Markov process of muscle motors

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Abstract

We study a Markov random process describing muscle molecular motor behaviour. Every motor is either bound up with a thin filament or unbound. In the bound state the motor creates a force proportional to its displacement from the neutral position. In both states the motor spends an exponential time depending on the state. The thin filament moves at a velocity proportional to the average of all displacements of all motors.

We assume that the time which a motor stays in the bound state does not depend on its displacement. Then one can find an exact solution of a nonlinear equation appearing in the limit of an infinite number of motors.

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1. Introduction

Recent progress in molecular motors studies brought a wave of new models and methods in theoretical considerations. The tools involved are spread from biochemistry and biophysics to mathematics and probability theory. As examples, we would like to mention works [1–3,4,6]. This list contains only some papers from different areas.

We concentrate here on the formal aspects of the problem and, more precisely, we describe a probabilistic model of the muscle motor which leads to a nonlinear Markov process. The latter notion was introduced by Mc-Kean [5]. Compared with the usual case, in a nonlinear Markov process transition probabilities are related to a nonlinear equation. With respect to probability theory, nonlinear Markov processes play a main role in the modelling. Because of nonlinearity, the model appears to have many effects atypical of usual Markov processes that give possibilities either to explain experimentally observed properties of the motors or to predict new ones. Following Howard’s book [7] we shall distinguish two classes of molecular motors: processive motors and non-processive ones. The distinction between these classes
leads to different types of models; however, the differences are relative. Perhaps one can construct a general model yielding all features of both sorts of motors. We consider here a model of non-processive motors which concerns motors involved in muscle activity.

The model is described in section 2. We study the model with explicitly broken spatial and time-reversal symmetry. We do not study the physical origin of this symmetry breaking. The nonlinearity appears in section 2.2.3 in the thermodynamical limit. The nonlinearity is revealed in nonlinear equations (13) for the velocity of the thin filament and the mean number of active motors.

In section 3 we discuss the behaviour of the system in dependence on the parameters of the model.

Section 4 is devoted to a brief discussion on possible developments of the proposed scheme. Namely, we discuss models with a non-harmonic force. Very briefly in section 4.2 we discuss opportunities of construction of multi-dimensional versions of similar models. Generalizations discussed in section 4 are more likely a sort of program for further studies.

2. Model

2.1. Informal description

All components of a molecular motor complex are protein molecules. As can be extracted from the biochemical and biophysical literature, there are several kinds of bio-molecular motors involved in different types of movements. It is possible to think of the motor as a molecular chain of some length whose ends can get stuck to other molecules. The motor is the main moving part of the whole complex.

In this work we study the motors producing muscle motions. Those motors are fixed at one of the ends of a long protein molecule called the thick filament. The thick filament is fastened in a cell. Thus, the motors do not move with respect to the cell they are located in. The second end of the motors may be attached or not attached to a thin filament, another long molecule in the cell disposed parallel to the thick filament. If both ends of a motor are attached then the motor can cause a tension acting on the thin filament. This tension is the cause of the thin filament motion, which is the ultimate goal of this device. Together with a thin string the ends of all motors attached to it move.

The binding to and unbinding from the thin filament of any motor are random. When binding a motor chooses a point on the thin filament to attach randomly. The tension the motor creates is defined by a displacement value between the two ends of the motor. Therefore, all bounded motors create different tensions. It is common to take the velocity of the thin filament moving proportional to the average of all bounded filament tensions.

Thus, the full picture of the work of the device is represented as follows. There are two parallel strings: thick and thin. Also there are motors attached to the thick filament at some distance from each other. At each moment of time some random number of motors are attached to the thin filament. Each of the motors creates some force in a direction and size equal to the displacement between the basis of the motor in the thick filament and the place of its attachment to the thin filament. The thin filament moves in the direction corresponding to the sign of the sum of these forces. The speed of the thin filament movement is proportional to the average force. In the limit of a large number of motors this dependence corresponds to mean-field type models.

We consider that the thin (as well as thick) filament represents a rigid rod, and we do not consider its possible deformations. Note that the number of motors working with one pair of thin–thick filaments can reach several millions. In such a dense network of motors distances
between any two motors on the thin filament are small. Therefore, it is possible to neglect deformation of the thin filament between points of attachments of the next motors participating in the work. Apparently a global deformation of the thin string is possible. We also do not consider such an opportunity.

Before going on to the formal descriptions we would like to briefly discuss some peculiarities of the proposed model. The main feature of the model is that the functional parameters of the model can be found. The functional parameters are the correlation function of the motors (particles) and the velocity of the thin filament. The cause of that is that those two parameters can be connected by a system of two differential equations (13). The explicit solution of the system allows one to evaluate an optimal velocity of the thin filament which depends on the unbound rate of the motors (16).

The proposed model is rather universal and the model or its modifications can be used for other physical or biological mechanisms. Therefore, in section 4 we briefly discuss some modifications of the model. The main feature of the modified models is that the correlation function and the velocity are connected by a finite system of differential equations (not necessarily two).

2.2. Formal description

The formalization of the muscle motor construction informally described above can be done in the following way. We introduce a random process of interacting particles with a non-local interaction. Each particle represents a motor. All particles are numbered by points from $\mathbb{Z}$.

2.2.1. One motor. Let us start with a random process $\zeta_k(t)$ describing the binding and unbinding process for the particle located at $k \in \mathbb{Z}$. The state space is the two-point set $D = \{0, 1\}$, where 0 means the unbinding and 1 means the binding particle state. Then the infinitesimal operator of $\zeta_k(t)$ is the following $2 \times 2$ matrix:

$$L_k^D = \begin{pmatrix} -c_b & c_b \\ c_u & -c_u \end{pmatrix},$$

where $Pr(\zeta_k(t) = 1/\zeta_k(0) = 0) = c_b t + o(t)$ and $Pr(\zeta_k(t) = 0/\zeta_k(0) = 1) = c_u t + o(t)$.

Then the probability $P_k(t)$ of the $k$th motor to be unbound at the time $t$ satisfies the equation

$$\frac{dP_k(t)}{dt} = -c_b P_k(t) + c_u (1 - P_k(t)), \quad (1)$$

which gives in the steady state

$$P_k = \frac{c_u}{c_b + c_u}. \quad (2)$$

Recall that all particles are permanently attached to the thick filament. One can consider that points of attachments form a one-dimensional lattice. However, the dynamics of the motor is defined only by a displacement between points of attachments of a particle to thin and thick filaments. Therefore, the state space $\mathcal{X}$ of the $k$th particle consists of pairs $(z, \epsilon)$ where $z \in \mathbb{R}$ is a displacement if $\epsilon = 1$ and $z = 0$ if $\epsilon = 0$. As before, the parameter $\epsilon$ indicates the bounded (if $\epsilon = 1$) and unbounded (if $\epsilon = 0$) positions of the particle. We define a random process $\xi_k(t)$ describing binding and unbinding actions and the displacement when binding, including the deterministic moving of a single particle.

Let $b(x)$ be a distribution density such that $\int x b(x) \, dx > 0$. This condition explicitly breaks spatial and time-reversal symmetry.
The infinitesimal operator of the process $\xi_k(t)$ defining the behaviour of the $k$th particle is

$$L_k f(x, \varepsilon) = c_b \left[ \int b(z) f(z, 1) \, dz - f(0, 0) \right] (1 - \varepsilon)$$

$$- \kappa x \frac{d}{dx} f(x, \varepsilon) \varepsilon + c_u \left[ f(0, 0) - f(x, 1) \right] \varepsilon. \quad (3)$$

Now in (3) the constant $c_b > 0$ is the rate at which the particle jumps to a point of $\mathbb{R} \times \{1\}$ from the state $(0, 0)$, that is $\Pr \left( \xi_k(t) \in \mathbb{R} \times \{1\} / \xi_k = (0, 0) \right) = c_b t + o(t)$. The constant $c_u > 0$ is the rate at which the particle jumps to $(0, 0)$ from any point in $\mathbb{R} \times \{1\}$. This means that the rate of unbinding does not depend on the point $x \in \mathbb{R}$ where the particle was attached at the unbinding moment. The function $b(x)$ is the probability density of the particle to bind at the point $x$ if the particle was at $(0, 0)$. Here $x$ is the displacement of the particle with respect to its neutral position. The constant $\kappa$ is positive. It can be seen from the second term of the sum in (3) that when the particle is on $\mathbb{R}$, that is $\varepsilon = 1$, then it is moving to the point 0 with velocity proportional to $x$. Thus we suppose (contrary to Newton but typically for biology) that the velocity is proportional to the force.

For the density $p_k(x, t)$ of the $k$th particle to be on $\mathbb{R}$ (to be bound) we obtain the following Kolmogorov equation:

$$\frac{\partial p_k(x, t)}{\partial t} = c_b b(x) p_k(t) + \kappa \frac{\partial}{\partial x} \left[ x p_k(x, t) \right] - c_u p_k(x, t), \quad (4)$$

where $P_k(t) = 1 - \int p_k(x, t) \, dx$. The probability $P_k(t)$ to be unbound satisfies (1).

2.2.2. Finite system of motors. Next we introduce the interaction between the particles. We cannot express the interaction in a Hamiltonian form. Instead we introduce a deterministic dynamics of all bound particles such that particle dynamics is highly correlated with each other. Moreover all particles are moving with the same velocity. To be more precise consider all particles in the interval $[-N, N] \subset \mathbb{Z}$ and the configuration space $\Omega_N = \{[-N, N] \}^\varepsilon$ of all particles in $[-N, N]$. The space $\Omega_N$ is a disjoint union $\bigcup_{x=-N,...,N} \Omega_{x,-N,...,N}$ of the sets $\Omega_{-N,...,N} = \prod_{i=-N}^{N} \mathbb{R}^{\varepsilon}$. We can consider any probability distribution on $\Omega_N$ as a collection of measures on spaces $\Omega_{x,-N,...,N}$.

The generator of the process involving all particles from $[-N, N]$ is

$$L_{[-N,N]} f((x_k, \varepsilon_k), k = -N, ..., N)$$

$$= c_b \sum_{k=-N}^{N} \left[ \int b(z) f \left( \ldots, (x_{k-1}, \varepsilon_{k-1}), (z, 1), (x_{k+1}, \varepsilon_{k+1}), \ldots \right) \, dz - f((x_i, \varepsilon_i), i = -N, ..., N) \right] (1 - \varepsilon_k)$$

$$+ c_u \sum_{k=-N}^{N} \left[ f \left( \ldots, (x_{k-1}, \varepsilon_{k-1}), (0, 0), (x_{k+1}, \varepsilon_{k+1}), \ldots \right) - f((x_i, \varepsilon_i), i = -N, ..., N) \right] \varepsilon_k$$

$$+ v_N \sum_{k=-N}^{N} \frac{\partial}{\partial x_k} f((x_i, \varepsilon_i), i = -N, ..., N) \varepsilon_k. \quad (5)$$
where
\[ v_N = -\lambda \frac{1}{2N + 1} \sum_{k=-N}^{N} x_k \varepsilon_k + F. \]

The first term in the velocity expression of \( v_N \) is an average of all speeds of all particles. The term \( F \) means the velocity which an external force adds to the common velocity \( \tilde{v}_N = -\lambda \frac{1}{2N+1} \sum_{k=-N}^{N} x_k \varepsilon_k \) of all particles.

Thus, all particles from the group working at any moment, i.e. connected to the thin filament, move with the same speed \( v_N \). This speed is kept until one of two possible events happens. Either a new particle joins the group of already working ones, i.e. is bound to a thin filament. This event is described by the first term in (5). Or one of the working motors stops its work and is unbound from a thin filament. This event is described by the second term in (5). Obviously, when any of these events occurs, the average speed \( v_N \) of a thin filament changes.

Further, we use the following notation. Let \( (\varepsilon_{-N}, \ldots, \varepsilon_{N}) \) be fixed. Then \( M_0 = \{ i : -N \leq i \leq N, \varepsilon_i = 0 \} \) and \( M^1 = (M^0)^c = \{ i : -N \leq i \leq N, \varepsilon_i = 1 \} \).

From now on we shall denote the vector \( ((x_k, \varepsilon_k), k = -N, \ldots, N) \) by \( X \) called configuration.

For a configuration \( X = ((x_k, \varepsilon_k), k = -N, \ldots, N) \) and \( i \in M^1 \) define the configuration \( u_i X \) for which the pair \( (x_i, 1) \) is substituted by \( (0, 0) \); for \( i \in M^0 \) and \( x \in \mathbb{R} \) define \( b_i^X \) as the configuration for which \( (0, \varepsilon_i = 0) \) is substituted by \( (x, 1) \).

Let \( p^N(X, t) \) be the measure density of all bound motors to be at the points defined by \( X \) at the time moment \( t \). Then \( p^N(X, t) \) satisfies the equation

\[
\frac{\partial p^N(X, t)}{\partial t} + \sum_{i=-N}^{N} \frac{\partial}{\partial x_i} [\varepsilon_i v_N p^N(X, t)] = c_b \sum_{i=-N}^{N} \varepsilon_i b(x_i) p^N(u_i X, t) + c_u \sum_{i=-N}^{N} (1 - \varepsilon_i) \int p^N(b_i^X, t) \, dx \\
- \left[ c_u \sum_{i=-N}^{N} \varepsilon_i + c_b \sum_{i=-N}^{N} (1 - \varepsilon_i) \right] p^N(X, t).
\]

2.2.3. Infinite systems of motors. Thermodynamical limit. We are interested in the behaviour of the motor system for a large number of motors which formally corresponds to the limit \( N \to \infty \). In this limit as for any mean-field model we substitute the force by its expectation value, i.e. \( v_N \) (6) by

\[ v = -\lambda \frac{1}{2N + 1} \sum_{i=-N}^{N} x p_i^N(x, t) \, dx + F. \]

This dependence of the velocity \( v \) on the distribution corresponds to the notion of the nonlinear Markov process as a process with distribution-dependent generator [5]. For such a process (7) becomes nonlinear due to the dependence of \( v \) on the unknown distribution \( p^N \).

Plugging \( v \) into (7) we get the nonlinear equation corresponding to the nonlinear Markov process describing interacting motors.
Let us denote by
\[ \nu_X(dx) = \frac{1}{2N + 1} \sum_{i=-N}^{N} \epsilon_i \delta_{x_i}(dx) \] (9)
the random measure describing the motor distribution on the thin filament. The expectation of this random measure is called the first correlation measure and its density is called the first correlation function, \( n(x, t) \). It is evident that
\[ n(x, t) = \frac{1}{2N + 1} \sum_{k=-N}^{N} p_k^N(x, t). \] (10)

For the nonlinear Markov process defined above the first correlation function \( n(x, t) \) satisfies the equation
\[ \frac{\partial n(x, t)}{\partial t} + v \frac{\partial n(x, t)}{\partial x} = c_{bb}(1 - N(t)) - c_en(x, t), \] (11)
where \( N(t) = \int n(x, t) \, dx \) and \( v \) as above is
\[ v = -\frac{1}{kappa_1} \int x n(x, t) \, dx + F. \] (12)

It follows from (11) that \( N(t) \) and \( v(t) \) satisfy the equations
\[ \dot{N} = c_b(1 - N) - c_uN, \] \[ \dot{v} = -\frac{1}{kappa_1}(vN + c_b(1 - N)m_1) + c_u(F - v), \] (13)
where \( m_1 = \int xb(x) \, dx \). Evidently for \( t \to \infty \) \( N \) and \( v \) tend to their limit values
\[ N = cb + cu, \] \[ v = -\frac{1}{kappa_1}cbm_1 - F \frac{1}{1 + \frac{1}{kappa_1}c_u}. \] (14)

3. Optimal speed

Let us study the dependence of \( v \) on \( c_u \) and \( c_b \). It is clear from (14) that for \( F \) small speed \( v \) is negative. Recall that at the moment of motor binding to the thin filament, the motor average displacement \( m_1 \) from the neutral position is positive. Hence, the force which the motor creates on the filament is negative. Hence, the speed is negative also.

It follows also from (14) that \( v \to 0 \) as \( c_u \to 0 \). Motors are practically not unbinding from the thin filament at small values \( c_u \). Therefore, they pass the neutral point and create force in the positive direction. As a result the balance of positive and negative forces stops the thin filament movement. It follows again from (14) that \( v \to F > 0 \) as \( c_u \to \infty \). The effect is caused by the very small number of motors attached to the thin filament. If \( x_m m_1 - F > 0 \) then \( \frac{dv}{dc_u} < 0 \) at \( c_u = 0 \) and hence there exists a value \( c_u^o \) where \( v \) is negative and maximal in absolute value \( |v| = v^o \). It is achieved at
\[ c_u^o = \sqrt{\frac{F^2}{m_1^2} + \frac{c_b m_1 - F}{m_1}} - \frac{F}{m_1}, \] (15)
If there is no external force \( F = 0 \) then \( c_u^o = \sqrt{c_b m_1} \) and
\[ v^o = \frac{\sqrt{c_b m_1}}{2\sqrt{\frac{1}{kappa_1}c_u} + \sqrt{c_b m_1}}. \] (16)
In the case $F > 0$ the velocity becomes positive for large unbinding intensity $c_u > \frac{c_i(xm_1 - F)}{F}$.

All the above values were obtained under the condition of small external force $F < \kappa m_1$. If $F > \kappa m_1$ then the velocity is positive at any $c_u$.

4. Generalizations

In this section we describe some generalizations of the above model. In particular, we give a short description of a one-dimensional model with a sort of elasticity of the thin filament. We also discuss some ideas for construction of a similar model in a multi-dimensional case.

For the generalization we change the velocity expression (12) to (17). That is, the velocity is now defined by averaging a function $\phi$. However, $\phi$ is not arbitrary. In order to have a finite system of equations connecting the correlation function and the velocity function $\phi$ must satisfy the following condition. There exists $k_0$ such that derivative $\phi^{(k_0+1)}$ is a linear combination of the functions $\{1, \phi, \phi', ... , \phi^{(k_0)}\}$.

4.1. One-dimensional models with non-harmonic force

Let us consider a more general case when the force acting on the thin filament depends on $x$ nonlinearly. Instead of (12) the speed of the thin filament is

$$v = \int \phi(x)n(x, t) \, dx + F,$$  

(17)

where $\phi(x)$ is some nonlinear function.

Now we substitute expression (17) in equation (11). Then the expression for the time derivative of $v$ is

$$\dot{v} = \int \phi \dot{n} \, dx = -v \int \phi \frac{\partial n}{\partial x} \, dx + c_b(1 - N(t)) \int \phi b(x) \, dx - c_u(v - F).$$  

(18)

Integrating by parts we obtain from the first term $v \int \phi'(x)n(x, t) \, dx$. Inserting the new variable $w = \int \phi'(x)n(x, t) \, dx$ we have $\dot{w} = \int \phi'(x)n(x, t) \, dx$ and using (11) again we get an expression for $\dot{w}$ containing the integral $\int \phi''(x)n(x, t) \, dx$.

If $\phi(x)$ is a polynomial, then repeating this procedure we finally obtain a finite system of ordinary differential equations.

The finite system of ordinary differential equations can also be obtained if $\phi(x)$ is any trigonometric polynomial or more generally any linear combination of quasipolynomials (i.e. usual polynomials multiplied by sinusoidal and exponential functions [8]).

Consider the simplest case $\phi(x) = -\kappa \sin(\alpha x)$. Denoting $w = \int \cos(\alpha x)n(x, t) \, dx$ and $m_x = \int \cos(\alpha x)b(x) \, dx$, $m_s = \int \sin(\alpha x)b(x) \, dx$ we have

$$\dot{N} = c_b(1 - N) - c_u N,$$

$$\dot{v} = -\kappa \alpha vw - xc_b(1 - N)m_s + c_u(F - v),$$

$$\dot{w} = \frac{\alpha v(v - F)}{x} + c_b(1 - N)m_e - c_u w.$$  

(19)

For any stationary point of this system the value $N$ is given by (14) as before, and $v$ and $w$ can be found from $\dot{v} = \dot{w} = 0$. It is interesting to find the number of stationary points of (19). Also it is interesting to study the limit cycles for this system if they exist.

For the case $\phi(x) = -\kappa \sinh(\alpha x)$ the equations for $N, v, w$ are similar to (19) with the only difference in the sign before the term $\frac{\alpha v(v - F)}{x}$. 
4.2. Multi-dimensional models

There is a more general framework where particles are located not between two filaments but between two surfaces. More generally, one can consider a manifold $M$ of any dimension. Instead of the quasipolynomials some finite dimensional linear space $L$ of functions on $M$ is considered. The ‘forces’ produced by particles compose a vector field on $M$. The most general situation in which the corresponding equations can be explicitly solved is the following. Let $G$ be any Lie group, $\pi$ be its real linear representation in finite dimensional space $H$. The manifold $M$ is an orbit of some point from $H$ or the union of several orbits. Let $L$ be the space of linear functionals on $H$ (i.e. $L = H'$). The vector field $v$ on $M$, produced by the particle attached to some point $y$ from $M$ is given by the formula $v(y) = \sum_{n=1}^{N} \varphi_n(y)v_n$, where $\varphi_n$ are some functions from $L$ and $v_n$ are elements of Lie algebra of $G$, realized as linear vector fields on $H$ by the representation $\pi$. It is evident that these vector fields are tangent to $M$. It is also important that these fields acting on functions on $M$ leave $L$ invariant.

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