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Feedback control of myosin head

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1. Introduction

Myosin is a molecular motor responsible for muscle contraction. To do so, it hydrolysed molecule of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and free phosphorus (P). The proper function of muscle is controlled by the concentration of several ions. In this contribution, we control the myosin velocity by ATP concentration with a PD (proportional-derivative) regulator system.

2. Mathematical model

Myosin movement characteristic size is in nanometers, so it is influenced by thermal fluctuations. Due to it, myosin moves chaotically. We limit our mathematical model to catching the movement of myosin head only. We describe its movement by the Fokker-Planck equation [5]

$$\frac{\partial \rho_i}{\partial t} = D\frac{\partial}{\partial x}\left[\frac{1}{k_B T}\left(\frac{\partial V_i(x)}{\partial x} + F_{Load}\right)\rho_i\right] + D\frac{\partial^2 \rho_i}{\partial x^2} + \sum_{j=1}^{N} k_{ij}\rho_j - \sum_{j=1}^{N} k_{ji}\rho_i, \tag{1}$$

where the indexes i and j denote the state of the myosin head. The equation is solved for ρ_i, which stands for the probability density of the presence of head in state i, given time t and space x. The other parameters are variables which influence the movement. The parameters are diffusion D, and the product of Boltzmann's constant k_B and thermodynamics temperature T. The potential $V_i(x)$ is produced by chemical reactions and F_{Load} is the external load. The potential dependences on x are as follows

$$V_2 = \Delta G\left(\sin\left(\frac{2\pi x}{L}\right) - \frac{1}{2}\sin\left(\frac{4\pi x}{L}\right) + \frac{1}{3}\sin\left(\frac{6\pi x}{L}\right)\right) + E, \tag{2}$$

$$V_3 = -\Delta G\left(\sin\left(\frac{2\pi x}{L}\right) - \frac{1}{2}\sin\left(\frac{4\pi x}{L}\right) + \frac{1}{3}\sin\left(\frac{6\pi x}{L}\right)\right) + E, \tag{3}$$

$$V_1 = E, \tag{4}$$

where E is spring energy. The spring corresponds with the myosin neck – the connector between myosin filament and the head. The amplitude of the Fourier series ΔG is free energy amount. It expresses in $\mathrm{k_B T}$ units according to [3] as

$$\Delta G = \frac{\Delta G_0}{k_B T} - \log\frac{[ATP]}{[ADP]\,[P]}\,. \tag{5}$$

The square brackets stand for the concentration of the chemical composition inside.

Parameters k are rates constants to switching between chemical states. The states are as follows: unbound (further numbered as 1), weakly-bound (2) and post-power stroke (3). The cycle is not reversible – the transition from unbound state to post-power stroke is forbidden.

2.1 Transition rates

The transition rates are modified from the article [5], where the five-state model was simplified to two-state one. The modification procedure to the tree-state model was based on the same paper.

The transition states recount in this way

$$\frac{1}{k_{12}} \approx \frac{1}{k_1} + \frac{1}{k_5}, \tag{6}$$

$$\frac{1}{k_{21}} \approx \frac{1}{k_1^-} + \frac{1}{k_5^-}, \tag{7}$$

$$\frac{1}{k_{31}} \approx \frac{1}{k_3} + \frac{1}{k_4} - \left(\frac{1}{k_3^-} + \frac{1}{k_4^-}\right), \tag{8}$$

$$\frac{1}{k_{23}} \approx \frac{1}{k_2}, \tag{9}$$

$$\frac{1}{k_{32}} \approx \frac{1}{k_2^-}. \tag{10}$$

The transition rates on the right side are the original one. Its numbering was kept. The rates k_l ($l = 1, 2, 3, 4, 5$) denote the transition rate outcoming from the state l. The rates k_l^- states for the rates going to the state l. According to the paper [5], the transition rate k_3 is a function of the ATP concentration.

Transition rates on the left side belong the three-state model. They have two indexes each. The first one is the original one, the second the ending one.

The structure of the transition rate k_{31} is different from the others. It is caused due to one-way direction transition between unbound and post-power stroke state.

2.2 Myosin velocity

One of the important parameters of the molecular motors is their velocity ν. In this model, it is possible to count it as

$$\nu = \frac{1}{3}\sum_{i=1}^{N} LJ_i, \tag{11}$$

where J_i is the flux given by

$$J_i = D\left[\frac{1}{k_B T}\left(\frac{\partial V_i(x)}{\partial x} + F_{Load}\right)\rho_i\right] + D\frac{\partial \rho_i}{\partial x}. \tag{12}$$

Data, shown in Fig. 1, are quality correct, not quantitative, see Fig. 2. In the case of values from that figure, there is no influence of concentration of ADP neither P.

The concentrations for Fig 1 are taken from [3] and shown in Table 1.

3. PD regulator

To correct velocity values, we need to influence (or control) some of the model parameters. The chosen one is the ATP concentration. Other concentrations are kept. The most common

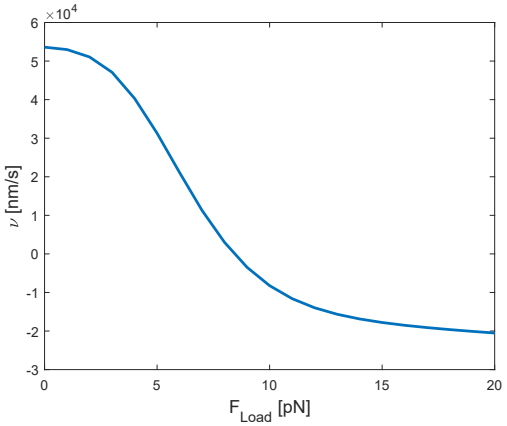

Fig. 1. Velocity with no interference of the feedback controller

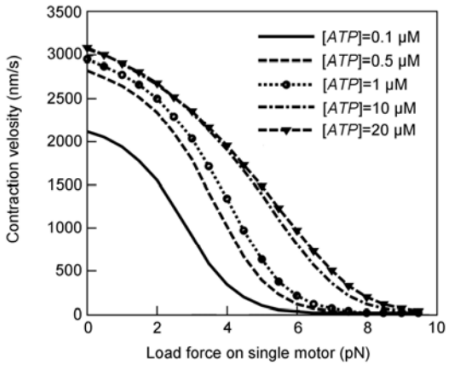

Fig. 2. Velocity dependence on an external load for different ATP concentrations, taken from [5]

Table 1. Adenosine triphosphate (ATP), adenosine diphosphate (ADP) and free phosphate (P) initial concentration taken from [3]

Molecule	ATP	ADP	P
Concentration [Mols]	4e-3	20e-6	2e-3

controller is the PID (Proportional, Integral, Derivative) one. The function u(t) which governed the regulator is

$$u(t) = K_p e(t) + K_i \int_0^t e(t')\mathrm{d}t' + K_d \frac{\mathrm{e(t)}}{\mathrm{t}}\,, \tag{13}$$

where e is the error. Constants K_p, K_i and K_d are coefficients of the proportional (index p), integral (index i) and derivative (index d), respectively.

The model describes the Markov process (the future state is influenced only by the present situation, not the past). Since the integral component needs the past for its functionality [1], only the PD controller is used.

The goal velocity is chosen to 3000 nms^{-1}. Parameters values were obtained by numerical experiments. Results are shown in Table 2.

Table 2. Found values of the PD regulator for the desired value of 3000 nms^{-1}. The values of concentration ATP are in a time when the velocity reaches the desired value.

F_{Load} [pN]	0	10	20
K_p	3.3e-04	3.3e-04	3.3e-04
K_d	1.8e-15	1.0e-18	9.0e-18
[ATP]	2.1e-13	1.2e-16	1.1e-15

4. Conclusions

The regulator constant K_p is constant for all studied loads. The constant K_d varies between the order of e-15 to e-18. The opposite signs of contraction velocities cause the big difference of the orders. The next research will be focused on the meaning of the ATP concentration provided by the PD regulator and on the controlling ADP and P concentrations.

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