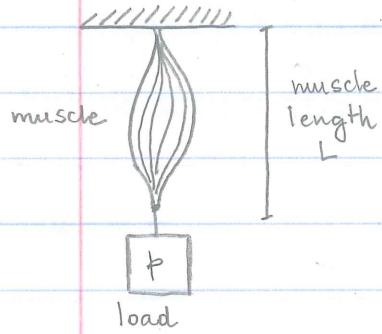


## LECTURE 11

The generation of tension at the extremity of a muscle is the result of a cascade of events: an action potential is synaptically transmitted from a neuron to muscle cells  $\Rightarrow$  the action potential triggers chemical reactions within the cells  $\Rightarrow$  intracellular filaments shorten (or try to).

Two scenarios are possible:



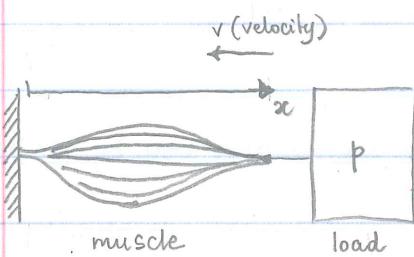
a) The muscle cells experience the cascade of electrical and chemical events that would put filaments into motion but, at the macroscopic level, there is no contraction of the muscle

ISOMETRIC TENSION is the tension generated by a muscle when the muscle

Ex.: Holding a load steady with the hand and forearm

Ex.: Stimulation of a muscle with high-freq. electrical stimuli

length is kept fixed  $\Rightarrow$  The state of a muscle generating isometric tension is called "TETANUS"

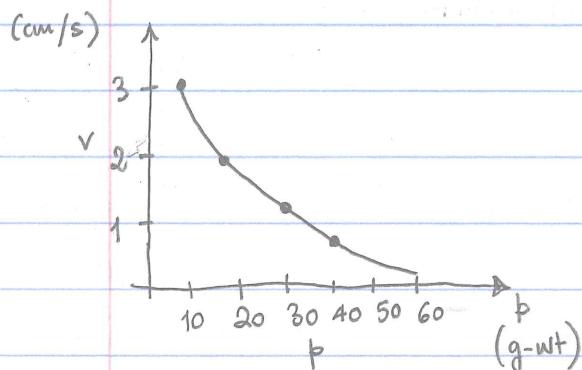


b) The motion of the filaments in the muscle occurs in a coordinated way and results in the shortening (i.e., contraction) of the muscle while the tension is kept fixed

ISOTONIC TENSION is the (constant) tension that is generated while the muscle length changes. It occurs when the maximal force of contraction of the muscle exceeds the total load on the muscle

(2)

With regard to a-b), we can estimate an empirical relationship (black box model) between the weight of the load  $p$  overcome by the isotonic tension and the rate of contraction  $v$  of the muscle:



The curve is fitted by the model:

$$(p+a)v = b(p_0-p) \quad (*)$$

↑  
FORCE - VELOCITY EQUATION

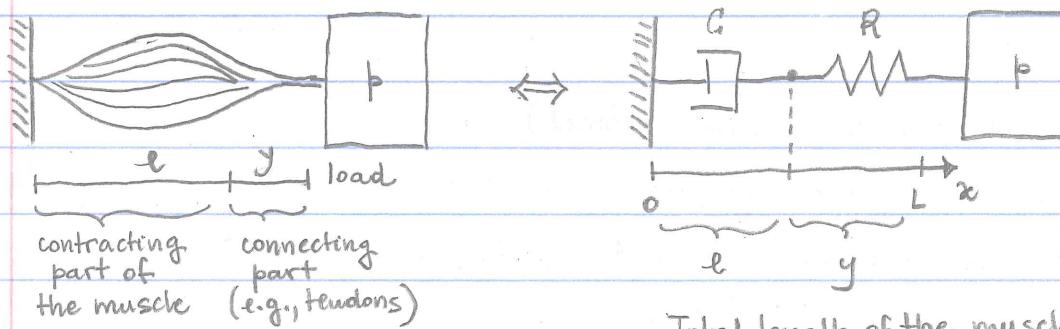
$g\text{-wt} \triangleq \text{grams weight}$

In equation (\*),  $a, b$  are parameters to be estimated. Also, one can note:

$v=0 \Rightarrow p=p_0$  The load " $p_0$ " provides the value of isometric tension when the muscle length is constant

$p=0 \Rightarrow v = b p_0 / a$  The contraction velocity has a finite maximal value achieved when no load is applied

The experimental setup for isotonic muscle contraction can be qualitatively depicted as the series of three elements:

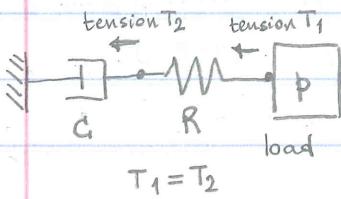


Total length of the muscle:

$$L = l + y$$

(3)

In this schematic, the interface between muscle and load is approximated as a purely elastic element (i.e., it can be extended or compressed but it cannot shorten its size)



Hence we have:

$$v = -\frac{de}{dx}$$

$$p = P(y) = \alpha(y - y_0)$$

Because R is  
a spring

During contraction, we have two events:

- The tension on C is the same as on R and it is equal to  $p$  (because they are in series)
- The velocity  $v$  is determined by the contractile part (i.e., the contraction of C is faster and larger than the possible displacement of R)

$$y_0 \triangleq \text{rest position of } R$$

$\alpha \triangleq$  parameter to be estimated

From these equations, we can derive a differential model for the tension  $T_1$  applied onto the load:

$$\frac{dT_1}{dt} = \frac{dP}{dy} \cdot \frac{dy}{dt} = \alpha \cdot \frac{d}{dt} (L - l) = \alpha \left( \frac{dL}{dt} + v \right)$$

Equivalently, the tension  $T_1$  can be expressed in terms of the load it reacts to:

$$\frac{dP}{dt} = \alpha \left( \frac{dL}{dt} + b \frac{p_0 - p}{p_0 + a} \right) \quad (\text{Hill Model})$$

This equation can be solved under special cases:

1) ISOMETRIC CONTRACTION : If the muscle is put into tetanus, then the

total length L must be constant  $\Rightarrow \frac{dL}{dt} = 0$

(4)

$$\text{Hence: } \frac{dp}{dt} = \alpha b \frac{p_0 - p}{p+a} \Leftrightarrow \frac{p+a}{p_0 - p} dp = \alpha b dt$$

$$\Leftrightarrow \int_{p(0)}^{p(t)} \frac{p+a}{p_0 - p} dp = \alpha b t \Leftrightarrow \int_0^{p(t)} \left[ \frac{-(p_0 - p)}{p_0 - p} + \frac{a + p_0}{p_0 - p} \right] dp = \alpha b t$$

Let us  
assume:  $p(0) = 0$

$$\Leftrightarrow \left( -p - (a + p_0) \ln(p_0 - p) \right) \Big|_0^{p(t)} = \alpha b t$$

$$\Leftrightarrow -p(t) - (a + p_0) \ln\left(\frac{p_0 - p}{p_0}\right) = \alpha b t$$

$$\text{Note: } e^{-\alpha b t} = e^{p(t)} \cdot \left(\frac{p_0 - p}{p_0}\right)^{a+p_0} \Rightarrow \text{As } t \rightarrow \infty, \text{ then } p(t) \rightarrow p_0$$

2) RELEASE AT CONSTANT VELOCITY: If the muscle is originally held at tension  $p_0$  and then allowed to move at constant velocity  $v = u^*$ , then the muscle will relax until it reaches the tension:

$$p(u^*) = \frac{b p_0 - a u^*}{u^* + b} \quad (\text{from the force-velocity equation})$$

The velocity is controlled and it refers to the entire muscle  $\Rightarrow u^* = -\frac{dL}{dt}$

$$\text{Hence we have: } \frac{dp}{dt} = \alpha \left( -u^* + b \frac{p_0 - p}{p+a} \right) \Leftrightarrow \frac{dp}{dt} = \alpha b \left( \frac{-p_0 + p(u^*)}{p(u^*) + a} + \frac{p_0 - p}{p+a} \right)$$

$u^* = b \frac{p_0 - p(u^*)}{p(u^*) + a}$

$$\Leftrightarrow \frac{dp}{dt} = \alpha b \frac{-p_0 b - a p_0 + p^* p + a p^* + b p^* + a p_0 - b p^* - a p}{(p^* + a)(p + a)}$$

$\uparrow$   
 $p^* \triangleq p(u^*)$

(5)

$$\frac{dp}{dt} = \alpha b \frac{(p_0 + a)(p^* - p)}{(p^* + a)(p + a)} \Leftrightarrow \frac{dp}{dt} = A \frac{p^* - p}{p + a}$$

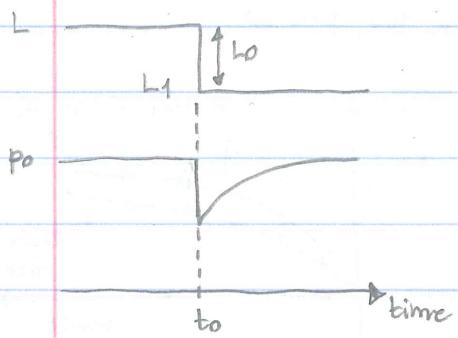
$A \triangleq \alpha b \frac{p_0 + a}{p^* + a}$

Integration by parts with initial condition:  $p(0) = p_0$

$$\frac{p+a}{p^*-p} dp = A dt \Leftrightarrow -p(t) - (a+p^*) \ln(p^*-p) \Big|_{p_0}^{p(t)} = At$$

$$\Leftrightarrow (p_0 - p(t)) + (p^* + a) \ln\left(\frac{p_0 - p(t)}{p^* - p(t)}\right) = At$$

3) RESPONSE TO A JUMP IN LENGTH: Let us assume that the muscle is



under isometric contraction (i.e., tension is  $p_0$ ) with length  $L$  and that, at some time  $t_0$ , the length is shortened (e.g., to  $L_1 < L$ )  $\Rightarrow$  The tension is expected to drop and then slowly return to  $p_0 \Rightarrow$  The Hill model predicts this response:

$$L = L_1 + L_0 - L_0 H(t - t_0)$$

where  $H(w) \triangleq \begin{cases} 1 & w > 0^+ \\ 0 & w < 0^- \end{cases}$

$$\left. \Rightarrow \frac{dL}{dt} = -L_0 \delta(t - t_0) \right. \uparrow$$

Dirac delta function

$$\frac{dp}{dt} = \alpha \left( -L_0 \delta(t - t_0) + b \frac{p_0 - p}{p + a} \right)$$

$$p(t_0^-) = p_0$$

By integrating from  $t_0 - \varepsilon$  to  $t_0 + \varepsilon$  with  $\varepsilon > 0$  small, and then letting  $\varepsilon \rightarrow 0$ :

(6)

$$\int_{t_0-\varepsilon}^{t_0+\varepsilon} \frac{dp}{dt} dt = \alpha \int_{t_0-\varepsilon}^{t_0+\varepsilon} -L_0 \delta(t-t_0) dt + \alpha b \int_{t_0-\varepsilon}^{t_0+\varepsilon} \frac{t_0-t}{p+a} dt$$

↓                    ↓                    ↓  
 $p(t_0^+) - p(t_0^-) = -\alpha L_0$

$\Rightarrow$  There is a drop in the tension

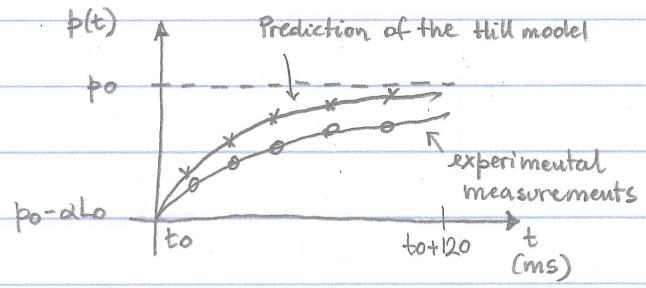
Then, by integrating from  $t_0^+$  to time  $t > t_0$ , we have:

$$\left. \begin{aligned} \frac{dp}{dt} &= \alpha b \frac{p_0 - p}{p + a} \\ p(t_0^+) &= p_0 - \alpha L_0 \end{aligned} \right\} \Rightarrow \int_{p_0 - \alpha L_0}^{p(t)} \frac{p+a}{p_0-p} dp = \alpha b (t-t_0)$$

$$\Leftrightarrow -p(t) + (p_0 - \alpha L_0) - (a + p_0) \ln \left( \frac{p_0 - p(t)}{\alpha L_0} \right) = \alpha b (t - t_0) \quad (**)$$

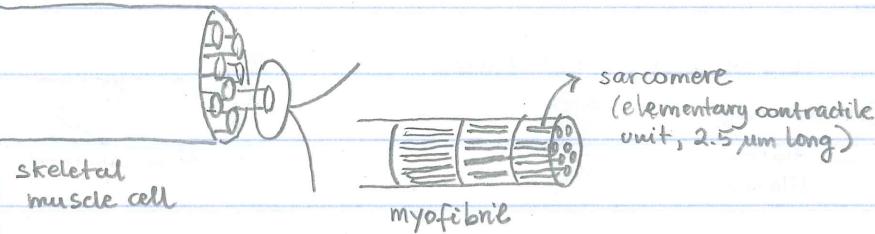
As for case 1), we have that  $p(t) \rightarrow p_0$  as  $t \rightarrow \infty$ .

However, when compared to actual measurements, the predictions of equation (\*\*) suggest a faster return to  $p_0$



The problem is that the Hill model is based on the force-velocity equation, which provides an instantaneous relationship  $\Rightarrow$  The relationship between force and velocity is not instantaneous and - to capture this - we need a model that explicitly describes the events in the muscle cells that lead to the generation of tension.

\* A subcellular model of muscle contraction (Huxley model)

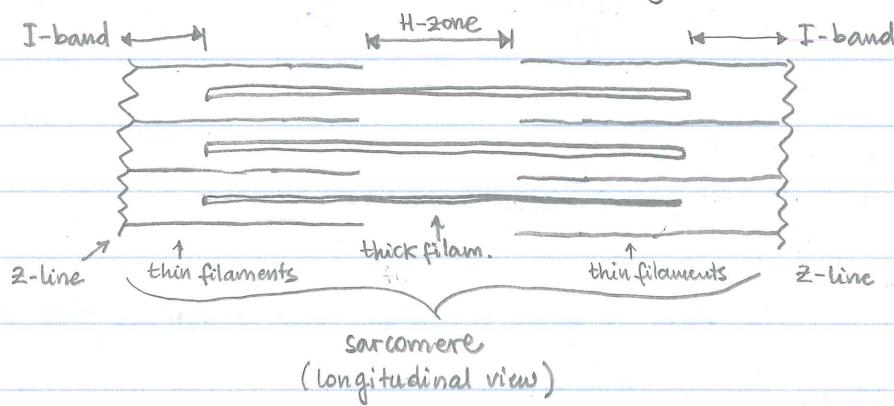


Each sarcomere contains thin and thick parallel filaments arranged geometrically:

- o o ← thin filaments
- o o ↑ o
- ↑ o thick filament

cross-section view

Furthermore, a longitudinal view of the filaments in the sarcomere shows that filaments are arranged such that thin and thick filaments alternatively overlap:



I-bands  $\triangleq$  zones where only thin filaments are present

H-zone  $\triangleq$  zone where only thick filaments are present

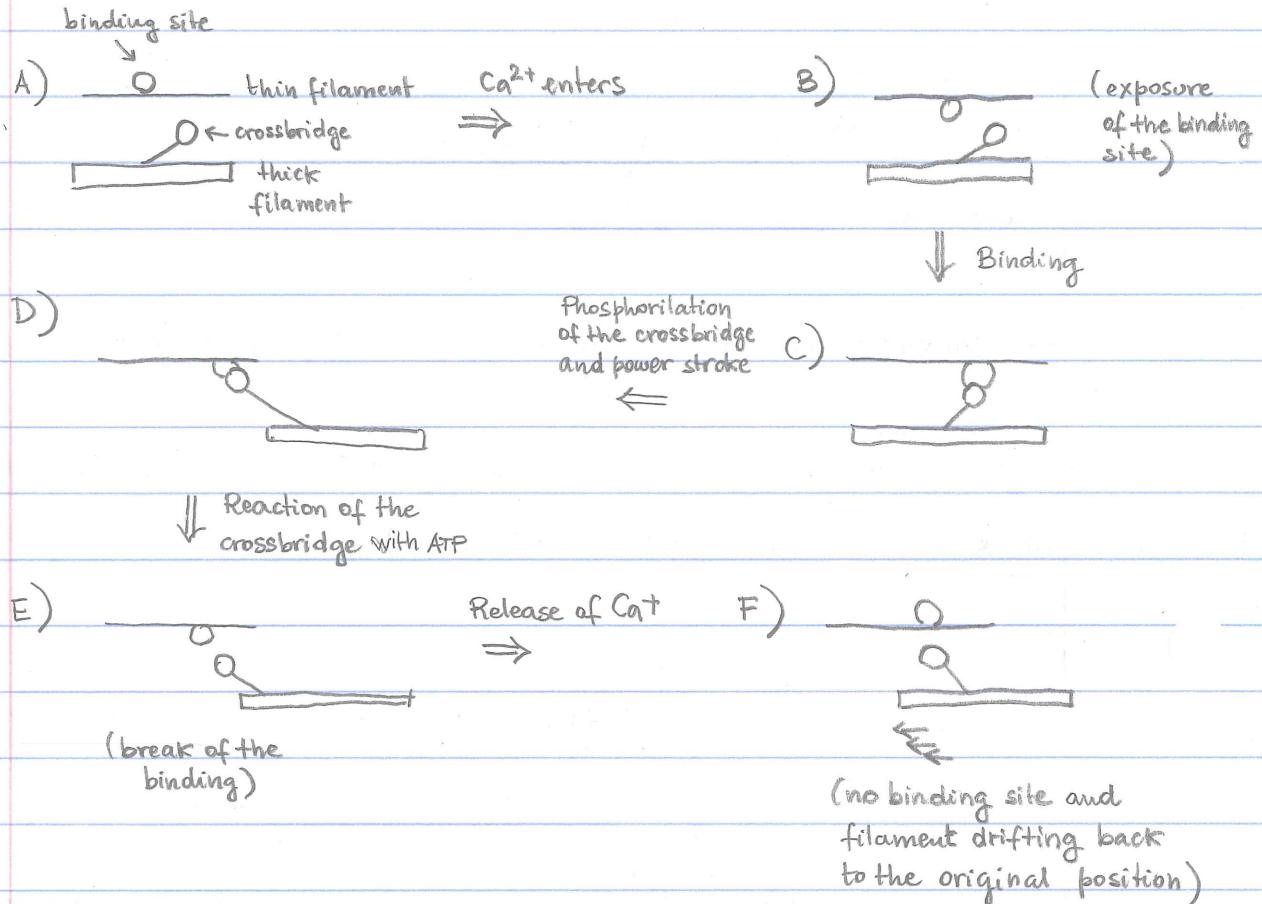
A-band  $\triangleq$  zone where thick filaments are present (with or w/o overlap)

During contraction, the overlap between thin and thick filaments increases, thus shortening I-bands and H-zone

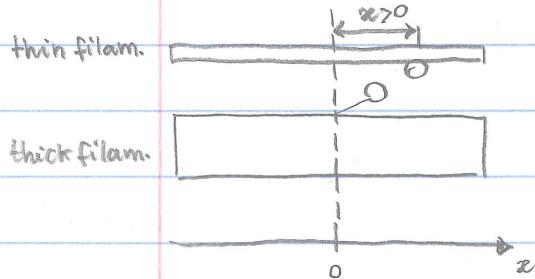
As the action potential enters the muscle cell,  $\text{Ca}^{2+}$  ion channels open and high concentrations of  $\text{Ca}^{2+}$  ions reach to the sarcomere  $\Rightarrow$  Thick filaments change structure because of  $\text{Ca}^{2+}$  ions, bind and pull on the thin filaments, thus causing

(8)

the muscle contraction. A schematic of the cycle includes the following phases:



We want to build a model that describes the dynamics of the crossbridge:



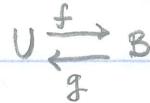
Let us assume that  $x=0$  is the position where the crossbridge is perpendicular to the thin filament ( $\Rightarrow$  no power stroke if binding at  $x=0$ )

Let us assume that, if the crossbridge binds on a binding site in position  $x > 0$ , there is a contraction. If it binds on a site at  $x < 0$ , the force exerted during power stroke is opposite to contraction.

Let us assume that a crossbridge can be either in bounded (B) state or

(9)

in unbounded ( $V$ ) state:



We assume that the rates of transformation depend on  $x$  (i.e.,  $f=f(x)$ ;  $g=g(x)$ ) and that, for each value of  $x$ , there are  $p > 0$  crossbridges able to bind on binding sites at position  $x$ , but only a fraction  $n(x,t)$  is actually bounded at time  $t \Rightarrow$  We can write:

$$\begin{aligned} \text{Total number of} \\ \text{crossbridges bounded} &\triangleq p \int_a^b n(x,t) dx \\ \text{along the segment } [a,b] \end{aligned}$$

Also, denoted with  $v(t)$  the velocity of the thin filament sliding along the thick filament, we have a flux of  $p n(b,t) v(t)$  new crossbridges entering the segment and a flux of  $p n(a,t) v(t)$  crossbridges leaving the segment  $\Rightarrow$  Hence:

$$\begin{aligned} p \frac{d}{dt} \int_a^b n(x,t) dx &= p v(t) (n(b,t) - n(a,t)) + \\ &+ p \int_a^b [f(x)(1-n(x,t)) - g(x)n(x,t)] dx \end{aligned}$$

Note the "+" sign here: there is a typo in the textbook (eq. 15.19 and 15.20) that is then fixed in eq. 15.21 and following ones

Hence we have:

$$\frac{\partial n}{\partial t} = v \frac{\partial n}{\partial x} + f(x)(1-n) - g(x)n \quad (\text{Huxley Model})$$

(10)

Note that the fraction  $n(x,t)$  can be related to macroscopic variables (e.g., tension  $p$ , force-velocity relationship, energy consumption). For instance:

Energy released  
when crossbridges  
bind

$$\phi(t) = \epsilon \cdot p \int_{-\infty}^{\infty} f(x) (1 - n(x,t)) dx$$

↑  
energy  
per single  
crossbridge

Assuming that each crossbridge is like a spring and generates a force  $r$  that depends on the displacement  $x$ , we have:

Total force  
exerted by the muscle

$$p(t) = p \int_{-\infty}^{\infty} r(x) n(x,t) dx$$

To determine the force-velocity relationship, we assume  $v = \text{constant}$  and  $dn/dt = 0$  (i.e., steady-state):

$$-v \frac{dn}{dx} = f(x)(1 - n(x)) - g(x)n(x)$$

↓

$$-v \frac{dn}{dx} = f(x) - (f(x) + g(x))n(x)$$

↓

$$-\frac{dn}{dx} = \frac{1}{\tau(x)} (n_{\infty}(x) - n(x))$$

where:  $n_{\infty}(x) = \frac{f(x)}{f(x) + g(x)}$        $\tau(x) = \frac{v}{f(x) + g(x)}$

If  $v \geq 0$ , then  $n(x)$  will converge rapidly to the asymptotic function  $n_{\infty}(x) \Rightarrow$  The isometric force  $p_0$  is given by:

(11)

$$p_0 = p \int_{-\infty}^{\infty} r(x) \frac{f(x)}{g(x)+f(x)} dx$$

Furthermore, as  $v \gg 0$ , we have that  $n(x)$  slowly changes (i.e., the time constant  $\tau(x)$  is large) and is generally small  $\Rightarrow$  The force  $p(t)$  is small

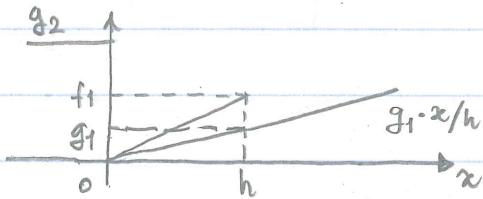
As the velocity  $v$  increases, the time during which a crossbridge is bound to a binding site reduces, and a large fraction of crossbridges is carried in the region  $x < 0$  before releasing the binding site, thus generating a force opposing contraction  $\Rightarrow$  There will be a critical velocity  $v^*$  at which the two forces balance and  $p=0$

A question remains, though: how do we choose  $f(x)$  and  $g(x)$ ?

The selection is arbitrary and typically driven by experimental observations.

For instance, the original selection by Huxley was:

$$f(x) = \begin{cases} 0 & x < 0 \\ f_1 \cdot x/h & 0 \leq x \leq h \\ 0 & x > h \end{cases}$$



$$g(x) = \begin{cases} g_2 & x \leq 0 \\ g_1 \cdot x/h & x > 0 \end{cases}$$

with  $g_1, g_2, f_1$ , and  $h$  to be estimated

The solution can be determined analytically in each one of the following regions:

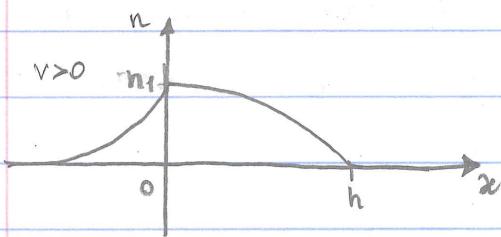
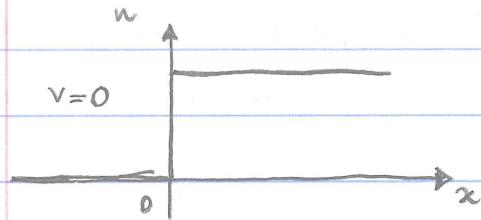
$$\text{I) } x \leq 0 : -v \frac{\partial n_I}{\partial x} = -g_2 \cdot n_I \quad n_I(-\infty) = 0$$

(12)

$$\text{II) } 0 < x \leq h: -v \frac{\partial n_{\text{II}}}{\partial x} = (1 - n_{\text{II}}) f_1 \frac{x}{h} - n_{\text{II}} g_1 \frac{x}{h} \quad n_{\text{II}}(0) = n_I(0)$$

$$\text{III) } x > h: -v \frac{\partial n_{\text{III}}}{\partial x} = -n_{\text{III}} g_1 \frac{x}{h}$$

- For this equation, the only bounded solution is  $n_{\text{III}} = 0$   
 $\Rightarrow$  This is consistent with the fact that, for  $x > h$ , no more binding occurs.



The peak value  $n_1$  decreases as the velocity increases ( $v \rightarrow v_{\max}$ )

#### REFERENCE:

Textbook (vol.2): chapter 15, sec. 15.1; 15.2; 15.2.1; 15.2.2; 15.3;  
 15.3.1; 15.3.2,