This is how c (wave speed) is selected – this means there is a unique wave speed for the travelling wave.

(ii). Thus, once we land on the u nullcline $\left(u = \frac{f(v)}{c}, \text{ i.e. } v' = \frac{f(v)}{c}\right)$ we slowly move on this. Specifically, on this we have

recall we set $u = v'$

$\Rightarrow cv' = f(v)$

$$\left.\begin{aligned} \varepsilon c v' &= f(v) - w + \varepsilon^2 v'' \\ \varepsilon f(v) &= f(v) - w + \varepsilon^2 v'' \end{aligned}\right\} \quad \boxed{cw' = \gamma v - w} \quad (2) \text{ from before}$$

to leading order in ε

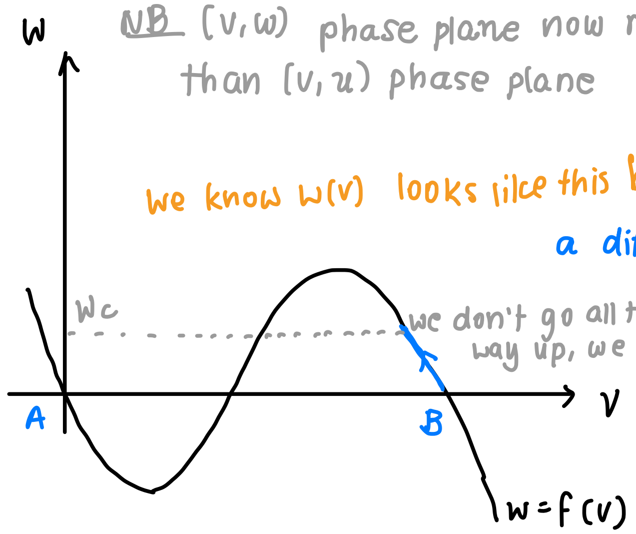
$\Rightarrow \boxed{w = f(v)}$ (1)

This takes us up the curve $u = \frac{f(v)}{c}$ until we reach $w = \gamma v$ (the eqm of (2))

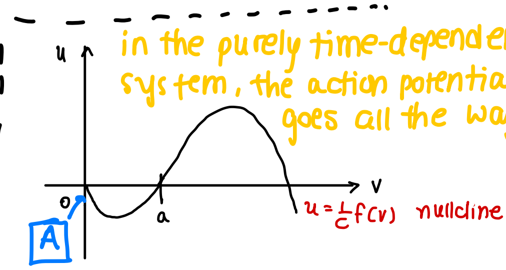
NB (v, w) phase plane now rather than (v, u) phase plane

We know $w(v)$ looks like this because $w = f(v) = v(v-a)(1-v)$

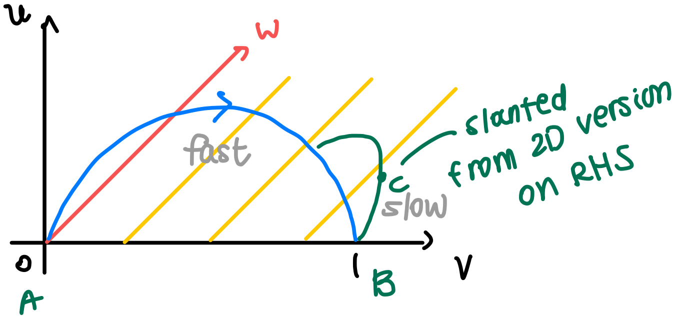
a different slice now

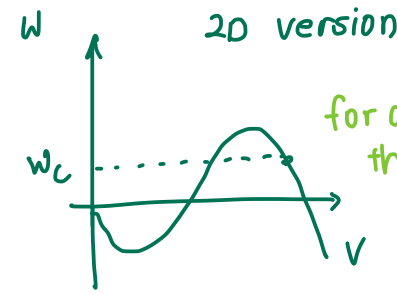


we don't go all the way up, we go in the 3rd dimension



in the purely time-dependent system, the action potential goes all the way up





for a traveling wave, the action potential w reaches a value w_c

Note that c is not the maximum of $w = f(v)$ unlike in the space-clamped model. Now c is where $w = \gamma v$. We need to find what this value w_c is, which we will find out in the next stage

(iii) Once we have reached this point we enter another fast phase. Again rescale $\boxed{\xi = \varepsilon J}$ to capture this, but this time $w = w_c$ (a nonzero constant, which we need to find out what value it is). Then the system is

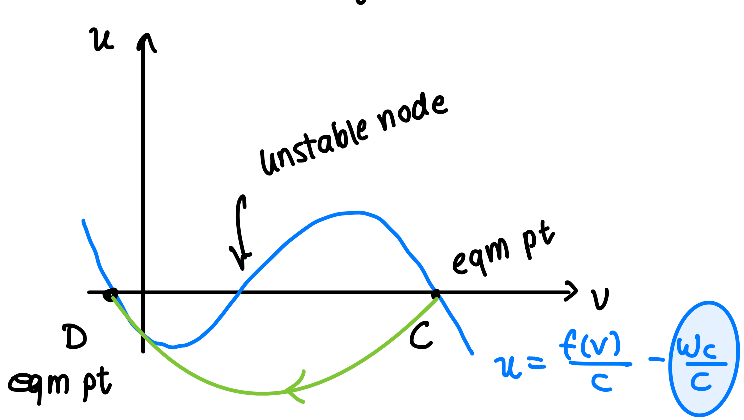
$$cv' = f(v) - w_c + v'' \qquad \text{where} \quad \bullet' = \frac{d\bullet}{d\xi}$$

The advantage of this now is we can again turn it into a phase plane, by writing it as a first-order system.

Phase plane system $\left\{ \begin{aligned} v' &= u \\ u' &= cu - f(v) \end{aligned} \right\}$ from before, becomes now

$$\Rightarrow \boxed{\begin{aligned} v' &= u \\ u' &= cu - f(v) + w_c \end{aligned}}$$

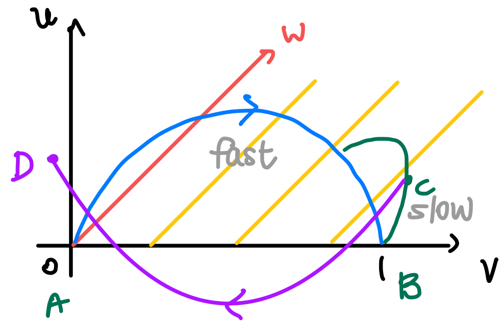
Going back into the (u, v) plane again we end up w/ something quite similar



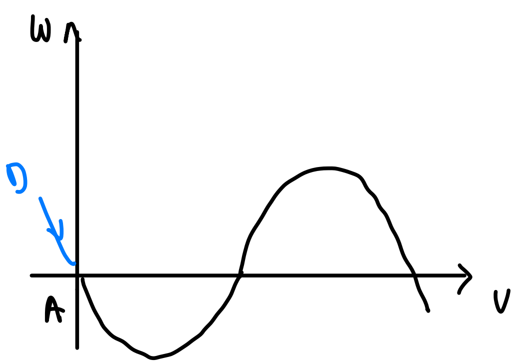
same curve as before but shifted down by this amount

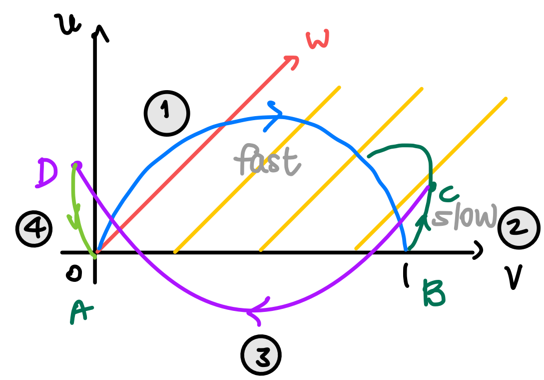
C & D are saddles and this time we have a trajectory that takes us from C to D.

This time it is w_c that we need to choose correctly (just like we had to choose the wave speed c correctly in part (i)).



(iv) Finally a slow phase takes us back to A again on the (v,w) phase plane.

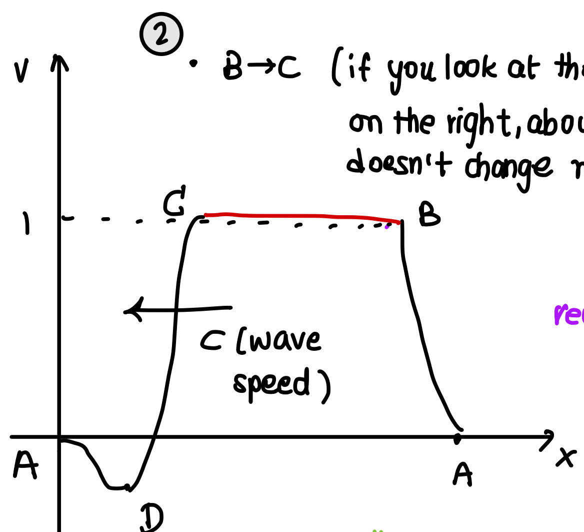




A→B,	B→C,	C→D,	D→A
fast	slow	fast	slow

The overall picture is a travelling wave that moves down the axon and looks like this

The trajectories
A→B
B→C
C→D
D→A
take a certain amount of time but we are interested in the voltage



2 • B→C (if you look at the plot on the right, above, B doesn't change much)

1 • A→B
v goes from 0 to 1
& it happens quickly

recall that since we chose $\tau = ct - x$, $c > 0$
we go from right to left

this is our wave train which propagates w/ speed c

③ $C \to D$ This takes us from $v \approx 1$ to $v \approx 0$ (but a bit negative)

* Same as the space-clamp version, but in that case the wave train above would be a time trace whereas the one above is moving down the axon.

The section above is about how a signal propagates from our brain to our muscles to say "do something". But the muscle then has to do something. This is what we will cover next.

Chapter 4: CALCIUM DYNAMICS

Calcium (Ca^{2+}) is important in muscle dynamics and cell signalling

Ca^{2+} is stored in cells in bones & released by hormonal stimulation. The internal store is called the sarcoplasmic reticulum.

It releases Ca^{2+} via calcium induced release

The intracellular fluid matrix is called the sarcoplasm.

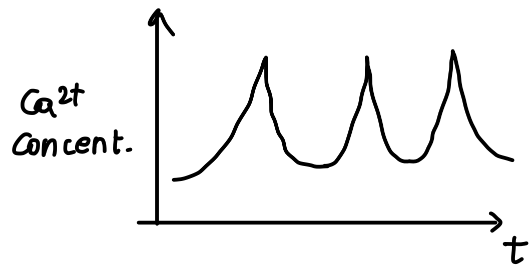
Extracellular Ca^{2+} concentrations are higher than intracellular concentrations so Ca^{2+} must be pumped out.

Muscle cells are bundles (fascicules) of muscle fibres (cells) each of which contains arrays of filament structures (microfibrils) which contract under the action of Ca^{2+}

Under stimulation from a nerve cell, an action potential is triggered and propagates along the fibre.

Na^+ floods in and this allows Ca^{2+} in too

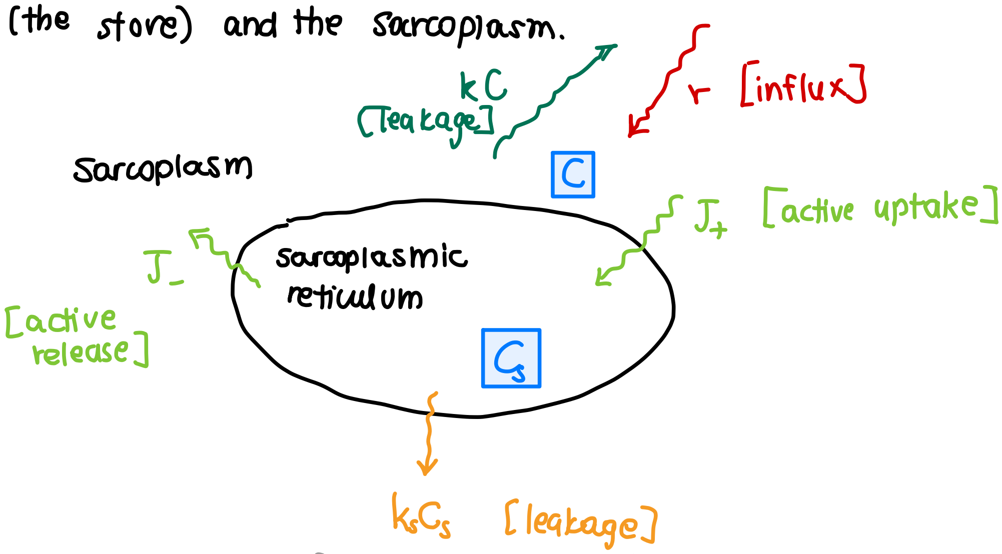
The release of Ca^{2+} is quite spiky



Can we derive a mathematical model for muscle contraction with a low Ca^{2+} concentration in steady state that is excitable under stimulus?

The two-pool model

We want to derive a model to explain how Ca^{2+} moves between the sarcoplasmic reticulum (the store) and the sarcoplasm.



(it makes sense that the leakage is proportional to the conc. C_s. If we double C_s, we'll have more leakage)

C = concentration of Ca^{2+} in the sarcoplasm

C_s = 〃 sarcoplasmic reticulum (SR)

J_+ = rate of take up of Ca^{2+} by the sarcoplasmic reticulum (by receptors) [active uptake]

J_- = rate at which the SR releases its internal store (calcium induced calcium release) [active release]

r = influx of Ca^{2+} into the sarcoplasm from the outside world because of an applied stimulus.

$k_s C_s$ = rate of leakage of Ca^{2+} from SR into the sarcoplasm [passive - proportional to concentration]

kC = rate of leakage of Ca^{2+} from sarcoplasm to outside world [passive - proportional to concentration]

$$\frac{dC_s}{dt} = J_+ - J_- - k_s C_s \overset{\text{def}}{=} F$$

$$\frac{dc}{dt} = r - kc - (J_+ - J_- - k_s C_s)$$

$$= r - kc - F$$

constants

We choose $J_+ = \dfrac{V_1 c^n}{K_1^n + C^n}$ (from experiments) Hill function again

NB V_1 is not a voltage, it is a concentration rate.

V_1, K_1, n are just numbers

these bits aren't important

$$J_- = \left(\frac{V_2 C_s^m}{K_2^m + C_s^m}\right)\underbrace{\left(\frac{C^p}{K_3^p + C^p}\right)}$$ Hill function

This is the important bit that causes the calcium induced calcium release.

Non-dimensionalisation

$C = K_1 u$, $C_s = K_2 v$, $t = \frac{1}{k}\hat{t}$, $F = V_2 f$ || $u, v, \hat{t}, f$ all dimensionless counterparts

$$\frac{du}{dt} = \mu - u - \frac{\gamma}{\varepsilon} f(u,v)$$

implicit function of u and v that we can plot

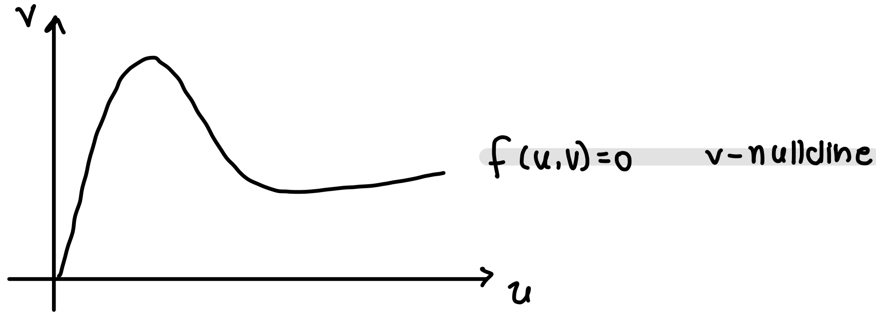
$$\frac{dv}{dt} = \frac{1}{\varepsilon} f(u,v) \quad \text{where } f = \beta\left(\frac{u^n}{1+u^n}\right) - \left(\frac{v^m}{1+v^m}\right)\left(\frac{u^p}{\alpha^p + u^p}\right) - \delta v$$

with $\mu = \dfrac{r}{kK_1}$, $\gamma = \dfrac{K_2}{K_1}$, $\varepsilon = \dfrac{kK_2}{V_2} \ll 1$, $\alpha = \dfrac{K_3}{K_1}$, $\beta = \dfrac{V_1}{V_2}$, $\delta = \dfrac{k_s K_2}{V_2} \ll 1$

as our dimensionless parameters.

This is a two-dimensional system (u,v) so we may use phase-plane antalysis.

$\varepsilon \ll 1$ means that we quickly jump onto the v-nullcline, $f(u,v)=0$



How to plot this curve?

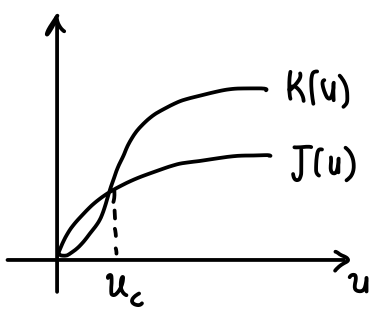
① $\delta \ll 1$ so ignoring the δ-term in $f(u,v)$ gives

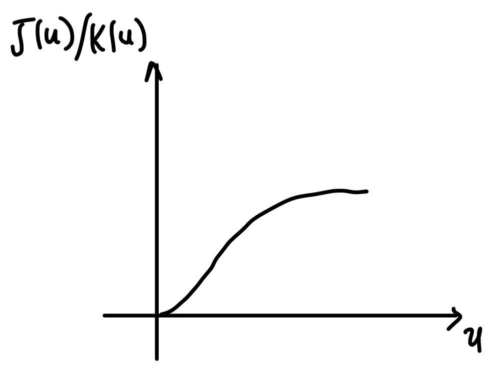
$$f = \beta\left(\frac{u^n}{1+u^n}\right) - \left(\frac{v^m}{1+v^m}\right)\left(\frac{u^p}{\alpha^p+u^p}\right) - \cancel{\delta v} = 0$$

0 since $\delta \ll 1$

in the nullcline

$$\frac{v^m}{1+v^m} = \frac{\frac{u^n}{1+u^n}}{\frac{u^p}{\alpha^p+u^p}} \overset{\text{def}}{=} \frac{J(u)}{K(u)}$$

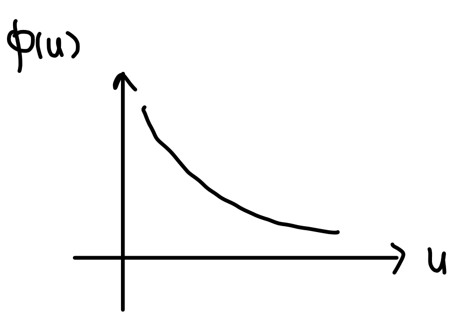


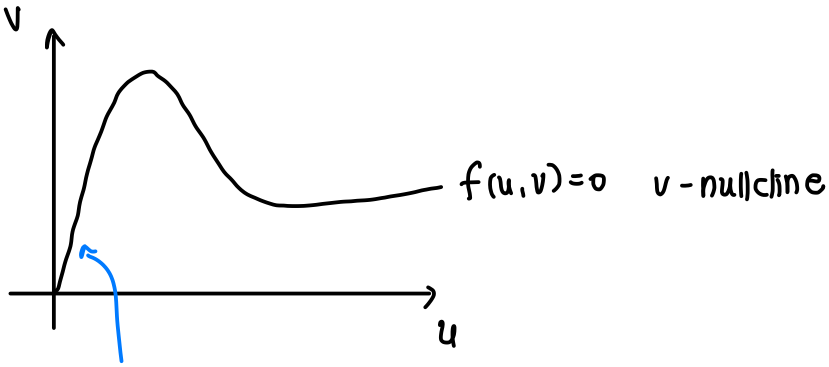


$$\Rightarrow \quad v^m = (1+v^m)\frac{J(u)}{K(u)} \quad \Rightarrow \quad v^m\left(1-\frac{J(u)}{K(u)}\right) = \frac{J(u)}{K(u)}$$

$$v^m\left(\frac{K(u)-J(u)}{\cancel{K(u)}}\right) = \frac{J(u)}{\cancel{K(u)}}$$

$$v = \left[\frac{J(u)}{K(u)-J(u)}\right]^{1/m} = \phi(u)$$





to approximate this part, set $v = \frac{V}{\delta}$

For the rest of this, see problem sheet.

Now let's look at the dynamics. v rapidly approaches the v-nullcline that we have found, because of the ε in the $\frac{dv}{dt}$ equation.

But now if we look at the $\frac{du}{dt}$ equation we have

$$\frac{du}{dt} = \mu - u - \frac{\gamma}{\varepsilon} f(u,v)$$

an ε here

so we don't just have $u = \text{const}$ unlike in the previous cases. This time we note that

since $\frac{dv}{dt} = \frac{1}{\varepsilon} f(u,v)$ $\Rightarrow$ $$\frac{du}{dt} = \mu - u - \gamma \frac{dv}{dt}$$

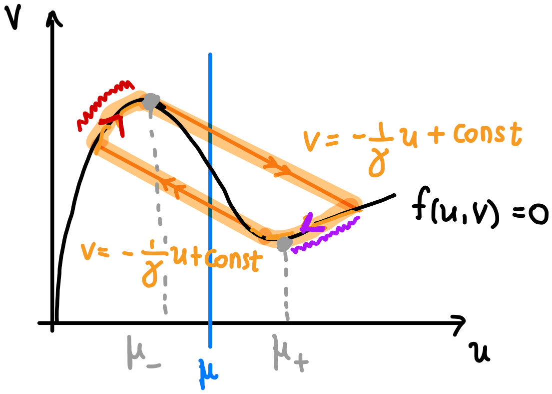
$$\Rightarrow \quad \frac{du}{dt} + \gamma \frac{dv}{dt} = \mu - u$$

On the fast timescale $\boxed{t = \varepsilon\tau}$ we have $\varepsilon \frac{dv}{dt} = f(u,v)$ becomes $\frac{dv}{d\tau} = f(u,v)$ giving the movement of v to the v-nullcline and $\frac{du}{d\tau} + \gamma \frac{dv}{d\tau} = \varepsilon(\mu - u)$

there are $\frac{d}{d\tau}$ not $\frac{d}{dt}$

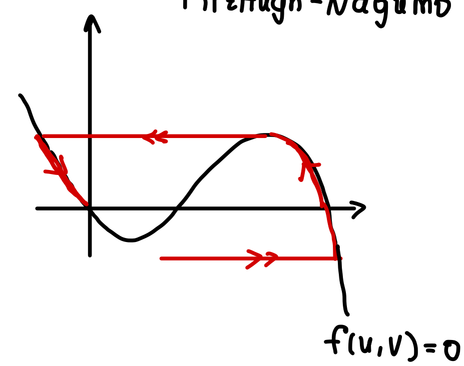
$\Rightarrow$ $u + \gamma v = $ const. to leading order in ε.

So we move to the v-nullcline along the line $v = \frac{\text{const} - u}{\gamma} = -\frac{1}{\gamma} u + \frac{\text{const}}{\gamma}$



μ_+ and μ_- are the points where the gradient of the curve $f(u,v)=0$ is $-\frac{1}{\gamma}$

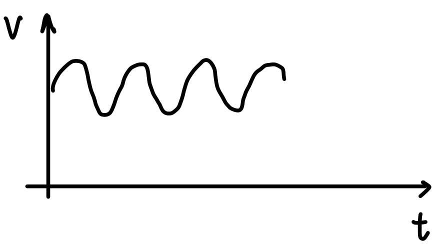
Recall from FitzHugh-Nagumo

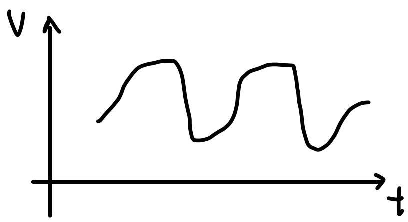


Case (i): $\mu_- < \mu < \mu_+$

Then $\frac{d}{dt}(u+\gamma v) = \mu - u$. When $u<\mu$, we move to the right
When $u>\mu$, we move to the left

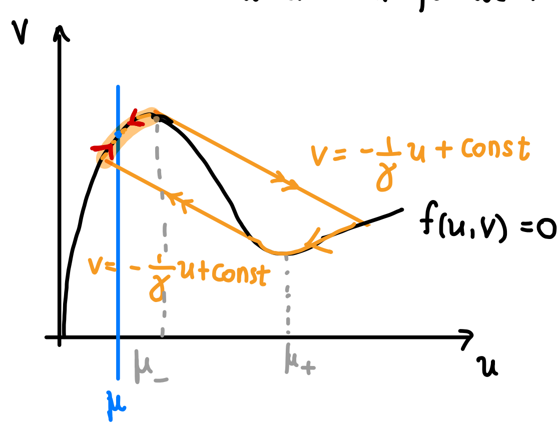
This leads to self-sustained or relaxation oscillations. $\frac{d}{dt}(u+\gamma v) = \mu - u < 0$ when $u > \mu_+$
> 0 when $u < \mu_-$





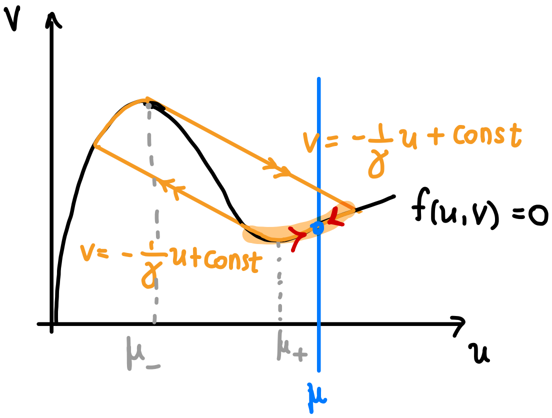
Case (ii): $\mu < \mu_-$

Then $\frac{d}{dt}(u+\gamma v) = \mu - u < 0$ when $u < \mu$ $(<\mu_-)$ we move to the right
when $u > \mu$ we move to the left



We need a bit of energy/excitation to move away from the blue equilibrium point, and then we get an excursion — a muscle contraction!

Case (iii): $\mu > \mu_+$



$\frac{d}{dt}(u+\gamma v) = \mu - u$. When $u < \mu$ we move to the right

$u > \mu$ we move to the left

The equilibrium lies at $u > \mu_+$, which is high. This leads to cramps ☹ and rigor mortis 💀

⇓

i.e. concentration of Ca^{2+} stays high always