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Mechanics of Molecular Motor and Application Issues

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ABSTRACT : *This paper deals with the mechanics of biomolecular motor and its application issues. First, the skeleton muscle anatomy has been reviewed. Next, the mathematical model has been formulated to describe crossbridge interactions in a sarcomere. Then, we have demonstrated how molecular motion on the order of nanometer distances is converted into the macroscopic movements. Further, the simulation study has been presented to discuss the design issues of molecular scale actuators. Finally, the results show that the presented motor theory could be utilized in various forms of nanomachines.*

KEY WORDS : crossbridge, molecular motion, skeleton muscle, myosin-actin, muscle contraction, force-velocity.

1. Introduction

A striking feature of living cells is their ability to generate motion and forces. These movements and forces are generated on the molecular level by protein molecules (or biomolecular motors) that are driven by chemical reactions consuming adenosine triphosphate (ATP)[8]. The biomolecular motors are proteins, or structures of multiple proteins in the interior of a living cell. Recent studies have shown that they have load carrying velocities of a few hundred nanometers per second, and are capable of generating mechanical forces amounting to a few piconewtons[1]. In addition, the protein complexes are responsible for muscle contraction, intracellular transport of materials and vesicles, and cell mobility[2].

Nowadays, technology is reaching into ever smaller dimensions. Nanotechnology, a field bridging science and technology, was born as result of increasingly sophisticated manipulation of small objects featuring dimensions from several nanometers to a few microns. To power tiny machines in nanotechnology, we can begin to find the solutions that already exist for nanometer or molecular scale biomotors, rather than following miniaturization process through semiconductor technology. Further, the engineers' breakthrough is in integrating a biomolecular motor with a fabricated device at the nano-scale instead of using man-made motors. Integrating biomotors with nano-scale devices enables the use of ATP as an energy source to yield energy efficient systems capable of operating as pumps, valves, and vehicles. Thus, most forms of mechanical movement in the nano-scale world could be powered by tiny protein machines known as biomolecular motors.

A biological muscle physiology literature contains numerous reports identifying the relationship between force and length during muscle contractions[3][5]. Interest in the actin-based myosin motor (or actomyosin) has been increased in recent years. As stated before, it is responsible for muscle contraction and intracellular transport. Further this actomyosin can be modeled as an actuator whose output force is a function of length, velocity, and level of activation[4][6][7]. In fact, the applications of muscle molecular motors within an engineering system can take several forms. The aim of this research is to elucidate the mechanism of energy transduce by the molecular motor in muscle.

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2. Mathematical Modelling of Molecular Motor

Molecular motors are remarkable cellular machines that convert chemical energy generated by the hydrolysis of ATP into mechanical work. Three different types of muscle tissues exist in the body; skeletal, smooth, and cardiac. Skeletal muscle is long, striated cells with multiple nuclei and it comprises the largest single organ of the body. Recently, there have been major advances in the understanding of how skeletal muscle develops force[1]. Muscle fibers (diameter: 50~70㎛) are just the building blocks for whole muscles, and are made up of bundles of contractile muscle called myofibrils. In addition, each myofibril (diameter:1~2㎛) is arranged in smaller repeating units called sarcomeres in series and parallel thin filaments of actin (length: 1.0~1.1㎛) and thick filaments of myosin (length: 1.5~1.6㎛). As depicted in Fig. 1, each sarcomere (length:≈2.5㎛) consists of one set of thick myosin filaments and two sets of thin actin filaments. The protein myosin is a macromolecular complex and is made up of a polypeptide chain with a globular head, which constitutes the crossbridge. Thus, these thick and thin filaments are linked at regular intervals by crossbridges made from extensions of the myosin molecules (length:≈160㎚, mass: 530kDa). Under low salt conditions, the actin (mass: 42 kDa) can be isolated as a soluble protein and is roughly dumb-bell shaped, which constitutes the thin filament in muscle.

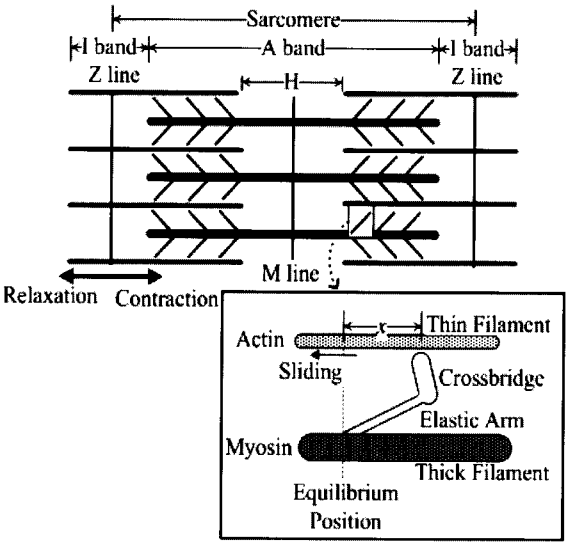

Fig. 1 Schematic representation of sarcomere and crossbridge model in skeletal muscle.

During the contraction of muscle, the thin filaments are pulled in over the thick filaments so that each sarcomere shortens and generates forces[5]. Each crossbridge is an independent force generator (or actuator) which interacts with a thin filament and pulls it towards the center of the sarcomere. The crossbridge then detaches from the thin filament and has to be reprimed by ATP before it can go through another cycle of force generation, like a single stroke of a rowing machine. In the paper, the modeling of crossbridge dynamics is based on the assumption of rigid myosin and actin filaments for simplicity.

At first, we consider some macroscopic aspects of how muscle works. An important property of biological muscle is the specific relationship between force generated by muscle and speed at which a stimulated muscle contracts under a given load[3].

The muscle velocity during shortening (or lengthening) is measured and then plotted against the resistive force (or load). As the load increases, the velocity of shortening decreases. This is intuitively obvious as you lift a light load compared to a heavy load; the light load can be moved much more quickly.

The generic form of this force-velocity relation, for each sarcomere in a muscle, is empirically given by the following hyperbolic function:

$$F=\frac{\beta F_I-\alpha V}{V+\beta} \tag{1}$$

where V is the shortening velocity of thin filament relative to the thick filament, F is the variable load describing the force generated by a muscle, F_I is the particular load at which the muscle doesn't change length (or isometric muscle force), α and β are empirical constants that are used to match the shape of the hyperbolic curve to the experimental data. When the velocity V is zero, then $F=F_I$. From Eq. (1), the maximum velocity of shortening occurring at $F=0$ leads to $V_m=\beta F_I/\alpha$. Furthermore, the normalized form of Eq. (1) can be described by

$$V_{NV}=\frac{1-F_{NF}}{1+\frac{F_{NF}}{z}}, \text{ with } z=\frac{\alpha}{F_I}=\frac{\beta}{V_m}$$

(2)

where V_{NV} and F_{NF} are a normalized velocity ($V_{NV}=V/V_m$) and a force ($F_{NF}=F/F_I$), respectively. Then, the normalized muscle power output is given by

$$H_{NP}=F_{NF}\cdot V_{NV}=\frac{zF_{NF}(1-F_{NF})}{z+F_{NF}} \tag{3}$$

One of the simplest models of muscle fibers, from a mechanical standpoint, is the two component model; contractile element(CE) where it all happening actin-myosin crossbridges, and series elastic component(SE) where elastic tissues in series with contractile element behaves like spring.

The length of whole muscle tendon is given by

$$L=l_{CE}+l_{SE} \tag{4}$$

where l_{CE} represents the length of contractile element, and l_{SE} is the length of series elastic element, i.e., $l_{SE}=x$ (also see Fig. 1).

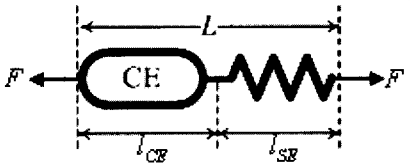

Fig. 2 Active state model of muscle contraction

The velocity of contraction for each sarcomere is given by

$$v=-\frac{dl_{CE}}{dt}=-\frac{dx}{dt} \tag{5}$$

where v is related to the load F by the force-velocity relationship given in (1).

Since the whole muscle is made up with numbers of sarcomeres (n_s) connected in series, the shortening velocity at which the contractile element is contracting is described by $V=n_sV$. Note that because the elements are in series they experience the same force. Assume that the load on the elastic element is a function of x, then $F=F(l_{SE})=F(x)$. Using the chain rule and the force-velocity relation, we can obtain time dependence of F as follows:

$$\frac{dF(x)}{dt}=\frac{dF}{dx}[\frac{dL}{dt}+v]$$
$$=k_s[\frac{dL}{dt}+\frac{\beta(F_I-F)}{F+\alpha}] \tag{6}$$

If we assume that the elastic element is linear, then $F(x)=k_s(x-x_0)$, where k_s is the stiffness of spring-like crossbridge, and x_0 is the resting length.

Now, we consider some microscopic aspects of how muscle works. We start our analysis by considering a large group of coupled independent motors, a situation typical for the actin-myosin motor in muscles. Let n_c denote the number motors (either attached or detached) positioned with their roots on the stiff thick myosin filament. As shown in Fig. 1, the actin binding site on the molecular track of thin actin filament is located distance x from crossbridge equilibrium position ($x=0$) in a sarcomere. The free energy of an attached crossbridge state, $U(x)$, is determined by the elastic energy stored in the extension of the elastic component of the myosin head. The force, $f(x)$, exerted by the extension of the elastic component of a single crossbridge is related to its extension such that, at constant concentration of ATP

$$f(x)=\frac{\partial U(x)}{\partial x} \tag{7}$$

where the force is developed in compliant corssbridge. According to Huxley's model[5], the crossbridge is described as a Newtonian spring, and the generated force depends on the displacement of the crossbridge from its equilibrium position ($x=0$). Various formula for $f(x)$ can be introduced, but for now we note that $f(0)=0$, since $x=0$ is the equilibrium configuration of an attached crossbridge, and that $f(x)$ is an increasing function of x. Deformation of a myosin head can be

described in terms of a potential energy, $U(x) = (1/2)k_s(x-x_0)^2$. After attaching to or detaching from the actin filament, a conformational change in the myosin head takes place. $x = 0$ is the location where the crossbridge and the actin binding site are exactly aligned and there is no stress. If $x > 0$ the force is contractile. If $x < 0$ the force opposes contraction. The ATP is hydrolyzed when the myosin is either weakly attached to actin or is detached. To generate force and mechanical work, a myosin head must be attached to actin in a state in which the Gibbs free energy decreases as the actin traverses through some distance, known as the power stroke. The amount of mechanical work that can be performed in these states is equal to the change in the Gibbs free energy (ΔU). The hydrolysis of ATP, with the release of ADP and inorganic phosphate (P_i), is known to be the power source for many molecular motors. The chemical reaction with the free energy change of one reaction cycle is described by

$$ATP \xrightarrow[ATPase]{Actomyosin} ADP + P_i,$$
$$\Delta U = \Delta U^0 - RT \ln\left(\frac{[ATP]}{[ADP][P_i]}\right) \quad (8)$$

where ΔU^0 is the standard reaction free energy, R is the universal gas constant, and T is the absolute temperature (K). All concentrations (represented in $[\circ]$) are defined as having molar units. According to Eq. (8), ΔU is approximately $-25\,RT$ (where $1RT \approx 4.1$ pN-nm) at standard condition, and the corresponding displacement is up to ~ 5 nm. In fact, the power/weight ratio is almost an automobile engine in macroscopic world.

In this paper, a simplified reaction mechanism has only 2 states; unbound (or detached) and strongly bound (or attached). The transitions between the two states occur stochastically with characteristic times $\tau_A(x)$ and $\tau_D(x)$. We assume that the rate parameters for attachment ($\tau_A^{-1}(x)$) and detachment ($\tau_D^{-1}(x)$) are functions of the displacement x. Two-state kinetic model with a detached state (D) and an attached state (A) of crossbridges is shown in Fig. 3.

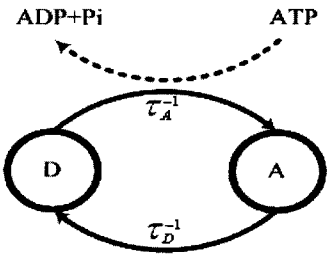

Fig. 3 Schematic diagram of two-state crossbridge reaction cycle

The crossbridge dynamics of attachment-detachment is described by a first-order kinetics. $p(x,t)$ is the distribution function representing the fraction of attached crossbridges with displacement x at time t. In fact, the force developed by the group of motors is proportional to $p(x,t)$ with $p(x,t) \geq 0$. Then, the velocity fluctuations resulting from the stochastic operation of a single motor can be neglected.

Consider the population of crossbridge binding sites throughout the muscle which lie in some interval. At time t, the fraction of crossbridges attached over the interval $x_1 \leq x \leq x_2$ is given by

$$\overline{P}[x_1 \leq x \leq x_2] = \int_{x_1}^{x_2} p(x,t)\,dx \quad (9)$$

Then, total fraction of crossbridges that are attached is given by

$$P = \int_{-\infty}^{+\infty} p(x,t)\,dx < 1 \quad (10)$$

A crossbridge is compliant with a restoring force that is a function of how far it is stretched. Deformation of a head can be described in terms of a potential energy, $U(x)$. Then, the force produced by the group of motors is given by

$$F = n_c \int_{-\infty}^{+\infty} \frac{\partial U(x)}{\partial x} p(x,t)\,dx \quad (11)$$

Using the relation in Eq. (7), the total force exerted by the

muscle is

$$F = n_c \int_{-\infty}^{+\infty} f(x)p(x, t)dx \tag{12}$$

From Eq. (12), the force is proportional to restoring force and number of attached crossbridges. At large velocities $p(x, t)$ has small amplitudes so the force is small.
Using conservation law for the fraction of bound crossbridges, the distribution of attached crossbridges obeys the following partial differential equation

$$\frac{d}{dt}\int_a^b p(\xi, t)d\xi = v[p(b, t) - p(a, t)] + (1-P)\int_a^b \frac{d\xi}{\tau_A(\xi)} - \int_a^b \frac{p(\xi, t)}{\tau_D(\xi)}d\xi \tag{13}$$

Now, differentiating with respect to x along with replacing b by x leads to

$$\frac{\partial p(x, t)}{\partial t} = \frac{1-P}{\tau_A(x)} - \frac{p(x, t)}{\tau_D(x)} + v(t)\frac{\partial p(x, t)}{\partial x} \tag{14}$$

where $v(t)$ stands for the shortening speed when it is positive, and lengthening when it is negative. Note that the common factor n_c has been cancelled in (13).
For clarity, the rate parameters are assumed to be constant. Under steady-state isotonic condition (no time dependence) $\partial p/\partial t = 0$, the steady distribution in Eq. (14) is described in the ordinary differential equation of the form

$$v\frac{dp(x)}{dx} = \frac{p(x)}{\tau_D} \tag{15}$$

Then we obtain

$$p(x) = p(b)\exp\left[\frac{x-b}{v\tau_D}\right] \tag{16}$$

where the initial condition $p(b)$ can be determined from Eq. (13). It turns out that

$$p(b) = \frac{1-P}{\tau_A v}, \text{ with } P = \frac{\tau_D}{\tau_A + \tau_D} \tag{17}$$

Thus we obtain

$$p(x) = \frac{1}{v(\tau_A + \tau_D)}\exp\left[\frac{(x-b)}{v\tau_D}\right], \; x < b \tag{18}$$

Then

$$F = \frac{n_c}{v(\tau_A + \tau_D)}\int_{-\infty}^{b} f(x)\exp\left[\frac{(x-b)}{v\tau_D}\right]dx \tag{19}$$

Since the force is largest at small velocities, in fact, at $v = 0$, the isometric steady-state force is described by

$$F = n_c \int_{-\infty}^{\infty} f(x)\frac{\tau_D(x)}{\tau_A(x) + \tau_D(x)}dx \tag{20}$$

If the amount of time the crossbridge is near a binding site is small, then binding is less likely. A greater number of crossbridges are carried into the $x < 0$ region, and thus generate a force opposed to contraction. When the number of crossbridges with $x < 0$ is equal to $x > 0$, the maximum velocity of shortening is reached. The force on the ends of the muscle if all crossbridges (n_c) are attached and had displacement x would be $n_c f(x)$. Since the whole muscle is made up with numbers of sarcomeres (n_s) connected in series, the shorting velocity is described by $V = n_s v$. The rate of attachment of new crossbridges is proportional to the number of crossbridges that are available for attachment at any given time. Then the rate of formation of new crossbridges is $n_c(1-P)/\tau_A$, where the constant $1/\tau_A$ is called the rate constant for attachment (with units of 1/time). Assuming that the rate of detachement of crossbridges is independent of their configuration, the rate that crossbridges break is proportional to the number of attached crossbridges. Then the rate at which the crossbridges break is

$n_c \int_a^b p(x)dx/\tau_D$.

Then total rate of detachment is

$$D = n_c P/\tau_D \tag{21}$$

An experiment is performed where a muscle is held at a fixed tension until it reaches its isometric length (no longer contracting). The tension is quickly reduced by reducing the load, F.

3. Numerical Simulations

In this section, we present simulation results for muscle actuator. Table 1 represents the force-velocity data from the muscle physiology literature[6].

Table 1 Force-velocity data for muscles

Model	α/F_I	F_I [N]	β/V_m	V_m [mm/s]
Rat	0.356	4.30	0.38	144
Frog	0.27	0.67	0.28	42
Cat	0.27	0.18	0.30	191
Skeletal muscle	0.224	-	0.224	-
Human A	0.81	200	0.81	1115
Human B	0.41	3000	0.39	756
Human C	0.41	2430	0.41	780
Human D	0.12	-	0.12	-

In this study, a reasonable envelope for the shape parameter (z) is described by $0.15 \le z \le 0.55$. as illustrated in Table 1. Based on Eqs (1) and (2), the shapes of force-velocity (-power) curves are reasonably well (but not uniquely) described in Fig. 4.

It should be noted that H_{NP} has a maximum when the load is about one third of F_I. In bicycling, for instance, we may have to choose the gear ratio giving our muscles a load close to this point, to achieve the highest performance.

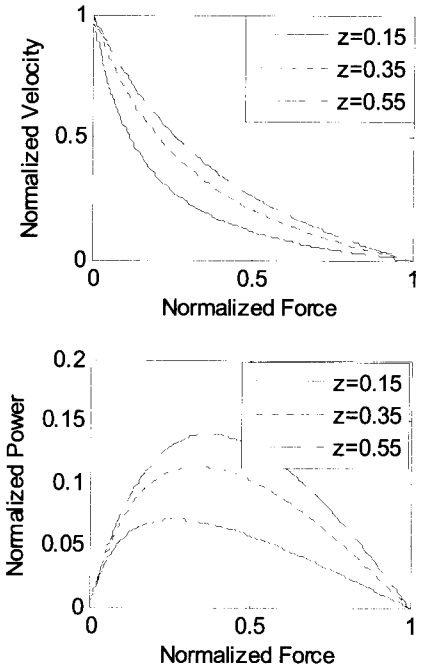

Fig. 4 Dimensionless relationships among force-velocity (upper) and power (lower) of muscle.

Fig. 5 shows the muscle lengths and force developed during isometric contraction. In the study, the normalized lengths have been utilized for convenience ($l_{CE} = 0.4L$ and $l_{SE} = 0.6$). The changes in length and force are described when a sudden decrease of length ($L \rightarrow 0.9L$ at 2 sec.) is imposed on an muscle fiber during contraction with $dL/dt < 0$. Since the total length remains constant, the contractile element can only be shorten by stretching the elastic element. Note that the contractile element has a limited maximal shortening velocity. The drop is absorbed primary by the elastic element and there exists a immediate decrease in muscle force. Then, the force recovers as the contractile element stretches again the elastic element.

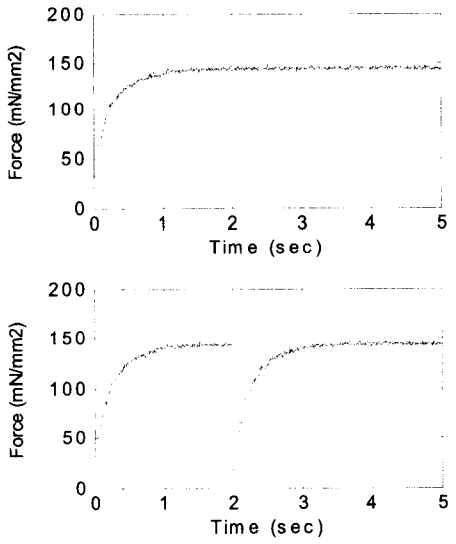

Fig. 5 Force and length responses: constant length (upper) and a step decrease in length (lower)

4. Conclusions

There has been tremendous interest in understanding molecular motor to incorporate them into novel devices. First, the dynamics of crossbridge model has been presented to describe the muscle actuator theory. The force-velocity relation has been analyzed during isometric contraction. Furthermore, the force-length response has been presented due to sudden changes in lengths of contractile element and series elastic element. Then, we have shown some macroscopic and microscopic aspects of how muscle works. Finally, the actomyosin model developed in the paper can be used in various forms of molecular scale actuators.

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