# 1 Membrane transport

# 2 Spatial Variation

We have initially considered biochemical and electrophysiological phenomena with negligible spatial variation. While space clamping is a useful experimental technique to simplify the study of neurons, it is clearly of interest to remove the space clamp to consider how a pulse in the membrane potential, that is a **nerve pulse**, propagates along an axon. Further examples of spatially heterogeneous physiology include calcium waves and cardiac electrophysiology, where higher spatial dimensions and phenomena such as spiral waves can be observed (in cardiac pathologies such as ventricular tachycardia, which can readily degenerate into ventricular fibrillation, *i.e.* effective cardiac arrest.)

## 2.1 Signal Propagation. Nerve Axons.

We no longer space clamp the axon and consider how a membrane potential pulse, or nerve pulse, can propagate. We make the following assumptions about the axon:

(a) The cell membrane is a cylindrical membrane separating two conductors of electric current, namely the extracellular and intracellular media. These are assumed to be homogeneous and to obey Ohm's law.

(b) The axon is axisymmetric. The coordinate $z$ denotes distance in the axial direction.

(c) A circuit theory description of current and voltages is adequate.

(d) Currents flow through the membrane in the radial direction only.

(e) Currents flow through the extracellular medium in the axial direction only, and the potential in the extracellular medium is a function of $z$ only. Similarly for the potential in the intracellular medium.

These assumptions are appropriate for unmyelinated nerve axons. Deriving the model requires consideration of the following variables

- $I_e(z,t)$: External current in the $z$ direction.
- $I_i(z,t)$: Internal current in the $z$ direction.
- $J(z,t)$: Total current through membrane per unit length.
- $J_{ion}(z,t)$: Total current through membrane per unit length due to ions.
- $V(z,t) = V_i(z,t) - V_e(z,t)$: Transmembrane potential.
- $r_i$: Internal resistance per unit length.

- $r_e$: External resistance per unit length.
- $C$: Membrane capacitance per unit length.
- $I_{\text{ext}}$: Applied external inward current per unit length.

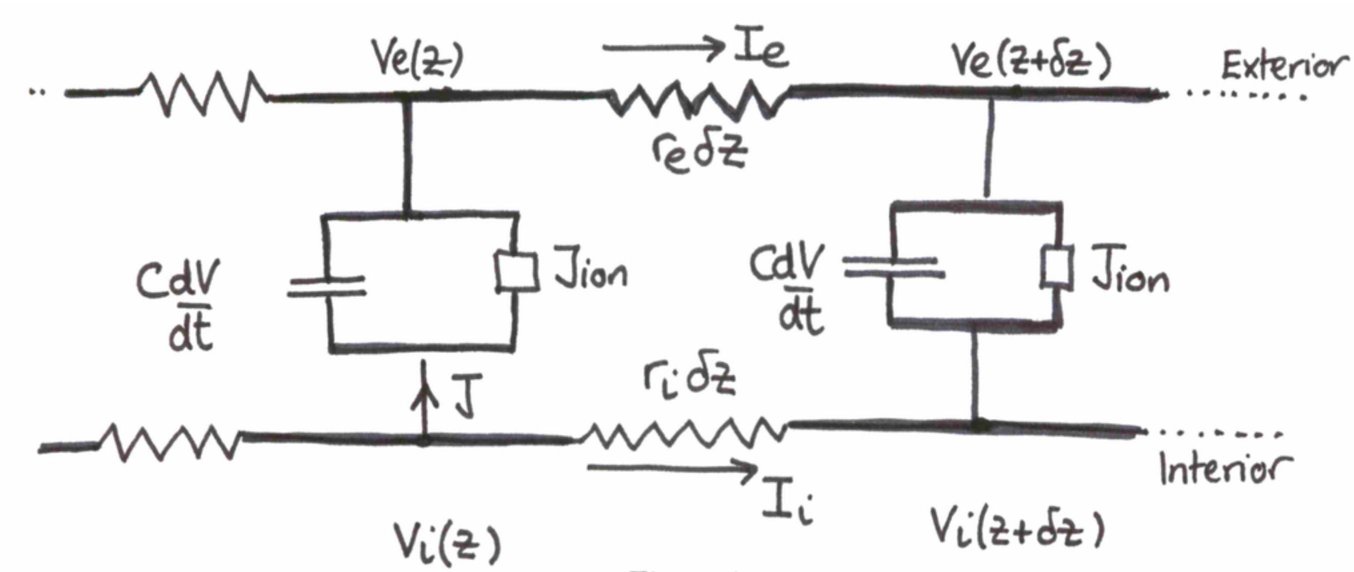


Figure 1: Electric circuit representation of the axon

Consider the axial current in the extracellular medium, which has resistance per unit length of $r_e$. We have

$$V_e(z+dz) - V_e(z) = -r_e I_e(z) dz \quad \Rightarrow \quad r_e I_e(z) = -\partial V_e/\partial z, \tag{1}$$

where the minus sign occurs because of the convention that positive current is a flow of positive charges in the direction of increasing $z$. Hence, if $V_e(z+dz) > V_e(z)$ then positive charges flow in the direction of decreasing $z$ given a negative current. Similarly,

$$r_i I_i(z) = -\partial V_i/\partial z.$$

Using conservation of current, we have

$$\begin{aligned} I_e(z+dz,t) - I_e(z,t) &= J(z,t)dz = I_i(z,t) - I_i(z+dz,t) \\ &\Rightarrow \; J(z,t) = -\partial I_i/\partial z = \partial I_e/\partial z. \end{aligned} \tag{2}$$

Hence

$$J = \frac{1}{r_i}\frac{\partial^2 V_i}{\partial z^2} = -\frac{1}{r_e}\frac{\partial^2 V_e}{\partial z^2}, \tag{3}$$

and so

$$\frac{\partial^2 V}{\partial z^2} = (r_i + r_e)J. \tag{4}$$

But we also have that

$$J(z,t) = J_{ion}(V,z,t) + C\frac{\partial V}{\partial t}, \tag{5}$$

and finally therefore

$$\frac{1}{(r_i + r_e)}\frac{\partial^2 V}{\partial z^2} = C\frac{\partial V}{\partial t} + J_{ion}(V,z,t). \tag{6}$$

This gives an equation relating the cell plasma membrane potential, $V$, to the currents across the cell plasma membrane due to the flow of ions $J_{ion}(V,z,t)$.

Thus, the Hodgkin-Huxley equations for a nerve pulse along an unmyelinated axon are given by

$$\begin{aligned}
\frac{1}{(r_i + r_e)}\frac{\partial^2 V}{\partial z^2} &= C\frac{\partial V}{\partial t} + g_{Na}m^3 h(V - V_{Na}) + g_K n^4(V - V_K) + g_L(V - V_L) - I_{ext} \\
\frac{\partial m}{\partial t} &= \alpha_m(V)(1-m) - \beta_m(V)m \\
\frac{\partial h}{\partial t} &= \alpha_h(V)(1-h) - \beta_h(V)h \\
\frac{\partial n}{\partial t} &= \alpha_n(V)(1-n) - \beta_n(V)n.
\end{aligned} \tag{7}$$

For a squid giant axon in a sea water bath, a canonical experiment, we have $r_i \gg r_e$ with $r_i \sim 1.5\Omega\ \mu\text{m}^{-1}$. Non-dimensionalising and simplifying as before gives

$$\begin{aligned}
\epsilon^2\frac{\partial^2 v}{\partial^2 x} &= \epsilon\frac{\partial v}{\partial \tau} + g(v,n) - I^*_{ext} \\
\frac{\partial n}{\partial \tau} &= k(v,n) \stackrel{def}{=} \frac{1}{\tau^*_n(v)}\left[n_\infty(v) - n\right],
\end{aligned} \tag{8}$$

where

$$g(v,n) \stackrel{def}{=} \left[m^3_\infty(v)(0.85 - n)(v-1) + \gamma_K n^4(v + v_K) + \gamma_L(v - v_L)\right],$$

and

$$z = x\frac{1}{\epsilon}\sqrt{\frac{1}{g_{Na}((r_i + r_e))}}.$$

The latter lengthscale emerges as the appropriate one to allow pulse-like solutions as we will see below.

A crude approximation of the Huxley-Hodgkin equations is given by the analogous Fitzhugh-Nagumo equations (where we set $I^*_{ext} = 0$).

$$\epsilon\frac{\partial v}{\partial \tau} = \epsilon^2\frac{\partial^2 v}{\partial x^2} + Av(v-a)(1-v) - w$$

$$\frac{\partial w}{\partial \tau} = -w + bv, \tag{9}$$

where $A \sim 8, b = 2, |a| \ll 1$.

### 2.1.1 A toy problem - the bistable equation

Before investigating the above equations and their travelling waves we will consider travelling waves for the following toy problem

$$\frac{\partial U}{\partial t} = \frac{\partial^2 U}{\partial x^2} - A(U - U_0)(U - U_1)(U - U_2), \tag{10}$$

where $A > 0$ and $U_0, U_1, U_2$ are constants satisfying $U_0 < U_1 < U_2$. Our motivation primarily is that asymptotics will reduce the travelling wave Fitzhugh-Nagumo equations to equations of the form (10).
The values $U = U_0$ and $U = U_2$ are stable steady solutions of the ordinary differential equation

$$\frac{dU}{dt} = f(U) = -A(U - U_0)(U - U_1)(U - U_2); \tag{11}$$

hence the use of the term *bistable* to describe equation (10).
We seek travelling wave solutions to equation (10). By a travelling wave solution we mean translation invariant solutions of (10) that provide a transition between the two stable steady (or rest) states, and travels with constant speed.

Thus we seek a solution

$$U(x, t) = U(\zeta), \tag{12}$$

where $\zeta = x - ct$ is referred to as the travelling wave coordinate, and positive values of $c$ correspond to a wave moving from the left to the right.

Substituting (12) into (10) we see that the travelling wave solution satisfies

$$\frac{d^2U}{d\zeta^2} + c\frac{dU}{d\zeta} - A(U - U_0)(U - U_1)(U - U_2) = 0. \tag{13}$$

This is an ordinary differential equation, and hence is easier to solve that a partial differential equation. For $U(\zeta)$ to provide a transition between two rest states, we require $f(U(\zeta)) \to 0$ as $\zeta \to \pm\infty$, where here $f(U) = -A(U - U_0)(U - U_1)(U - U_2)$.

It is convenient to write (13) as two first-order differential equations

$$\begin{aligned} \frac{dU}{d\zeta} &= W \\ \frac{dW}{d\zeta} &= -cW - f(U), \end{aligned} \tag{14}$$

so that we can employ familiar phase-plane techniques. We now seek solutions that connect the rest states $(U, W) = (U_0, 0)$ and $(U, W) = (U_2, 0)$ in the $(U, W)$ phase plane. Such a trajectory, connecting two different steady states, is called a *heteroclinic* trajectory. The steady states at $U_0$ and $U_2$ are both saddle points, while the steady state at $U_1$ is a node or a spiral point (straightforward to demonstrate). Since the steady states at $U_0$ and $U_2$ are both saddle points while the steady state at $U_1$ is a node or spiral point, the goal is to determine whether the parameter $c$ can be determined so that the trajectory which leaves $U_0$ at $\zeta = -\infty$ connects with the saddle point $U_2$ at $\zeta = \infty$.

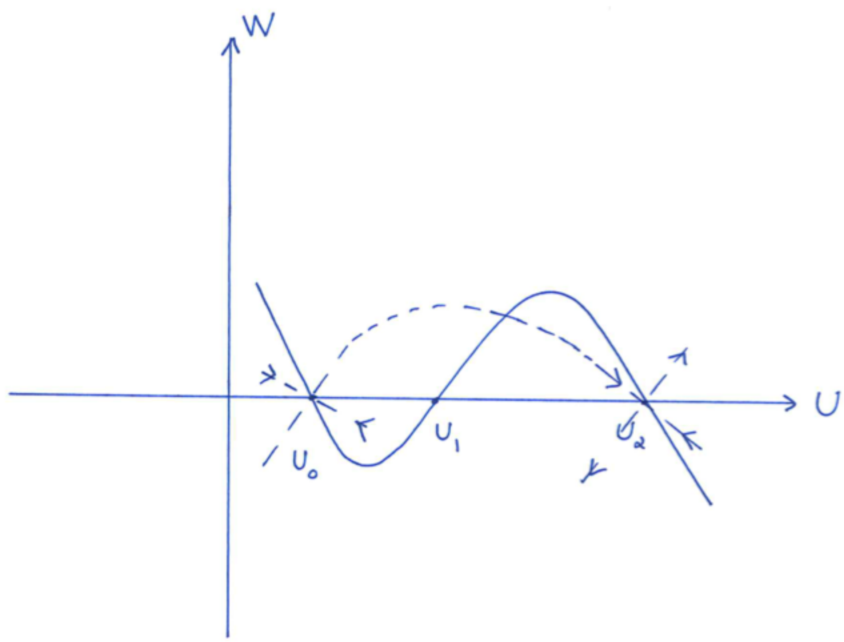


Figure 2: Heteroclinic trajectory

**Uniqueness** In fact for the given boundary conditions this value of $c$ is the only one possible for the solution of the travelling wave equations, and as a result, this solution is unique up to translation, as proved on **Exercise sheet 2**.

Suppose we seek to determine the sign of $c$. Suppose a monotone increasing ($U_\zeta > 0$) connecting trajectory exists, and we multiply (13) by $U_\zeta$ and integrate from $\zeta = -\infty$ to $\zeta = \infty$. Then it is straightforward (verify) to show that

$$c = -\frac{\int_{U_0}^{U_2} f(U)dU}{\int_{-\infty}^{\infty} W^2 d\zeta} \tag{15}$$

so that $c$ is the opposite sign to the area under the curve $f(U)$ from $U_0$ to $U_2$. For example, if the area is positive, then the travelling wave solution moves the state from $U_0$ to $U_2$, and the state $U_2$ is said to be dominant.

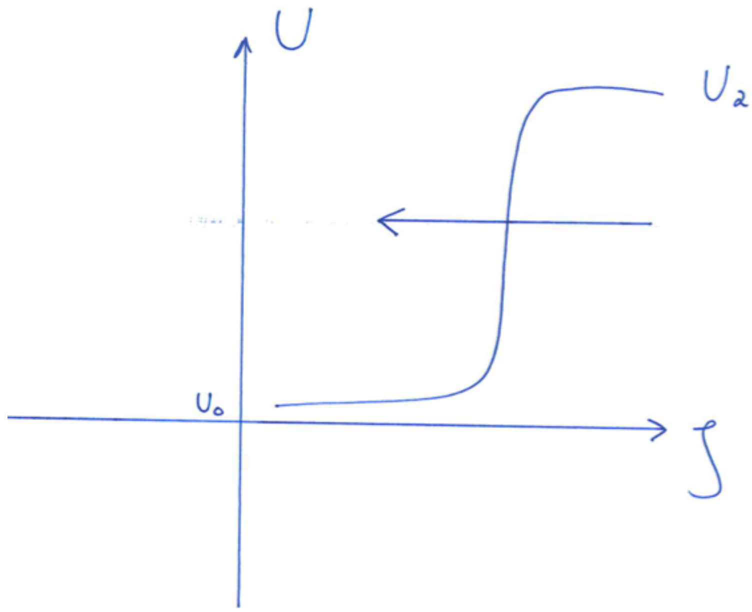


Figure 3: Travelling wave solution

Note that if the boundary conditions are reversed, so that $(U(-\infty), U(+\infty)) = (U_2, U_0)$ then the wave speed is given by $-c$ (verify this).

In general, for most functions $f(U)$, it is necessary to calculate the speed of propagation of the travelling wave solution numerically. However, in special cases we can determine the wave speed analytically. Again considering $f(U) = -A(U - U_0)(U - U_1)(U - U_2)$ where $U_0 < U_1 < U_2$.We wish to find a heteroclinic connection between the smallest zero $U_0$ and the largest zero $U_2$, so we guess that

$$W = -B(U - U_0)(U - U_2). \tag{16}$$

Substituting into (13) gives

$$B^2(2U - U_0 - U_2) + cB - A(U - U_1) = 0. \tag{17}$$

This is a linear function of $U$ that can only be made zero if we choose

$$B = \pm\sqrt{\frac{A}{2}}, \ c = \pm\sqrt{\frac{A}{2}}(U_2 - 2U_1 + U_0). \tag{18}$$

It the follows from (16) that

$$\begin{aligned} U(\zeta) &= \frac{U_0 + U_2}{2} + \frac{U_2 - U_0}{2} \tanh\left(\sqrt{\frac{A}{2}}\frac{U_2 - U_0}{2}\zeta\right) \\ c &= -\sqrt{\frac{A}{2}}\,(U_2 - 2U_1 + U_0) \end{aligned} \tag{19}$$

solves the travelling wave equation (13) with the boundary conditions $(U(-\infty), U(\infty)) = (U_0, U_2)$. Note that the sign of $c$ is negative: for $U_1 \ll 1$, the value of $c$ in equation (15) is negative.
**Reflected solution.** The solution with the boundary condition

$$(U(-\infty), U(+\infty)) = (U_2, U_0)$$

can be obtained by letting $\zeta \to -\zeta, \quad c \to -c$ in equation (19).

### 2.1.2 Fitzhugh Nagumo Travelling Waves

We now reconsider the equations (9). With the travelling wave coordinate

$$y = x - c\tau, \ c > 0,$$

and $v(y) = v(x, \tau)$, we obtain

$$\begin{aligned} \epsilon^2 \frac{d^2 v}{dy^2} + \epsilon c \frac{dv}{dy} + Av(v-a)(1-v) - w &= 0 \\ c\frac{dw}{dy} - w + bv &= 0. \end{aligned} \tag{20}$$

Below we shall explicitly assume that $c \sim O(1)$, and we will consider boundary conditions appropriate for a propagating nerve pulse.

Physically, we expect diffusive interaction to induce a super-threshold excitation immediately ahead of the nerve pulse, at which point the kinetic terms become large, leading to a rapid increase in $v$. Thus we may expect a solution exhibiting a sharp transition layer at the front of the pulse where $v$ shifts rapidly up to an excited state, corresponding to the upper branch of $w = Av(v-a)(1-v)$. Again, from the nature of the kinetics, we expect sometime after excitation, there will be a rapid decrease in $v$ when it rapidly drops to the lower branch of $w = Av(v-a)(1-v)$. Thus, we anticipate a solution to the above travelling wave equations of the form shown in figure **??**

### 2.1.3 Analysis of the Travelling Wave Fitzhugh-Nagumo Equations

We now reconsider the equation

$$\begin{aligned} \epsilon^2 \frac{d^2 v}{dy^2} + \epsilon c \frac{dv}{dy} + f(v, w) &= 0, \\ c\frac{dw}{dy} + g(v, w) &= 0, \end{aligned} \tag{21}$$

where

$$f(v, w) = Av(v-a)(1-v) - w \tag{22}$$

$$g(v, w) = -w + bv, \tag{23}$$

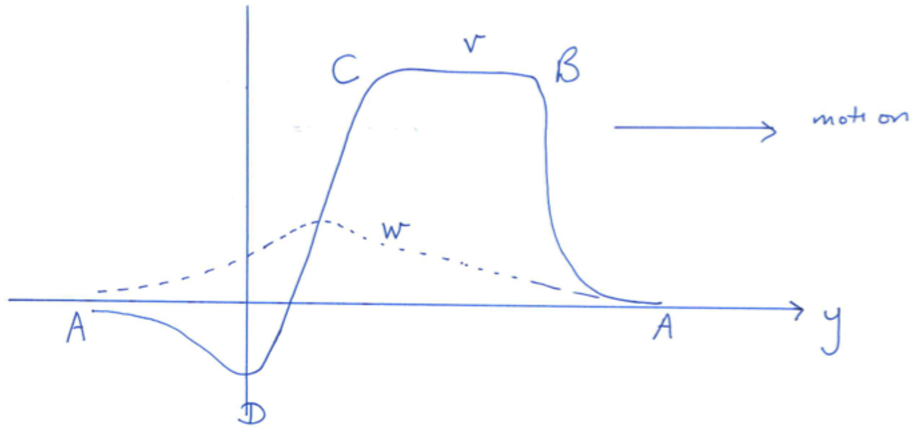


Figure 4: Illustrative nerve pulse

and $v = w = 0$ at $\pm\infty$ (corresponding to a pulse solution). We extract information about the travelling-wave pulse solution by exploiting the fact that $0 < \epsilon \ll 1$. We anticipate this to be fruitful due to similarities with the system without diffusion. We expect the solution to stay close to the $f(v,w) = 0$ nullcline wherever possible, with rapid transitions between the two outer branches. The spatially independent Fitzhugh-Nagumo equations are

$$\epsilon \frac{dv}{dt} = f(v,w), \tag{24}$$

$$\frac{dw}{dt} = g(v,w). \tag{25}$$

Under the change of variables to travelling wave coordinates note that $d/dt \to -cd/dy$. The nullclines in this case are shown in figure 5.
Returning to the full system (25), we start by setting $\epsilon = 0$, and consider the dynamics of the *outer* solution.
**Outer solution**
We then obtain

$$\begin{aligned} f(v,w) &= 0 \\ c\frac{dw}{dy} + g(v,w) &= 0. \end{aligned} \tag{26}$$

For a given value of $w$, the equation $f(v,w) = 0$ has three solutions for $v$ as a function of $w$. We denote these $V_-(w)$, $V_0(w)$ and $V = V_+(w)$. Only the left and right $v = V_\pm(w)$ solution curves are stable. Thus the outer solutions reduces to

$$c\frac{dw}{dy} + G_\pm(w) = 0, \tag{27}$$

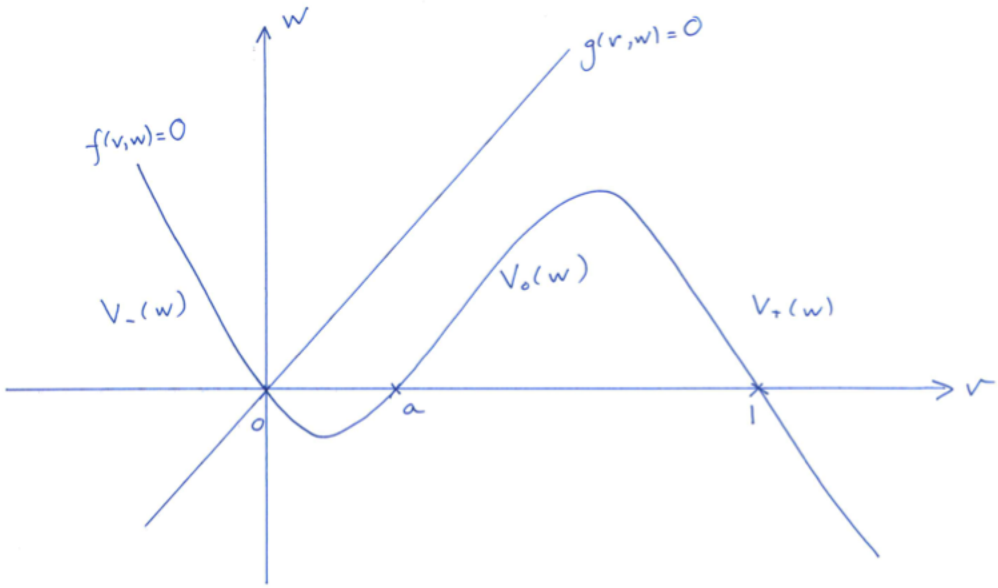


Figure 5: Phase plane for spatially-independent Fitzhugh-Nagumo equations.

where $G_{\pm}(w) \equiv g(w, V_{\pm}(w))$. The region of space whee $v = V_+(w)$ is called an excited region, and a region in which $v = V_-(w)$ is called a recovering region. The outer equations are valid wherever diffusion is not large.

However, we anticipate that there are region of space (interfaces) where diffusion is large and the above approximation to the phase plane dynamics is not correct.

**Inner solution**

We consider rapid transition regions by rescaling as follows:

$$Y = \frac{y}{\epsilon}, \tag{28}$$

so that

$$\frac{d}{dy} \to \frac{1}{\epsilon}\frac{d}{dY}. \tag{29}$$

The governing equations are then

$$\frac{d^2v}{dY^2} + c\frac{dv}{dY} + f(v,w) = 0, \tag{30}$$

$$\frac{c}{\epsilon}\frac{dw}{dY} + g(v,w) = 0. \tag{31}$$

Considering only leading-order terms gives

$$\frac{dw}{dY} = 0, \quad \frac{d^2v}{dY^2} + c\frac{dv}{dY} + f(v,w) = 0. \tag{32}$$

Hence in rapid transition regions, $w$ is constant. For fixed $w$, if $f(v,w)$ has three roots, two of which are stable, then there is a wave speed $c = c(w)$ for which the equation has a heteroclinic orbit connecting the two stable roots of $f(v,w) = 0$. This heteroclinic orbit corresponds to a moving transition layer, travelling with speed $c$. Since the roots of $f(v,w) = 0$ are function of $w$, $c$ is also a function of $w$.

**Travelling wave pulse**

We are now in a position to describe the travelling pulse in detail. A travelling pulse consist of a single excitation front followed by a single recovery back (see figure 4). Suppose we are far to the right of the travelling wave. The medium is at rest and a wave front has been excited that is moving from the left to the right.

As the wave front is moving from left to right, then $v = V_{-}(0)$ on its right, $v = V_{+}(0)$ on its left, and the wave is travelling at speed $c = c(0) > 0$.

- **Wavefront AB**

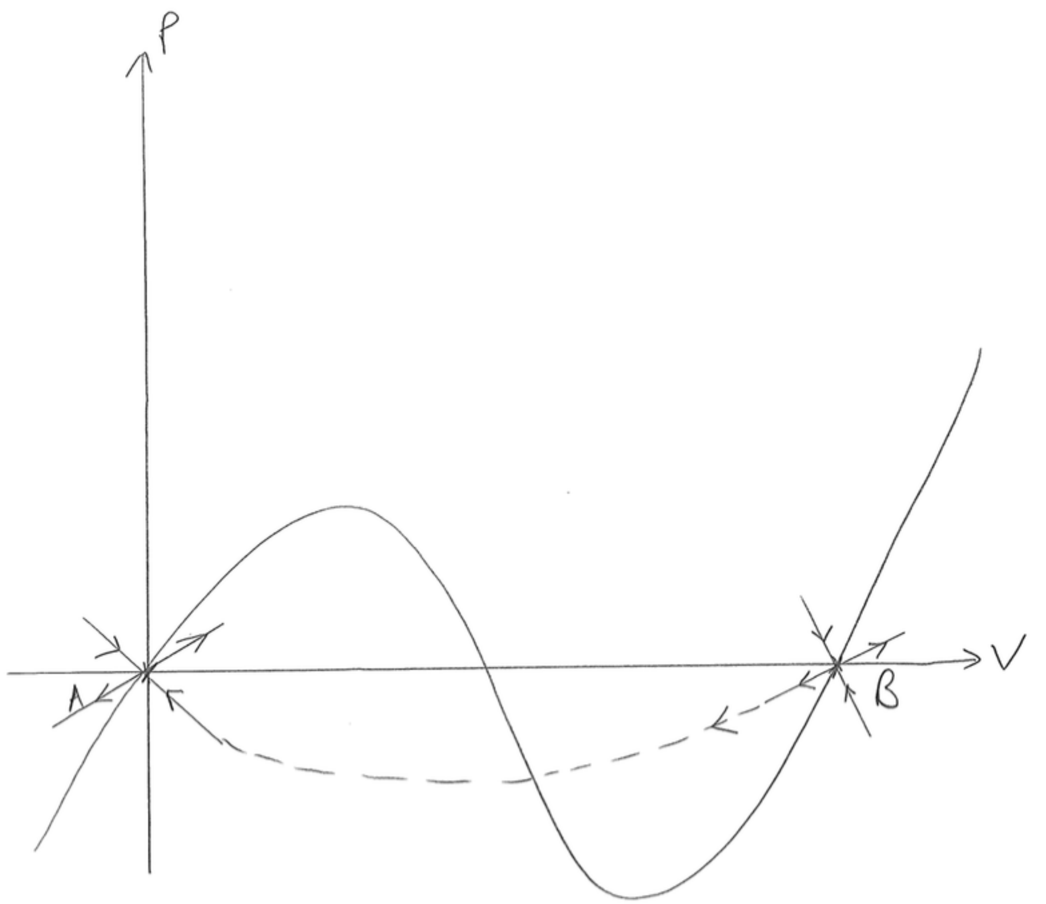


Figure 6: Phase plane for AB.

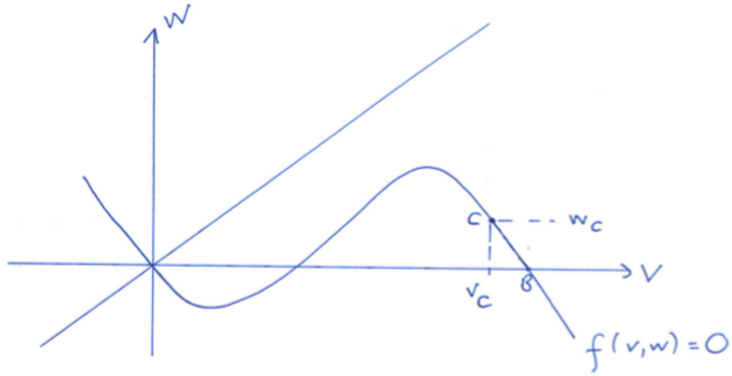


Figure 7: Phase plane for BC.

To leading-order we have that $w = 0$, The equation for $v$ is then

$$\frac{d^2v}{dY^2} + c\frac{dv}{dY} + f(v,0) = 0. \tag{33}$$

Note that in the wavefront, we have $v_Y < 0$ (see figure 4) . The phase plane for the bistable equation, with $P = v_Y$, is shown in figure 6 . The value of the wave speed $c(0)$ is selected so that $v$ goes from 0 (as $Y \to \infty$) to $v_B = 1$ (for $f(v,0) = Av(v-a)(1-v)$) (as $Y \to -\infty$).

- **Wavefront BC** Immediately to the left of the wavefront, the medium is excited and satisfies the outer dynamics on the upper branch $v = V_+(w)$ so that

$$w = Av(v-a)(1-v), \; c\frac{dw}{dy} = -g(w,v). \tag{34}$$

  We integrate equation (34)b from 0 to $w_C$ (to be determined) (see figure 7).

- **Waveback CD** There then follows a second transition layer which provides a transition between the excited region on the right and the recovering region on the left. We again consider $Y = y/\epsilon$, but now $w = w_C$ and the phase plane is

$$\frac{d^2v}{dY^2} + c\frac{dv}{dY} + f(v,w_C) = 0. \tag{35}$$

  We now select $c(w_C)$ so that $v$ goes from $v_C$ (as $Y \to \infty$) to $v_D$ (as $Y \to -\infty$), where $v_C$ and $v_D$ are the roots of $f(v,w_C) = 0$. See figure (8).

- **Waveback DA** Finally, we have

$$f(v,w) = 0, \; c\frac{dw}{dy} = w - bv$$

  and we integrate $w$ back to zero (see figure 9).

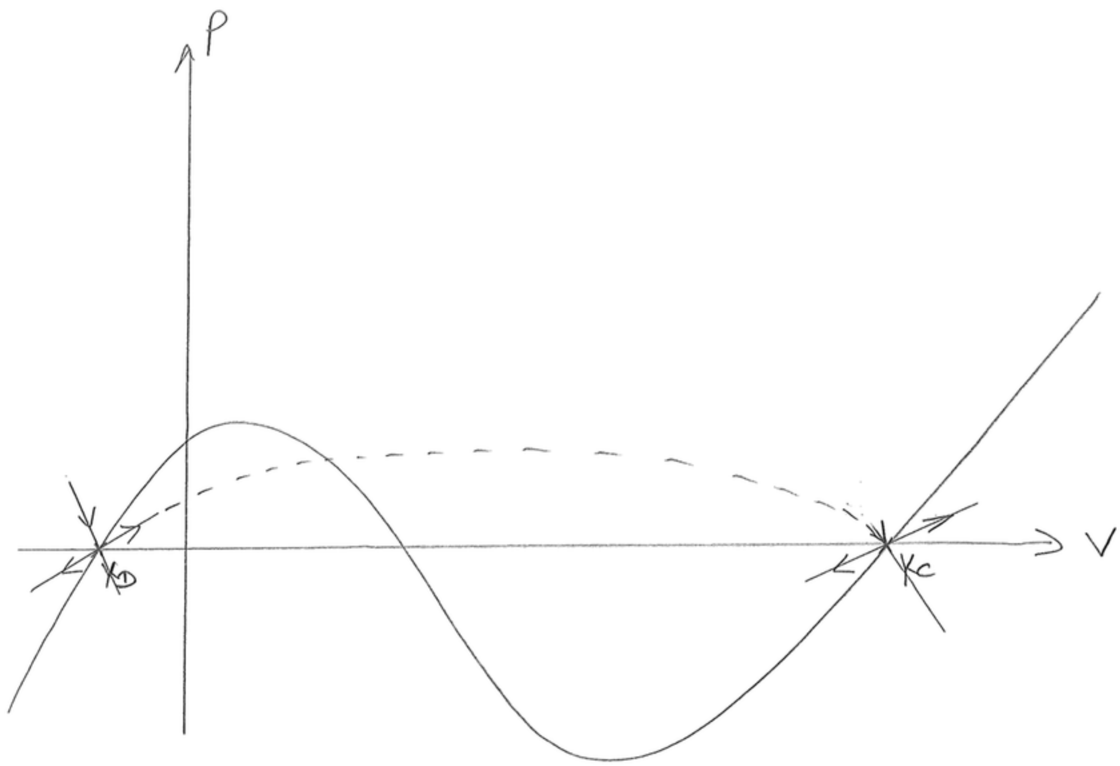


Figure 8: Phase plane for CD.

The remaining challenge is to determine the wave speed $c$, and the values of $v_C$, $v_D$ and $w_C$. We do this by considering the equations for the wavespeed, together with information about the roots of $f(v, w_C) = 0$.

We have that the wavespeed in AB given by $c(0)$. We have wave speed in CD given by $c_R(w_C)$. Now in the transition region $AB$, the governing equation is (33) and we have an up jump moving to the right. Multiplying (33) by $v_Y$ and integrating, using the fact that $v_Y \to 0$ as $Y \to \pm\infty$ we obtain, as in §2.1.1

$$c(0) = \frac{\int_{V_-(0)}^{V_+(0)} f(v,0)dv}{\int_{-\infty}^{\infty} v_Y^2 dY}. \tag{36}$$

It is straightforward (verify this) to show that

$$c_R(w_C) = -\frac{\int_{V_-(w_C)}^{V_+(w_C)} f(v,w_C)dv}{\int_{-\infty}^{\infty} v_Y^2 dY} = -c(w_C). \tag{37}$$

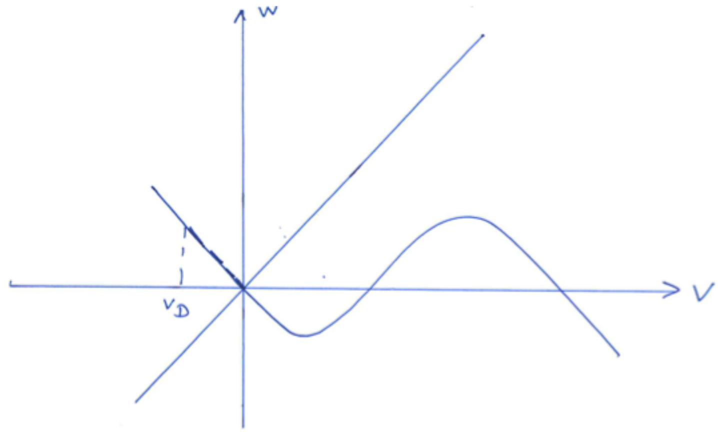


Figure 9: Phase plane for DA.

Now, from §2.1.1 we have

$$c(0) = \sqrt{\frac{A}{2}}(1 - 2a). \tag{38}$$

For a constant wavespeed travelling wave solution to exist we must have

$$c(w_C) = \sqrt{\frac{A}{2}}(U_2^* - 2U_1^* + U_0^*) = -\sqrt{\frac{A}{2}}(1 - 2a), \tag{39}$$

where $U_0^*, U_1^*, U_2^*$ are the roots of $Av(v - a)(1 - v) = w_C$, and $U_0^* < U_1^* < U_2^*$. Since $U_0^*, U_1^*, U_2^*$ are the roots of $Av(v - a)(1 - v) = w_C$, we also have, by Vieta's formula (look it up!), that

$$U_0^* + U_1^* + U_2^* = 1 + a \tag{40}$$

Combining (39) with (40) we obtain

$$U_1^* = \frac{2 - a}{3}. \tag{41}$$

Since this is a root of $Av(v - a)(1 - v) = w_C$, we can use this to determine $w_C$, and find that

$$w_C = \frac{2A}{27}(2 - a)(1 - 2a)(1 + a).$$

We then solve

$$Av(v - a)(1 - v) = \frac{2A}{27}(2 - a)(1 - 2a)(1 + a), \tag{42}$$

using the fact that we have one root already ($U_1^*$) to determine the remaining roots

$$U_0^* = -\frac{1}{3} + \frac{2}{3}a, \; U_2^* = \frac{2}{3} + \frac{2}{3}a, \tag{43}$$

where we relate $v_C = U_2^*$ and $v_D = U_0^*$.