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THE MEASUREMENT OF SINGLE MYOSIN HEAD IN FOKKER-PLANCK FRAMEWORK AND INFORMATION GAIN

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Abstract: Muscles on a molecular level are created by actin and myosin filaments. In this scale, it is necessary to take into an account thermal fluctuations – describe in terms of Brownian motion. Due to the motion, it is impossible to predict exact position of a single myosin head. Nevertheless, for obtaining some physical parameters – like information gain, a knowledge of the myosin head position is necessary. For this purpose, we developed a model, in the Fokker-Planck framework, which allows us to numerical determination of the myosin head location (measurement) from probability densities of mechano-chemical states of the myosin head.

Keywords: myosin; Fokker-Planck; measurement; information; mutual information

1 Introduction

Every muscle in the human body is created by actin and myosin filaments. They are slipping to each other and can be connected mutually by myosin heads [1]. The head position is thus important for mechano-chemical state determination of the whole system. In our model, a continuous movement of the myosin head in cytoplasm solution is replaced by three discrete states, they are called the unbound state, the weakly bound state and post-power stroke [2].

The myosin operates in nanoscale [1] in muscle cells, where it is important to take into an account thermal fluctuation (Brownian motion) [3]. Due to this unpredictable chaotic movement inside the whole muscle cell, it is impossible to have an exact determination of state and position, respectively. Thus, it can be helpful to use a statistical description of the myosin head movement along the actin filament [4]. In our model, it is described with the overdamped Fokker-Planck equation [5] which solving the probability densities distribution of the myosin head position in given mechano-chemical state. This approach is used also by others authors [4, 6].

In biological processes, it is necessary for the appropiate function to have precise state and at least approximate position of the organelles [7]. The information about it is used for a feedback controlled mechanism. So far, it has not been precisely determined, what the control mechanism is [7] and sometimes it is compared with Maxwell's demon [8]. On the other hand, the control mechanism is included into myosin and then the whole myosin itself acts as a Maxwell's demon [9]. Maxwell's demon is usually described as a hypothetical being which is able to influence microscopical system - for example, separate hot particles from the cold one [10].

The aim of the presented paper is to numerical determination of the myosin head location (measurement). According to the measurement outcome, we want to determine the information gain to the system of the actin-myosin complex.

2 A comparison of actin-myosin complex with a classical mechanical system

For better imagination, it is possible to think about myosin like an anchored spring with a weight with a magnetic properties, the "magnetic weigth". The spring represents a myosin neck, which is elastic part of the myosin. The weight represents the myosin head. And the "magnetic" property is due

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to an occasional connection between two filaments - the myosin and the actin, respectively. Thus from this point of view, the myosin head could be considered like a "paramagnetic" material, which behaves "magnetically" only in certain circumstances. An external magnetic field turns randomly oriented spin moments to its direction [11]. In the actin-myosin system, the situation is a little bit more complex. A lot of chemical substances decide about attachment and detachment of the myosin head to the actin filament. The most important are Ca^{2+}, Mg^{2+} and adenosine triphosphate (ATP), which provides energy to muscle contraction [12]. For visualization of the simplification see figure 1.

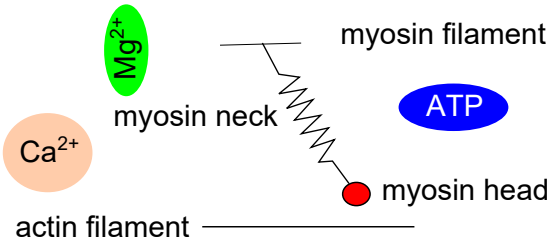
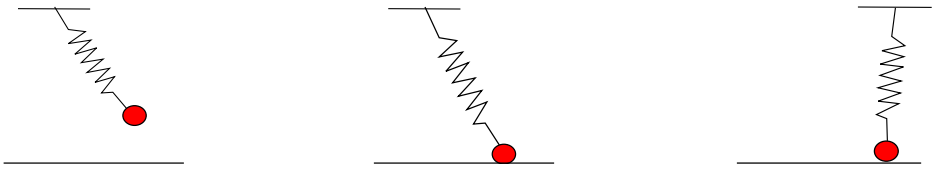


Figure 1: The mechanical simplification of the actin-myosin complex by a spring. The red ellipse denotes "magnetic weight" with paramagnetic property due to the ability to detach to the actin filament. The other colours ellipses represent some important chemical substances for muscle contraction in surroundings – beige is Ca^{2+}, green is Mg^{2+} and blue stands for an ATP molecule.

3 Mathematical description of myosin head movement

As we have mentioned before in section 1, the myosin head continuous movement is replaced to the three state discrete model. These states are called the unbound state, the weakly bound state and the post-power stroke [2], see figure 2.



(a) The unbound state **(b)** The weakly bound state **(c)** The post-power stroke state

Figure 2: A schematic representation of three state model of the myosin head (red ellipse) in relation to the actin filament (long black line). In unbound state, fig. 2a, the myosin head is detached from the actin filament, and the myosin neck (spring) is relaxed. In the weakly bound state, fig. 2b, the myosin head is touching actin filament. The myosin neck is stretched. In the post-power state, fig. 2c, the myosin moved together with the actin filament.

Due to the Brownian motion, the overdamped Fokker-Planck equation (sometimes called the Smoluchowski equation [13]) is used for mathematical description, which provides probability density ρ_i of the myosin head location along actin filament for a given state i [4]. The equation has a form

$$\frac{\partial \rho_i(x,t)}{\partial t} = D\frac{\partial}{\partial x}\left(\frac{1}{k_B T}\frac{\partial \varphi_i(x)}{\partial x}\rho_i(x,t) + \frac{\partial}{\partial x}\rho_i(x,t)\right) + \sum_{j=1}^{3} k_{ij}\rho_j(x,t) - \sum_{j=1}^{3} k_{ji}\rho_i(x,t) \quad \forall j \neq i, \tag{1}$$

where t is time variable, $D = 5.47 \cdot 10^7$ nm^2/s diffusion coefficient which represents the myosin head ability to move among surrounding molecules in the aqueous solution. The parameter k_B is the Boltzmann constant, T is the temperature. The function $\varphi(x)$ is called the effective potential [14], that is the potential energy [4]. It is primarily caused by Ca^{2+} concentration. The transition rates k_{ij} and k_{ji} are

primary depending on ATP concentration. These rates determine a shift between the distinguished chemical states. The allowed shifts are from unbound to weakly bound and vice versa, from weakly bound to post-power stroke states, which is also reversible, whereas the last transition is irreversible – from post-power stroke to unbound state. The model uses parameters k_{ij}, not the concentrations themselves.

The potential φ makes the difference among mechano-chemical states. For the unbound state, the $\varphi_1(x) = const.$, while in the rest of the states, the potential is shaped by Fourier series

$$\varphi_2(x) = \Delta G \left[\sin\left(\frac{2\pi x}{L}\right) - \frac{1}{2}\sin\left(\frac{4\pi x}{L}\right) + \frac{1}{3}\sin\left(\frac{6\pi x}{L}\right)\right] \tag{2}$$

for the weakly bound state and

$$\varphi_3(x) = -\Delta G \left[\sin\left(\frac{2\pi x}{L}\right) - \frac{1}{2}\sin\left(\frac{4\pi x}{L}\right) + \frac{1}{3}\sin\left(\frac{6\pi x}{L}\right)\right] \tag{3}$$

for the post-power stroke state, respectively. The parameter $L = 36\,\mathrm{nm}$, which is characteristic length for myosin movement [1, 6].

The equation (1) is modified to the Master equation according to the WPE algorithm [15]

$$\frac{\mathrm{d}}{\mathrm{d}t}p_i^n = -(B_i^{n-1/2} + F_i^{n+1/2})p_i^n + F_i^{n-1/2}p_i^{n-1} + B_i^{n+1/2}p_i^{n+1} + \sum_{j=1}^{3} k_{ij}p_j^n - \sum_{j=1}^{3} k_{ji}p_j^n \quad \forall j \neq i, \tag{4}$$

where upper indexes denote position in the computation mesh (node number), $p \approx \rho\Delta x$ represents the probability of finding the motor at the node n at time t. Parameters $B^{n+1/2}$ and $F^{n+1/2}$ describe the forward and backward transition fluxes between nodes n and $n+1$, respectively.

$$F_i^{n+1/2} = \frac{D}{(\Delta x)^2}\frac{\Delta\varphi_i^{n+1/2}/k_BT}{\exp(\Delta\varphi_i^{n+1/2}/k_BT) - 1}, \tag{5}$$

$$B_i^{n+1/2} = \frac{D}{(\Delta x)^2}\frac{-\Delta\varphi_i^{n+1/2}/k_BT}{\exp(-\Delta\varphi_i^{n+1/2}/k_BT) - 1}, \tag{6}$$

where

$$\Delta\varphi_i^{n+1/2} = \varphi(x_{n+1}) - \varphi(x_n). \tag{7}$$

The equation (4) is solved in `MATLAB` by `ode15s` function.

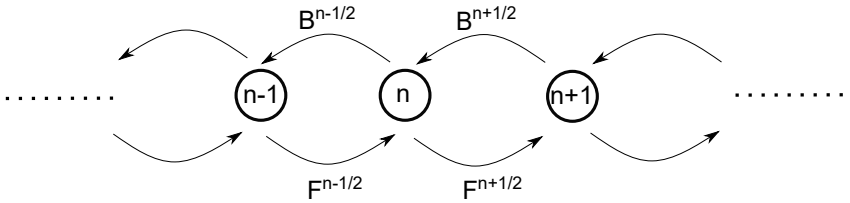


Figure 3: Transition fluxes between node n and its neighbours in the computation mesh. Fluxes B and F describe the forward and backward transition fluxes.

4 Measurement and information gain

The importance of measurement in molecular biological systems was mention in section 1. In our model, we do not have a precise position of the myosin head, only its probability densities in three given chemical states, see section 3. To perform a measurement, we find a way of measuring the mechano-chemical state and the position of the myosin head at once.

The key role in our model of measurement has a pseudorandom number generator, which is included in MATLAB. It generates a single number between 0 and 1, which describe both, the state and the position of the myosin head. These interval limits are clear due to the definition of probability value [16]. The probability distribution function for the generator is created by the total (one for all three states) cumulative probability density function. Thus, the generated number represents the state and the position of the myosin head, see fig. 4.

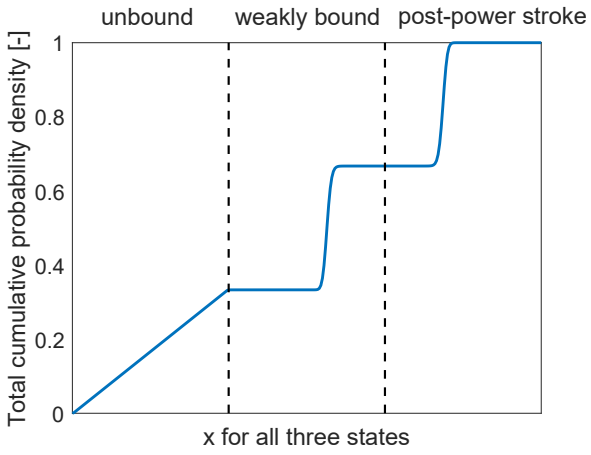


Figure 4: Illustrative total cumulative probability density distribution function. The dashed black line denotes the transition between two states.

Although the generator provides us with a precise position $\tilde{x}$, the measurement is not error-free procedure. We presume the error has the Gaussian form

$$\rho_e(x|\tilde{x}) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[-\frac{(x-\tilde{x})^2}{2\sigma^2}\right], \tag{8}$$

where σ^2 is called the standard deviation and corresponds to measurement precision.

The result of the measurement $\rho_m(\tilde{x})$, is obtained as the convolution of probability density function before measurement $\rho_0(x)$ and measurement error $\rho_e(x|\tilde{x})$

$$\rho_m(\tilde{x}) = \int \rho_0(x)\rho_e(x|\tilde{x})\mathrm{d}x. \tag{9}$$

If we make a comparison between the measurement error and particle's probability density via the Bayes' theorem[17] ($\rho_e(x|\tilde{x})$ has a meaning of conditional probability)

$$\rho_1(\tilde{x}|x) = \frac{\rho_e(x|\tilde{x})\rho_0(x)}{\rho_m(\tilde{x})}. \tag{10}$$

It can serve as a new initial condition for numerical simulation after measurement.

After measurement, we are able to calculate Kullback–Leibler distance, or relative entropy [17].

$$I(\tilde{x}) = \int \rho_1(\tilde{x}|x)\log_2\frac{\rho_1(\tilde{x}|x)}{\rho_0(x)}\mathrm{d}x. \tag{11}$$

It quantities the distinguishability of these two distributions, ρ_0 and ρ_1 obtained before and after measurement, respectively. The $I(\tilde{x})$ is always positive [17]. The used logarithm determines information units, in our case binary logarithm produces bits. If we used natural logarithm, the result is in nats [18].

The mutual information $\langle I\rangle$ can be defined as the average value of the relative entropy

$$\langle I\rangle = \int I(\tilde{x})\rho_m(\tilde{x})\mathrm{d}\tilde{x} = \iint \rho_m(\tilde{x})\rho_1(x|\tilde{x})\log_2\left(\frac{\rho_1(\tilde{x}|x)}{\rho_0(x)}\right)\mathrm{d}x\mathrm{d}\tilde{x}. \tag{12}$$

The parameter $\langle I \rangle$ measures the amount of information obtained by the measurement [17], that is the information gain.

5 Results

Some possible values of relative entropy I and mutual information $\langle I \rangle$ are shown in table 1. They are generated for a single measurement after short time ($5 \cdot 10^{-7}$ s) if simulation. The standard deviation σ^2 is set equal to 10 for this case. It represents a kind of error which can be done by a real measurement, for example, tiny human mistake or error of an used equipment.

Measured state	*unbound*	*weakly bound*	*post-power stroke*
Relative entropy I [bits]	4.680	2.120	2.125
Mutual information $\langle I \rangle$ [bits]	0.217	0.098	0.098

Table 1: The values for relative entropy I and mutual information $\langle I \rangle$. The precise values depend on the generated position. Thus, they can variate.

If we stoped the random generator, we use the same mechano-chemical state and position of the myosin head. In this case, the relative entropy and the mutual information also vary, see figure 5 and 6, respectively. The values have the maximum at $\sigma^2 = 3.557$. Thus, the maximums are $I = 1.869$ bits and $\langle I \rangle = 0.111$ bits. The fact why for some values of σ^2 ($\sigma^2 < 3.557$) do not exists, provides us with a prove, every measurement is influenced by an error. Otherwise the measurement is unphysical. And the Gaussian distribution cannot close enough to Dirac impulse to be replaced with. The decrease of both values is logical. The most precious information is the exact position which is allowed. If we are unable to determine position with reasonable precision, it is not too valuable. The qualitative difference between $I(\sigma^2)$ on figure 5 and $\langle I \rangle(\sigma^2)$ on figure 6 is caused by the Gaussian shape of the probability density $\rho_m(\tilde{x})$, which is in the definition of $\langle I \rangle$, equation (6).

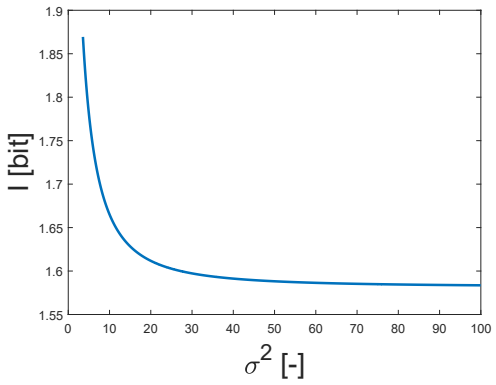


Figure 5: Dependence of relative entropy I on standard deviation σ^2. The σ^2 lies in an interval from 0 to 100. The I does not exist for values $\sigma^2 < 3.557$.

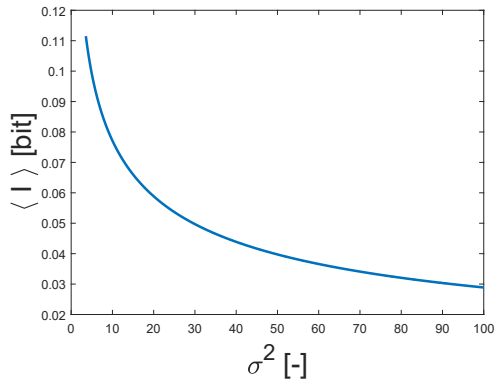


Figure 6: Dependence of mutual information $\langle I \rangle$ on standard deviation σ^2. The σ^2 lies in an interval from 0 to 100. The $\langle I \rangle$ does not exist for values $\sigma^2 < 3.557$.

6 Conclusion

In this paper, we presented a simplification of myosin head as a spring with a ”magnetic weight”, which can serve for the better imagination of the actin-myosin movement problem. Then, we showed the possibility of the mechano-chemical state and the position measurement with just one pseudo-random number. The probability density distribution function was obtained by overdamped Fokker-Planck equation solved with the WPE algorithm and `MATLAB` function `ode15s`. The main result of the presented paper is information gain in form of mutual information and its dependence on the measurement error.

In next work, we will focus on multiple measurements of our system and also add a feedback control mentioned in the introduction.

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