STRUCTURAL MODEL OF MUSCLE CONTRACTION

By

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Chapter 1

Introduction

Mathematical modeling is a powerful method of representing many types of systems, allowing scientists to develop a better understanding of the mechanisms that govern them. This is especially true in biology, where it is often uneconomical, inefficient, or simply impossible to conduct certain experiments. Simulation is now considered to be on equal footing with theory and experiments in the process of scientific discovery.

The mechanisms of muscle contraction are of great interest to many scientists. Consequently, they have been studied extensively. Researchers in the medical field are especially interested in developing a tool that would allow them to further investigate and predict how muscles would respond under a variety of conditions imposed by disease.

The Huxley model, first formulated by A. F. Huxley in 1957 [5], is the accepted paradigm of muscle force production [2]. It was considered to be the first unifying theory of muscle contraction, as it succeeded in simultaneously considering mechanical, chemical, thermal, and structural changes in the muscle during contraction. Throughout this paper, when we refer to *the model of muscle contraction*, we mean A.F Huxley's original theory of muscle contraction, and not a specific equation. Although the Huxley equation is still used today, the original mathematical formulation is limiting, and has since been extended to provide a more versatile mathematical model. G. Zahalak is credited with this extension, known as the Huxley-Zahalak equation [12], which is also founded upon A.F. Huxley's original theory.

This thesis is organized into two main sections. Chapter 2 reviews the biological background upon which A.F. Huxley's theory of muscle contraction is based. This includes the biochemical and physical structure of muscle, as well as the mechanism of contraction. We present a concise derivation of the Huxley [5] and the Huxley-Zahalak equations [12] and discuss how they are used to calculate the total force generated in the muscle.

In Chapter 3 we begin by presenting the complete solution to the Huxley equation. This is followed by a derivation of the force equation from this solution and comparison of the results with A.V. Hill's famous force-velocity curve [4]. Although a method for solving the Huxley-Zahalak equation is discussed, we only present an outline of its analytical solution. The chapter concludes with a discussion of numerical schemes.

The aim of this thesis is threefold. First to present a comprehensive review of A.F. Huxley's theory of muscle contraction. Second to introduce the Huxley and the Huxley-Zahalak equations, which describe muscle contraction in mathematical terms. Third, to solve these equations analytically for constant speed of contraction.

Chapter 2

The Model of Muscle Contraction

A strong understanding of the biological theory of muscle contraction is essential to clearly formulate and solve the corresponding mathematical model. In this chapter we describe the physical and chemical structure of the muscle and introduce two models used to simulate muscle contraction. The first is the Huxley equation, a structural model expressed as an ordinary differential equation (ODE), formulated in 1957 by A.F. Huxley [5]. The second model is a reformulation of the Huxley equation as a first-order hyperbolic partial differential equation (PDE) by G.I. Zahalak in 1990 [12]. Both of these models can be used in conjunction with Hooke's law of elasticity to calculate the force generated in a muscle during contraction.

2.1 The Physical and Biochemical Structure of Muscle

There are two main types of muscle in the body. The first is *skeletal muscle*. As the name suggests, it is most often associated with the skeleton; for example, the muscles in the limbs. The second type is *smooth muscle*. Examples of smooth muscle are the muscles of the airway, heart, and intestinal tract [1]. Although there are several differences between these two types of muscle, the most relevant to this paper is the difference in structure. Skeletal muscle has a fixed architecture, whereas the architecture of smooth muscle is more plastic [1].

Skeletal muscle is responsible for producing voluntary movement. It is capable of both powerful and controlled contractions [2]. Skeletal muscle is also known as *striated muscle* due to its highly organized structure in both cross-sectional and longitudinal directions (Figure 2.1).

A.F. Huxley's theory of muscle contraction was originally developed for skeletal muscle.

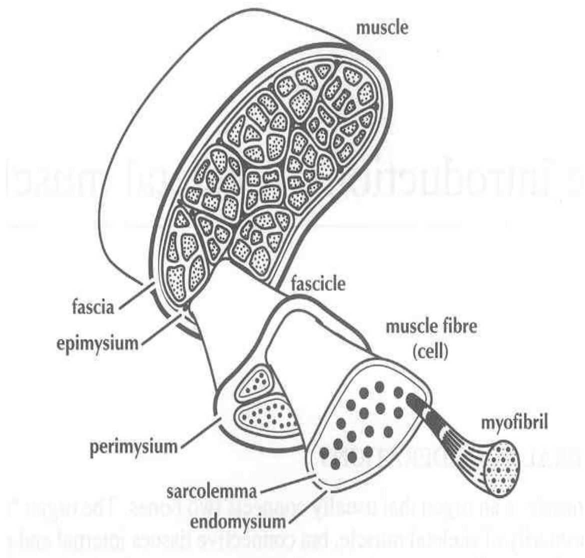

Figure 2.1: The structure of skeletal muscle, showing the cross-sectional and longitudinal organization (adapted from [2]).

The muscle is made of many bundles of fibers, with each fiber consisting of a single muscle cell. The muscle cell contains discrete bunches of *myofibrils*, that are segmented longitudinally by repeating units called *sarcomeres*. The sarcomeres form the basic functional unit of the muscle (Figure 2.2).

The biochemical makeup of the sarcomere is also important for muscle contraction. Each sarcomere is composed of two types of filaments: *actin* and *myosin*.

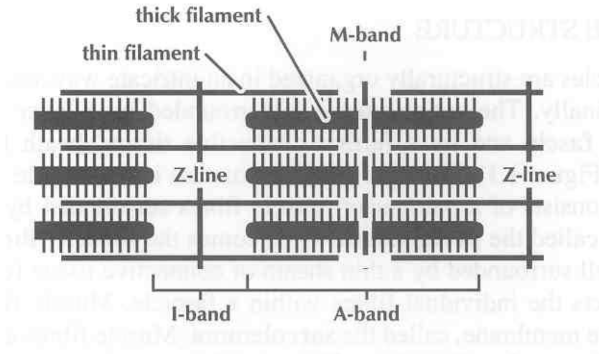

Figure 2.2: Diagram of the structure of a sarcomere (adapted from [2]).

The myosin filament is a relatively thick (12 nm in diameter) filament, composed of the protein myosin (Figure 2.3)[2]. The myosin molecule has two functional regions: a head and a tail. The myosin tails wind around each other to form the filament, while the heads protrude, positioned to bind to sites on the actin filaments. These heads are spaced along the filament at 14 nm intervals, and are offset by 60° from their neighbors [2].

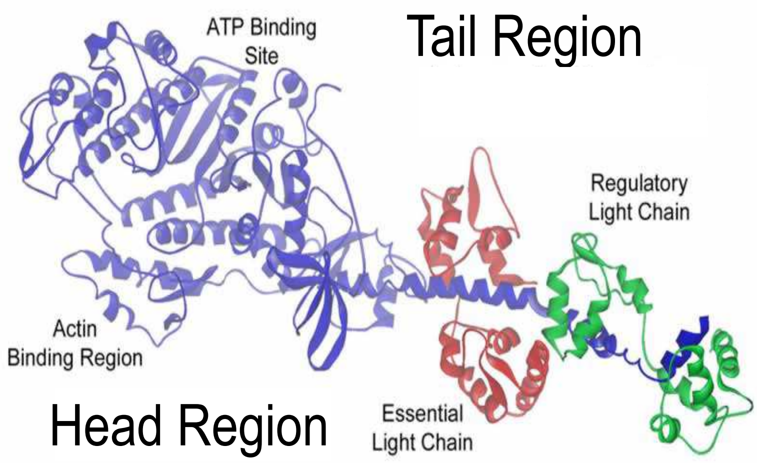

Figure 2.3: Molecular structure of myosin (adapted from [9]).

The actin filament is smaller in diameter (6 nm) than the myosin filament [2]. It is composed of the protein actin (Figure 2.4). The actin molecules are globular in shape and bind together to form a helical chain that contains binding sites for the myosin heads. The actin filament also contains other proteins that operate along with the nervous system to control muscle contraction and provide supporting structures for the filaments [2].

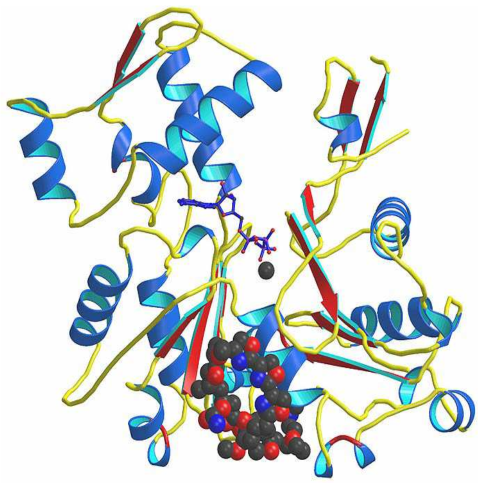

Figure 2.4: Molecular structure of actin (adapted from [10]).

The myosin and actin filaments are arranged in the sarcomere in a specific way, giving the muscle a unique physical structure. Each myosin filament is surrounded by six actin filaments, and then these subgroups are arranged in a hexagonal shape (Figure 2.5). In this manner the three-dimensional structure of the muscle is assembled.

A.F. Huxley's model of muscle contraction [5], and consequently the Huxley [5] and Huxley-Zahalak [12] equations, are directly based on the physical and chemical properties of the muscle mentioned here.

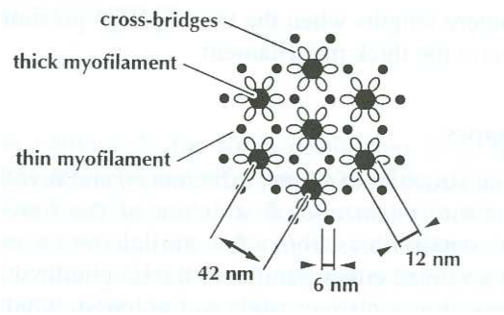

Figure 2.5: The three dimensional structure of the myofibrils (adapted from [2]).

2.2 The Theory of Muscle Contraction

Force development in the muscle is a function of the shortening, or *contraction*, of the muscle fibers. The mechanism of muscle contraction proposed in 1954 by H.E. Huxley and Hansen [7], as well as A.F. Huxley and Niedergerke [6], remains widely accepted today. In order to explain how contraction occurs, the model must answer two questions:

1. *How does the muscle physically shorten in length?*

2. *What causes this shortening to occur?*

A.F. Huxley proposed the *sliding filament model* and the *crossbridge theory* to answer these two questions [5].

The sliding filament model addresses the first question. It is based on two assumptions: first, that the lengths of the myosin and actin filaments remain constant during contraction, and second, that shortening is generated in each sarcomere as the myosin and actin filaments slide past each other, producing an overall shortening effect in the muscle [2]. The sliding filament model is supported by the structure of the muscle and evidence obtained by examining muscle at different stages of contraction with an electron microscope (Figure 2.6).

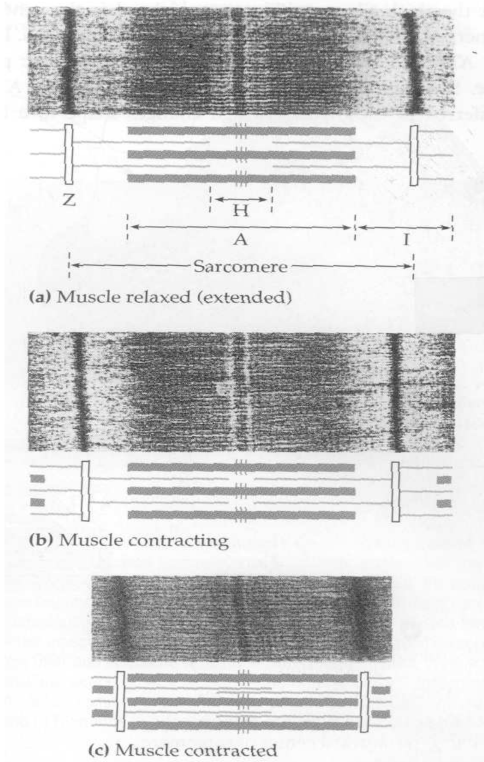

Figure 2.6: Electron microscopy of skeletal muscle at various stages of contraction showing the concept of the sliding filament theory (adapted from [1]).

The second assumption suggests a mechanism which describes how the shortening is thought to occur. It is further explained by A.F. Huxley's crossbridge theory, which proposes that the myosin and actin proteins interact to produce the sliding motion of the filaments [5].

The myosin heads, referred to as *crossbridges* by A.F. Huxley, are considered to be elastic elements that oscillate about their equilibrium positions (i.e., their points of attachment to the myosin filament) due to thermal energy. While the heads are oscillating, they are continuously attaching and detaching from myosin binding sites on the actin filaments. During the time that they are attached, the myosin heads exert a force on the actin filament according to Hooke's law of elasticity, causing the filaments to slide past each other. The rates of attachment and detachment differ on either side of the equilibrium in order to ensure that force is always being exerted in the direction of contraction (i.e., towards the center of the sarcomere).

By combining the sliding filament model and the crossbridge theory, A.F. Huxley was able to explain, in biological terms, a mechanism of muscle contraction which accounts for the unique nature of muscle.

2.3 The Huxley Equation

The mechanism of contraction proposed by A.F. Huxley is firmly based on established biological knowledge of striated muscle and stated in precise mathematical terms. The Huxley equation describes the two-dimensional model of muscle contraction shown in Figure 2.7 using an ODE.

The goal of this section is to derive the Huxley equation. We begin the derivation by stating some assumptions and introducing the notation. A.F. Huxley made the following assumptions in deriving the equation [5]:

1. Individual crossbridges are independent.

2. At any instant in time, crossbridges can only bind to one actin site.

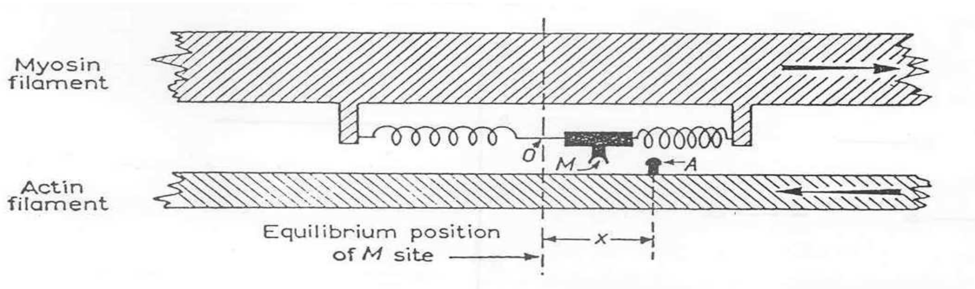

Figure 2.7: Diagrammatic representation of the Huxley model (adapted from [5]).

3. The functions that describe the rates of attachment and detachment are dependent on the distance from the equilibrium point.

Let M be a myosin head connected to a myosin filament by an elastic element with spring constant k and equilibrium point O, and let A be a myosin binding site located on the actin filament. Then we define $M-A$ to be a myosin-actin crossbridge.

The rates of attachment and detachment depend on x, where x is the distance from O to A, and are given per unit time. Let $f(x)$ be the rate of attachment and $g(x)$ the rate of detachment. These functions are shown in Figure 2.8.

Now consider a large number of $M-A$ pairs with the same x at each instant in time, t. Then the proportion of $M-A$ pairs is a function of time and is denoted by $n(t)$. We can write the rate of change of $n(t)$ as

$$\begin{array}{l}\text{The rate of}\\ \text{change of } n(t)\end{array} = \left\{\begin{array}{c}\#\text{ detached}\\ M-A\text{ pairs}\\ \text{at time } t\end{array}\right\}\left(\begin{array}{c}\text{rate of}\\ \text{attach.}\end{array}\right) - \left\{\begin{array}{c}\#\text{ attached}\\ M-A\text{ pairs}\\ \text{at time } t\end{array}\right\}\left(\begin{array}{c}\text{rate of}\\ \text{detach.}\end{array}\right),$$

which can be expressed as

$$\frac{dn}{dt} = (1-n)f(x) - ng(x). \tag{2.1}$$

Letting $v = -\dfrac{sV}{2}$,where s is the sarcomere length and V is the speed of shortening in the muscle ($V > 0$), and substituting $\dfrac{dn}{dt} = \dfrac{dx}{dt}\dfrac{dn}{dt} = v\dfrac{dn}{dx}$ we can rewrite (2.1) as

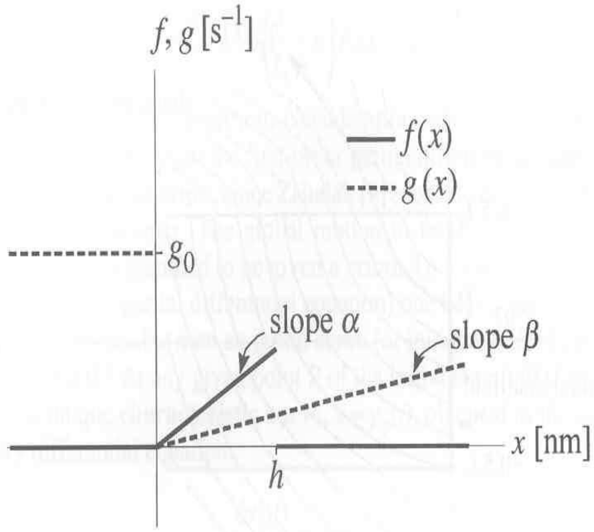

Figure 2.8: The functions describing the rates of attachment and detachment of the $M - A$ pairs. The variable h is the distance from O at which $M - A$ crossbridges are no longer able to form, and the values of α, β, and g_0 are given in Table 2 (adapted from [2]).

$$-v\frac{dn}{dx} = (1-n)f(x) - ng(x). \tag{2.2}$$

A.F. Huxley was able to solve (2.2) analytically for the case when the sliding velocity of the filaments, v, was constant and the rate functions f, g were as shown in Figure 2.8. We present the complete analytical solution to (2.2) for this case in Section 3.1.

2.4 The Huxley-Zahalak Equation

The Huxley equation (2.2) considers the case when the $M-A$ pairs have the same value of x. However, at any given instant in time t, for a large sample of $M-A$ pairs, it is probable that x would have a random distribution over the range $[-0.5l_a, 0.5l_a]$, where l_a is the distance between A sites [2].

The Huxley-Zahalak equation incorporates this random distribution of x into the model by reformulating (2.2) and considering the proportion of attached $M-A$ pairs as a function of both time and position; i.e., $n = n(x,t)$.

The following derivation of the Huxley-Zahalak equation is based on the law of mass conservation [3, 11]. Let $n(x,t)$ = proportion of $M-A$ pairs. Then for a segment of muscle, (x_1, x_2) over an interval of time, (t_1, t_2) we have

$$\left\{\begin{array}{l} \#M-A \text{ pairs} \\ \text{in } (x_1, x_2) \\ \text{at time } t_2 \end{array}\right\} - \left\{\begin{array}{l} \#M-A \text{ pairs} \\ \text{in } (x_1, x_2) \\ \text{at time } t_1 \end{array}\right\}$$
$$= \left\{\begin{array}{l} \#M-A \text{ pairs} \\ \text{entering filament} \\ \text{at } x_1 \text{ over } (t_1, t_2) \end{array}\right\} - \left\{\begin{array}{l} \#M-A \text{ pairs} \\ \text{leaving filament} \\ \text{at } x_2 \text{ over } (t_1, t_2) \end{array}\right\},$$

which can be expressed as

$$\frac{Dn(x,t)}{Dt} = [1 - n(x,t)]\, f(x) - n(x,t)g(x), \tag{2.3}$$

where D is the total derivative. Expanding the left hand side of (2.3) using the chain rule we have

$$\frac{Dn(x,t)}{Dt} = \frac{\partial n(x,t)}{\partial t} + \frac{dx}{dt}\frac{\partial n(x,t)}{\partial x}. \tag{2.4}$$

Substituting $\frac{dx}{dt} = v$, where $v < 0$, into (2.4) and combining with (2.3), we obtain

$$\frac{\partial n(x,t)}{\partial t} + v\frac{\partial n(x,t)}{\partial x} = [1 - n(x,t)]\, f(x) - n(x,t)g(x). \tag{2.5}$$

We note that (2.5) is the same as (2.2) except that (2.5) is written from a viewpoint that is not fixed in space, but rather one that is moving with the A sites. This PDE is subject to periodic boundary conditions $n(-0.5l_a, t) = n(0.5l_a, t)$, and the initial condition $n(x, 0) = n_0(x)$, where v and $n_0(x)$ are known.

It is appropriate in this case to use periodic boundary conditions for two reasons. First, if we consider the range $[-0.5l_a, 0.5l_a]$, $h \ll l_a$ (see Table 1, and Figure 2.8). So by definition, the rate functions only allow the M elements to bind with the closest A element. Thus there is no interaction between adjacent A sites (i.e., each A is *unaware* of its neighbors). In addition, the segmentation of the muscle fibers into theoretically identical actin sites suggests that the same PDE governs each of these sites. The rate functions, $f(x)$ and $g(x)$ are also defined for each A on a range that is contained within $[-0.5l_a, 0.5l_a]$, so they conform easily to a periodic domain.

The initial condition represents the distribution of $M-A$ pairs prior to stimulation of the muscle; i.e., at time $t = 0$. For this thesis, we choose the initial condition (Figure 2.9 to be as in [12]

$$n_0(x) = \begin{cases} 0 & \text{for } -0.5l_a < x < 0, \\ 0.8 & \text{for } 0 \leq x \leq h, \\ 0 & \text{for } h < x < 0.5l_a. \end{cases} \tag{2.6}$$

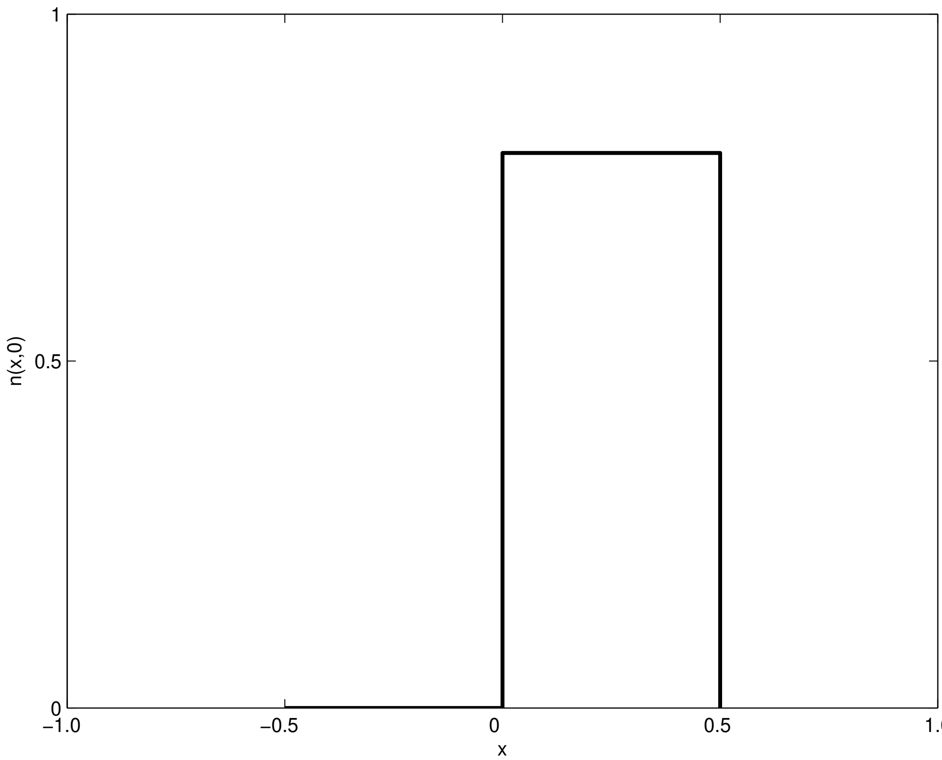

Figure 2.9: The initial distribution $n(x,0) = n_0(x)$.

The Huxley-Zahalak equation (2.5) has been solved analytically by the method of characteristics [2]; an outline of the solution is presented in Section 3.3.

2.5 Relating Crossbridge Interactions to Force Generation in the Muscle

Given the sliding velocity, v, and the initial distribution, $n_0(x)$, the Huxley equation (2.2) enables us to calculate the proportion of $M - A$ pairs, $n(x)$. We calculate the amount of force generated by an average $M - A$ pair by integrating over x using Hooke's law of elasticity, weighted by the proportion of attached pairs, $n(x)$. The $M - A$ pairs act in series, so to calculate the total force in the muscle, we sum the force contributed by each individual $M - A$ pair. It is only necessary to consider the contributions of $M - A$ pairs in half of the sarcomere in the longitudinal direction because the $M - A$ pairs combine to exert force in opposite directions on each side of the sarcomere [2].

If A is the cross-sectional area of the muscle, m the number of myosin elements per unit volume, s the sarcomere length, and k, x as before, the total force generated in the muscle is given by

$$F(t) = \frac{mAs}{2} \int_{-\infty}^{\infty} kxn(x,t)dx. \tag{2.7}$$

Formally we consider the integral over the range $[-\infty, \infty]$. However, because we restrict the M to bind with only one A at any given time, in practice we may integrate over the domain of x where the PDE is defined, namely $x \in [-0.5l_a, 0.5l_a]$.

2.6 Dimensional Analysis and Biological Constants

The purpose of this section is to present a dimensional analysis for the Huxley and the Huxley-Zahalak equations and to state the values we have chosen for the biological constants associated with these equations.

Dimensional analysis is important for two reasons. First, it ensures that the units of the equations are balanced and that they make physical sense. Second, it allows us to connect the solution to physical quantities and make meaningful conclusions about the results in light of the physical phenomena the models are representing.

The formulation of the Huxley and the Huxley-Zahalak equations presented in Section 2.3 and 2.4 results in $n(x)$ and $n(x,t)$ being dimensionless. The dimensions of the other quantities involved in the equations (as presented in [5, 2]) are shown in Table 2.1, along with the units we have chosen for them.

Table 2.1: Dimensions and units of the variables in Huxley (2.2) and Huxley-Zahalak (2.5) equations.

Quantity	Dimensions	Units
x	length	nm
t	time	s
α, β, g_0	time^{-1}	s^{-1}
v	length·time^{-1}	nm·s^{-1}
l_a	length	nm
k	stiffness	pN · nm
m	volume^{-1}	nm^{-1}
A	area	nm^2
s	length	nm

We now demonstrate that the units cancel in the Huxley and the Huxley-Zahalak equations, giving $n(x)$ and $n(x,t)$ in the desired dimensionless form.

For the Huxley equation (2.2):

$$-\frac{\text{nm}}{s}\frac{1}{\text{nm}} = \frac{1}{\text{s}} - \frac{1}{\text{s}}.$$

For the Huxley-Zahalak equation (2.5):

$$\frac{1}{\text{s}} + \frac{\text{nm}}{\text{s}}\left(\frac{1}{\text{nm}}\right) = \frac{1}{\text{s}} - \frac{1}{\text{s}}.$$

As mentioned at the end of Section 2.1, the Huxley and Huxley-Zahalak equations are based directly on the biological and chemical properties of muscle. Due to this, several biological constants are required to solve these equations. It is important to keep in mind that these values are determined empirically and are subject to experimental error and varying experimental conditions. The values we have chosen are in line with those used by others in the field [5, 12] and are shown in Table 2.2.

Table 2.2: Biological Constants

Biological Constant	Symbol	Chosen Value
Distance between A sites	l_a	43 nm
Limit of attachment range	h	6 nm
Sarcomere length	s	43 nm
Rate function parameters	α	43.3 s^{-1}
	β	10 s^{-1}
	g_0	209 s^{-1}
Cross-sectional area	A	nm^2
Number of M elements	m	16 nm^{-3}
Spring constant	k	0.6 $\mathrm{pN} \cdot \mathrm{nm}^{-1}$

The value chosen for A is dependent on the cross-sectional area of the muscle that is being modelled, so it is variable depending on the experimental design.

Chapter 3

Analytical Solutions and Numerical Methods

In this section we present the analytical solutions to A.F Huxley's ODE (2.2) and the Huxley-Zahalak PDE (2.5). We solve the differential equations analytically for the case when the sliding velocity, v, is constant. To our knowledge there is no analytical solution in the literature for either (2.2) or (2.5) that is not restricted by this assumption. However, the behavior of muscle during contraction under a non-constant velocity is of interest to the medical community. Therefore, in addition to the analytical solution, we also suggest numerical methods that may be used to solve these equations for non-constant v.

3.1 The Analytical Solution of the Huxley Equation

To solve the Huxley equation (2.2) we must consider three cases: $x < 0$, $0 < x < h$, and $x > h$. This is necessary due to the piecewise definition of the rate functions $f(x)$ and $g(x)$ (Figure 2.8). In the following derivation of the solution we use $-\frac{sV}{2}$

in place of v in order to remain consistent with Huxley.

Case 1: $x \leq 0$, $f(x) = 0$, and $g(x) = g_0$, so (2.2) becomes

$$\frac{dn(x)}{dx} = \frac{2g_0}{sV}n, \tag{3.1}$$

which can be solved using the method of separation of variables to give

$$n_1(x) = C_1 e^{\frac{2g_0 x}{sV}}, C_1 \in \mathbf{R}. \tag{3.2}$$

Case 2: $0 < x \leq h$, $f = \dfrac{\alpha x}{h}$, and $g = \dfrac{\beta x}{h}$ so (2.2) becomes

$$\frac{dn(x)}{dx} = -\frac{2}{sV}(1 - n(x))\frac{\alpha x}{h} - n(x)\frac{\beta x}{h}. \tag{3.3}$$

This can be rewritten in the general form

$$\frac{dn(x)}{dx} + \frac{2xn(x)}{sVh}(\alpha + \beta) = \frac{2\alpha x}{sVh}. \tag{3.4}$$

We solve (3.4) using the integrating factor $\mu = e^{\int \frac{x^2}{sVh}(\alpha+\beta)}$ to obtain

$$n_2(x) = \frac{\alpha}{(\alpha + \beta)} + C_2 e^{x^2 \frac{\alpha+\beta}{sVh}}, C_2 \in \mathbf{R}. \tag{3.5}$$

Case 3: $x > h$, $f = 0$, and $g = \dfrac{\beta x}{h}$ so (2.2) becomes

$$\frac{dn(x)}{dx} = \frac{2\beta x}{sV}. \tag{3.6}$$

Again by the method of separation of variables,

$$n_3(x) = C_3 e^{\frac{2x^2 g1}{2}}, C_3 \in \mathbf{R}. \tag{3.7}$$

Now, to solve for the constants C_1, C_2, and C_3 we use the fact that the solution must be continuous at $x = 0$ and $x = h$. Define the following constraint equations:

$$n_1(0) - n_2(0) = 0, \tag{3.8}$$

$$n_2(h) - n_3(h) = 0. \tag{3.9}$$

In order to solve the system, we require another constraint equation. Following [5] we take

$$n_3(h) = 0. \tag{3.10}$$

Using Maple (see Appendix 1) to solve (3.8), (3.9), and (3.10) for C_1, C_2, and C_3 we find that

$$C_1 = \frac{\alpha\left(e^{\frac{h(\alpha+\beta)}{(sV)}} - 1\right)}{e^{\frac{h(\alpha+\beta)}{(sV)}}(\alpha+\beta)}, \tag{3.11}$$

$$C_2 = -\frac{\alpha}{e^{\frac{h(\alpha+\beta)}{(sV)}}(\alpha+\beta)}, \tag{3.12}$$

and

$$C_3 = 0. \tag{3.13}$$

Substituting (3.11), (3.12), (3.13), into (3.2), (3.5), and (3.7) respectively and rearranging, we obtain the solution

$$n(x) = \begin{cases} 0 & \text{for} x > h, \\ \dfrac{\alpha}{(\alpha+\beta)}\left[1 - e^{\left(\dfrac{h(\alpha+\beta)}{sV}\right)\left(\dfrac{x^2}{h^2}{}^{-1}\right)}\right] & \text{for } 0 < x \leq h, \\ \dfrac{\alpha}{(\alpha+\beta)}\left[1 - e^{-\left(\dfrac{h(\alpha+\beta)}{sV}\right)}\right] e^{\dfrac{2g_0 x}{sV}} & \text{for } x \leq 0. \end{cases}$$

This is consistent with the original solution found by A.F. Huxley [5].

3.2 The Force Equation and the Solution to the Huxley Equation

Given the above analytical solution to (2.2), it is possible to derive an equation for total force in the muscle. We begin with

$$F(t) = \frac{mAs}{2}\int_{-\infty}^{\infty} kxn(x,t)\,dx. \tag{3.14}$$

To account for the fact that $n(x)$ is defined in a piecewise manner, we rewrite (3.14) as

$$F(t) = \frac{mAsk}{2}\left[\int_{-\infty}^{0} xn_1(x)\,dx + \int_{0}^{h} xn_2(x)\,dx + \int_{h}^{\infty} xn_3(x)\,dx\right]. \tag{3.15}$$

Consider each integral separately, and take $v = -\dfrac{sV}{2}$.

Case 1: $x \leq 0$

$$\begin{aligned}
\int_{-\infty}^{0} xn_1(x)\,dx &= \lim_{\kappa\to-\infty}\int_{\kappa}^{0} xn(x,t)\,dx \\
&= \lim_{\kappa\to-\infty}\int_{\kappa}^{0} \frac{\alpha}{(\alpha+\beta)}\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right) xe^{-\left(\frac{g_0}{v}\right)x}dx \\
&= \frac{\alpha}{(\alpha+\beta)}\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\lim_{\kappa\to-\infty}\int_{\kappa}^{0} xe^{-\left(\frac{g_0}{v}\right)x}dx
\end{aligned}$$

Integrating by parts, let $u = x, du = dx, dw = e^{-\left(\frac{g_0}{v}\right)x}dx, w = -\dfrac{v}{g_0}e^{\left(-\frac{g_0}{v}\right)x}$

$$\begin{aligned}
&= \frac{\alpha}{(\alpha+\beta)}\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\lim_{\kappa\to-\infty}\left(-x\left(\frac{v}{g_0}\right)e^{-\left(\frac{g_0}{v}\right)x}\Big|_{\kappa}^{0} - \int_{\kappa}^{0} -\frac{v}{g_0}e^{-\left(\frac{g_0}{v}\right)x}dx\right) \\
&= \frac{\alpha}{(\alpha+\beta)}\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\lim_{\kappa\to-\infty} -\left(\frac{v}{g_0}\right)^2 e^{-\left(\frac{g_0}{v}\right)x}\Big|_{\kappa}^{0} \\
&= \frac{\alpha}{(\alpha+\beta)}\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\left(-\frac{v}{g_0}\right)^2.
\end{aligned}$$

Hence,

$$\int_{-\infty}^{0} xn_1(x)\,dx = \frac{\alpha}{(\alpha+\beta)\,l_a}\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\left(-\frac{v}{g_0}\right)^2. \tag{3.16}$$

Case 2: $0 < x \leq h$

$$\begin{aligned}
\textstyle\int_0^h xn_2\left(x\right)dx &= \textstyle\int_0^h \frac{\alpha}{(\alpha+\beta)} x\left(1 - e^{\left(\frac{\alpha+\beta}{2v}\right)\left(h^2-x^2\right)}\right)dx \\
&= \frac{\alpha}{(\alpha+\beta)} \textstyle\int_0^h x\left(1 - e^{\left(\frac{\alpha+\beta}{2v}\right)h^2} e^{\left(\frac{\alpha+\beta}{2v}\right)\left(-x^2\right)}\right)dx \\
&= \frac{\alpha}{(\alpha+\beta)} \textstyle\int_0^h \left(x - xe^{\left(\frac{\alpha+\beta}{2v}\right)h^2} e^{\left(\frac{\alpha+\beta}{2v}\right)\left(-x^2\right)}\right)dx \\
&= \frac{\alpha}{(\alpha+\beta)} \left(\frac{x^2}{2}|_0^h - e^{\left(\frac{\alpha+\beta}{2v}\right)h^2} \textstyle\int_0^h xe^{\left(\frac{\alpha+\beta}{2v}\right)\left(-x^2\right)}dx\right) \\
&= \frac{\alpha}{(\alpha+\beta)} \left(\frac{h^2}{2} - e^{\left(\frac{\alpha+\beta}{2v}\right)h^2} \left(-\left(\frac{v}{\alpha+\beta}\right)e^{\left(\frac{\alpha+\beta}{2v}\right)\left(-x^2\right)}\right)|_0^h\right) \\
&= \frac{\alpha}{(\alpha+\beta)} \left(\frac{h^2}{2} + \left(\frac{v}{\alpha+\beta}\right) - \left(\frac{v}{\alpha+\beta}\right)e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right).
\end{aligned}$$

Thus,

$$\int_0^h xn_2\left(x\right)dx = \frac{\alpha}{(\alpha+\beta)} \left(\frac{h^2}{2} + \left(\frac{v}{\alpha+\beta}\right) - \left(\frac{v}{\alpha+\beta}\right)e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)dx. \quad (3.17)$$

Case 3: $x \geq 0$

$$\int_h^\infty xn_3\left(x\right)dx = \int_h^\infty 0\,dx = 0.$$

Therefore,

$$\int_h^\infty xn_3\left(x\right)dx = 0. \quad (3.18)$$

Combining the solutions (3.16), (3.17), and (3.18), (3.15) becomes

$$
\begin{aligned}
F(t) &= \frac{mAsk}{2l}\left[\frac{\alpha}{(\alpha+\beta)}\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\left(-\frac{v}{g_0}\right)^2\right. \\
&+ \left.\frac{\alpha}{(\alpha+\beta)}\left(\frac{h^2}{2}+\left(\frac{v}{\alpha+\beta}\right)-\left(\frac{v}{\alpha+\beta}\right)e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\right] \\
&= \frac{mAsk\alpha}{2(\alpha+\beta)}\left[\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\left(-\frac{v}{g_0}\right)^2\right. \\
&+ \left.\left(\frac{h^2}{2}+\left(\frac{v}{\alpha+\beta}\right)\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\right)\right] \\
&= \frac{mAsk\alpha}{2(\alpha+\beta)}\left[\frac{h^2}{2}+\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\left(\frac{v}{\alpha+\beta}-\left(\frac{v}{g_0}\right)^2\right)\right].
\end{aligned}
$$

Hence,

$$
F(t)=\frac{mAsk\alpha}{2(\alpha+\beta)}\left[\frac{h^2}{2}+\left(1-e^{\left(\frac{\alpha+\beta}{2v}\right)h^2}\right)\left(\frac{v}{\alpha+\beta}-\left(\frac{v}{g_0}\right)^2\right)\right]. \qquad (3.19)
$$

3.3 Comparison of the Analytical Solution with Hill's curve

Now that we have derived an analytic formula (3.18) for the force generated in the muscle, we can use it to calculate the force for several different speeds of contraction. With a judicious choice of constants it is possible to reproduce A.V Hill's force-velocity curve [4, 2]. This is the same method that A.F. Huxley used to show that his model accurately simulated muscle contraction (Figure 3.1).

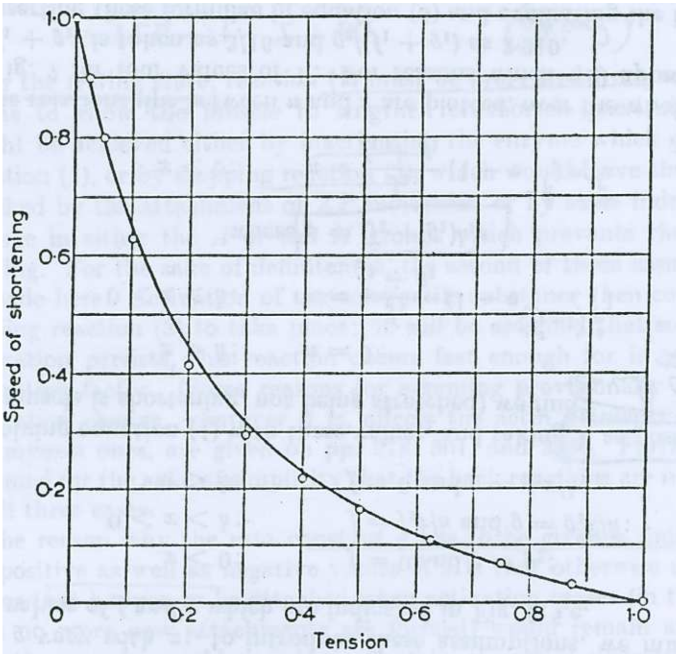

Figure 3.1: The relationship between speed of shortening and force. Circles correspond to the solutions to A.F Huxley's force equation; the straight line is Hill's characteristic equation (adapted from [2]).

3.4 The Analytical Solution of the Huxley-Zahalak Equation

The Huxley-Zahalak equation (2.5) can be solved analytically using the method of characteristics. This section reviews the method of characteristics and outlines the solution to the Huxley-Zahalak equation by this method.

Since the Huxley-Zahalak equation is formulated from the point of view of a moving observer on a particular A site, we can rewrite $n(x,t)$ as $n(x(t),t)$. Then, as in Section 2, we use the chain rule

$$\frac{Dn(x,t)}{Dt} = \frac{\partial n(x,t)}{\partial t} + \frac{dx}{dt}\frac{\partial n(x,t)}{\partial x} \tag{3.20}$$

where $\dfrac{\partial n(x,t)}{\partial dt}$ represents the change in $n(x,t)$ at the fixed point A and $\dfrac{dx}{dt}\dfrac{\partial n(x,t)}{\partial x}$ represents the change due to the fact that the A site is moving to a region of potentially different $n(x,t)$.

We also know that A moves with speed $\dfrac{dx}{dt} = v$, where $v < 0$ in contraction. Then we can replace the PDE by two ODEs

$$\frac{dx}{dt} = v, \tag{3.21}$$

$$\frac{dn}{d\gamma(t)} = (1 - n(t))f(\gamma(t)) - ng(\gamma(t)). \tag{3.22}$$

The solution of (3.21) by integration gives us the general equation of a family of curves. We call these curves *characteristics*:

$$x = vt + x_0 \tag{3.23}$$

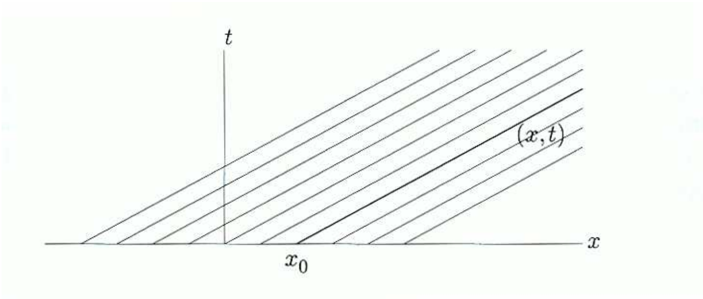

Figure 3.2: An example of characteristics. The solution is equal to $n(x_0, 0)$ along the curves. Note that these characteristics represent the case when $v > 0$, which is not so in our equation (adapted from [3]).

where x_0 is the solution on the initial manifold. This is more clearly shown by Figure 3.2. Integrating (3.22) and taking the continuity of the solution into account we are able to find that the solution n_p is

$$n_p(x_p+vt) = \begin{cases} 0 & \text{for } t < \dfrac{h-x_p}{v}, \\ \dfrac{\alpha}{(\alpha+\beta)\, l_a}\left[1 - e^{\left(\dfrac{\alpha+\beta}{2v}\right)\left(h^2-(x_p+vt)^2\right)}\right] & \text{for } \dfrac{h-x_p}{v} \le t < -\dfrac{x_p}{v}, \\ \dfrac{\alpha}{(\alpha+\beta)\, l_a}\left[1 - e^{\left(\dfrac{\alpha+\beta}{2v}\right)h^2}\right] e^{-\dfrac{g_0}{v}(x_p+vt)} & \text{for } -\dfrac{x_p}{v} \le t, \end{cases}$$

where n_p gives an expression for the solution along a particular characteristic curve [2]. This is actually the solution on the initial manifold, so for a given initial $n_0(s)$ profile we are able to derive a solution for any $n(x, t)$.

3.5 Numerical Methods

We noted above that the analytical solution is restricted to the case when the sliding velocity, v, is constant. It would be very valuable to have a solution for the case when v is not constant. One way to achieve this would be to solve the Huxley-Zahalak

PDE (2.5) using numerical methods. Although we did not do this for this thesis, we suggest two possible methods here.

The first is the *Upwinding Method of Lines (UML)* [8]. UML is a popular method for solving PDEs and is partly based on the method of characteristics. The idea behind the method of lines is to discretize one dimension (in our case, space), while leaving the other dimension (time) continuous. This way we obtain a system of coupled ODEs that we can solve using an appropriate software package [8]. *Upwinding* refers to the scheme we chose to discretize the space variable. In this case, because $v < 0$, we use a forward difference. Thus, the upwind scheme uses a two-point stencil, as shown in Figure 3.3.

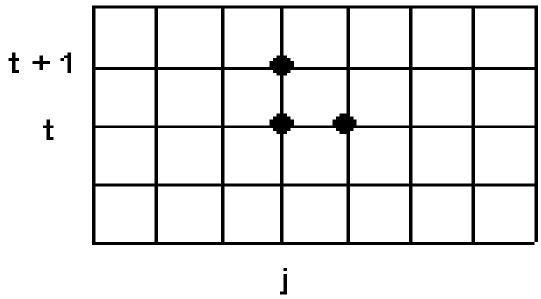

Figure 3.3: Graphic representation of the UML scheme (adapted from [8]).

Written explicitly the UML scheme is

$$\frac{dn_j(t)}{dt} = -v\frac{n_{j+1}(t) - n_j(t)}{\Delta x} + \left(\frac{1}{l_a} - n_j(t)\right) f_j - n_j(t) g_j, \quad j = 1, ..., J,$$

where J is the number of discrete points in the space variable and $f(x_j) = f_j$, $g(x_j) = g_j$.

One advantage of the upwind scheme is that it obeys the CFL condition [8]. The CFL condition, which for the PDE $n_t + vn_x = 0$ is $|v|\Delta t \leq \Delta x$, is a necessary requirement for convergence of the numerical solution. The CFL condition also ensures stability of the numerical solution when using the upwind method [8]. Note that because we are not solving $n_t + vn_x = 0$, the actual stability restriction on a numerical solution may be different then the stable CFL condition.

However, the UML introduces large amplitude errors [8]. This reduction in amplitude is why we also suggest a second method, known to more accurately preserve the amplitude of the wave over time.

This second method is called the *Lax-Wendroff* (LW) scheme [8]. LW is based on a quadratic interpolation using three points, and assuming straight characteristics with slope v [8], as shown in Figure 3.4.

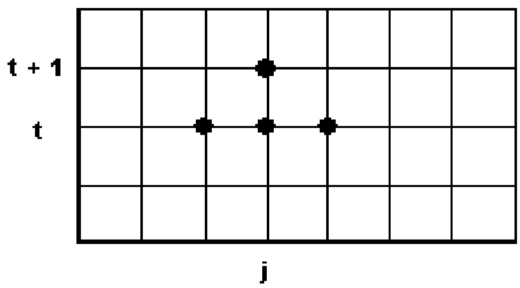

Figure 3.4: Graphic representation of the Lax-Wendroff scheme (adapted from [8]).

Traditionally, LW is used to solve hyperbolic conservation laws [8]. Adapting it to the Huxley-Zahalak equation, the scheme can be written as

$$n_j^{k+1} = \frac{1}{2}\nu(1+\nu)n_{j-1}^k + (1-\nu^2)n_j^k - \frac{1}{2}\nu(1-\nu)n_{j+1}^k + \left(\frac{1}{l_a} - n_j^k\right) f_j - n_j^k g_j, j = 1, ..., J,$$

where j is as above, $k = 1, ..., K$ represents the discretization of time, and $\nu = v\dfrac{\Delta x}{\Delta t}$. Here $n_j^k \approx n(j\Delta x, k\Delta t)$.

Lax-Wendroff is stable for any choice of ν that obeys the CFL condition [8]. Although LW better preserves the amplitude of the solution, it introduces a greater phase error than the UML scheme. A large phase error means that the solution is not simulating the movement of the wave at the correct speed. In addition, the LW scheme introduces spurious oscilations into the solution, particularly when the solution involves discontinuities [8].

In our case, the phase error introduced by LW may be less of an obstacle to interpreting the solution than the amplitude error introduced by UML. The lag in propagation of the solution could be taken into account during later force calculations, but the reduced amplitude of the distribution would dramatically change the force calculation if modelled over a sufficiently long time interval.

Chapter 4

Summary and Conclusion

The aim of this thesis was to present A.F. Huxley's model of muscle contraction, as well as the Huxley and the Huxley-Zahalak equations. These equations are based on A.F. Huxley's theory of muscle contraction and can be used as a first step toward calculating the force generated in a muscle during contraction. The second step involves Hooke's law of elasticity.

In order to set the stage, we began with a comprehensive review of the biochemical and physical structure of the muscle (Section 2.1). We then discussed the mechanism of muscle contraction, including A.F. Huxley's sliding filament model and crossbridge theory (Section 2.2). We proceeded by presenting the derivation of the Huxley equation

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

and relating $n(x)$ to the calculation of the force generated in the muscle (Section 2.3 and 2.4). We continued to build on the theory by introducing the Huxley-Zahalak equation

$$\frac{\partial n(x,t)}{\partial t} + v\frac{\partial n(x,t)}{\partial x} = \left[1 - n(x,t)\right] f(x) - n(x,t)g(x)$$

subject to periodic boundary conditions $n(-0.5l_a, t) = n(0.5l_a, t)$ and an initial condition $n(x, 0) = n_0(x)$ (Section 2.4). We concluded Chapter 2 with a dimensional analysis and definition of the biological constants.

Chapter 3 focused on solving these equations, resulting in the following analytical solution to the Huxley equation

$$n(x) = \begin{cases} 0 & \text{for } x > h, \\ \dfrac{\alpha}{(\alpha+\beta)} \left[1 - e^{\left(\frac{h(\alpha+\beta)}{sV}\right)\left(\frac{x^2}{h^2} - 1\right)} \right] & \text{for } 0 < x \leq h, \\ \dfrac{\alpha}{(\alpha+\beta)} \left[1 - e^{-\left(\frac{h(\alpha+\beta)}{sV}\right)} \right] e^{\frac{2g_0 x}{sV}} & \text{for } x \leq 0. \end{cases}$$

where we are able to calculate total force

$$F(t) = \frac{mAsk\alpha}{2(\alpha+\beta)} \left[\frac{h^2}{2} + \left(1 - e^{\left(\frac{\alpha+\beta}{2v}\right) h^2} \right) \left(\frac{v}{\alpha+\beta} - \left(\frac{v}{g_0} \right)^2 \right) \right],$$

and the Huxley-Zahalak equation

$$n_p(x_p+vt) = \begin{cases} 0 & \text{for } t < \dfrac{h - x_p}{v}, \\ \dfrac{\alpha}{(\alpha+\beta)\, l_a} \left[1 - e^{\left(\frac{\alpha+\beta}{2v}\right)\left(h^2 - (x_p+vt)^2\right)} \right] & \text{for } \dfrac{h - x_p}{v} \leq t < -\dfrac{x_p}{v}, \\ \dfrac{\alpha}{(\alpha+\beta)\, l_a} \left[1 - e^{\left(\frac{\alpha+\beta}{2v}\right) h^2} \right] e^{-\frac{g_0}{v}(x_p+vt)} & \text{for } -\dfrac{x_p}{v} \leq t. \end{cases}$$

In addition, two numerical methods, the Upwinding Method of Lines and the Lax-Wendroff Scheme, were introduced as possible methods for solving the equations when v was not constant.

In the future it would be valuable to develop an accurate and stable numerical solution that would enable us to solve the Huxley-Zahalak equation for non-constant v. In addition, although the Huxley model was originally based on the properties of striated muscle, it is our understanding that it is possible to modify the model so that could be used to model smooth muscle contraction. These modifications would produce a powerful tool which could be used by the medical community to study the contraction properties of smooth muscle in various areas of the body. An example of particular interest to our collaborators involves determining the differences between the contraction behavior of airway smooth muscle in asthmatic patients and healthy patients.

In conclusion, the Huxley model is a powerful and time-tested model that still holds a prominent place in current muscle modelling efforts.

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