Functional Algorithm based on Noise Rectifying, Inspired by Bio Molecular Mechanism

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Here, we show a simple model of a kind of nano machine as an example. We design a simple model for a machine which works in the presence of thermal noise, and mathematically calculate physical motion (time evolution) of the modeled machine. As a calculation result, we show we can design the model, which works by rectifying thermal noise and autonomously regulates the motion (direction switching, velocity control) according to environment. Understanding and trying to apply such processing algorithms for stochastic functioning would give us useful suggestions to design autonomously regulating and functioning machines under various (unknown) circumstances.

1 Introduction

The influences of viscosity and thermal fluctuation (thermal noise) become effective in the nanoscale world[1]. This means that nano-sized bio molecular machines operate under intense thermal noise conditions which are agitated by solvent molecules. So what is it that enables them to operate under such noisy conditions? By studying and understanding the functional characteristics of biomolecular machines[2]–[4], great expectations are held for the discovery of clues to building nano machines, machines that operate reliably under very noisy conditions, and signal processing technology. To turn these expectations into reality, one effective approach is to turn nanoscale functional characteristics into a physically consistent models to grasp an understanding of the algorithm behind functional expression. In this paper, we focused on the protein motor to design a simple mathematical model for a nano machine that operates under conditions of thermal noise. We will report on one example of such a model in which its movement (over time) was mathematically and physically calculated. Summarizing the results of calculations, a machine that functions randomly can be designed under large noise conditions by rectifying the thermal noise. The mathematical model shows that machines that function randomly will control their movement (switching directions, adjusting speed of movement) naturally and autonomously in accordance with external conditions (e.g., ligand concentration) based on probability. Understanding the algorithm behind the movement of such machines that function randomly, and thinking of ways of finding practical applications for them may help us find useful ideas in designing machines that can control their functions autonomously under a variety of environmental conditions.

2 The model design and simulations

2.1 The model design

First is an explanation of the outline of our simulations.

Here we used a simple mathematical model to examine a nano-sized (a diameter of 30 nm) particle (hereinafter referred to as functional particle) with a function that enables it to move linearly along a rail under thermal noise conditions. The interaction between the functional particle and the rail (we will not discuss the mechanism behind this in this paper) exerts a force on the particle. This driving force can be thought of as a potential force, and this allows the movement of the functional particle to be described as particle movements in potential force. The movement of the functional particle is dependent on the size of the particle (thermal noise, viscosity) and the potential force. It could move in all directions, but for the purpose of simplification and to ascertain the true nature of this movement, we will examine only the movement of the particle within one-dimensional periodic potential (Fig. 1). Furthermore, the shape of the potential is described as a combination of straight lines to simplify calculations (Fig. 1). This is the type of mathematical model often used when examining moving particles such as protein motors[5].

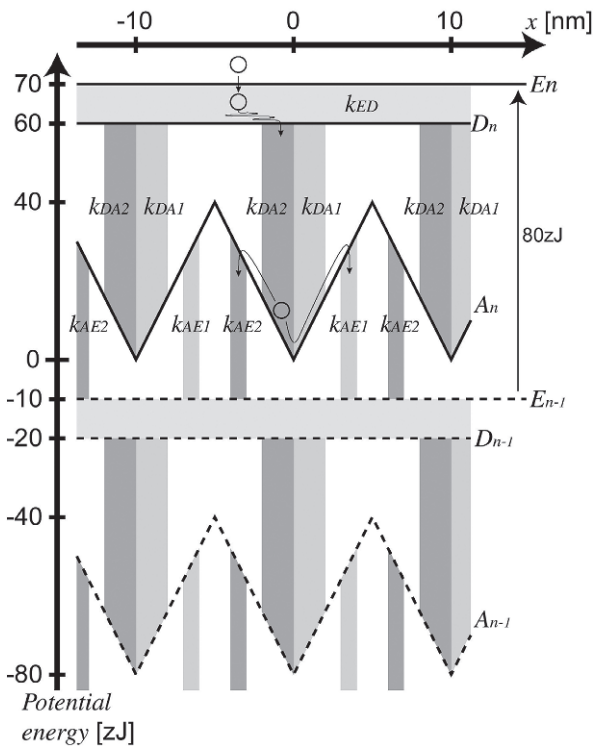


Fig. 1 A model using the periodic potential (10 nm periodicity)
The graph shows two periods both vertically and horizontally. White circles indicate the functional particle (ϕ = 30 nm). The gray parts between the potentials show the range within which transitions between states are permitted. Along the horizontal axis are the *x* coordinates [nm], and the vertical axis indicates potential energy [zJ]. The functional particle moves along the *x*-axis while undergoing successive transitions between the *D*: Detached state and *A*: Attached state starting from the *E*: Empty state (no-ligand state, the *n* indicates the number of the state). The functional particle switches between the state potentials indicated in the graph as *En*, *Dn* and *An* (small letters indicate the reference number of the potential), driven by thermal noise. It makes transitions randomly (arrows) between state potentials within the area in which transitions are permitted (gray parts). Assuming the transition rate between the various states too, is periodic, its value within one period (0–10 nm) is $En \rightarrow Dn$: k_{ED}= 50 to 2 x 10^9 with a variable parameter (total x range)
$Dn \rightarrow An$: k_{DA1}= 1.0 × 10^8 (x = 0 to 2 nm), k_{DA2}= 2.0 × 10^6 (*x* = 8 to 10 nm)
$An \rightarrow E_{n-1}$: k_{AE1}= 1.0 × 10^7 (*x* = 3 to 4 nm), k_{AE2}= 5.0 × 10^6 (*x* = 6 to 7 nm)
The unit is [/sec]

It is similar to a fine particle (electric or magnetic charge) that moves in accordance with a periodic potential set up by the periodic positioning of electric charges or magnetic charges. However this functional particle undergoes cyclical attaching and detaching of ligands (signaling molecules, energy supplying molecules, etc.) creating different states of potential (hereinafter referred to as state potential, Fig. 1: *En, Dn, An*). In other words, different interaction potentials may be created depending on the state (e.g., the internal structure of the fine particle), even if the positioning of the electric or magnetic charge on the rail were to be the same. A prerequisite of this transition between the different states is that it is coupled with consumption of energy through the cyclical attaching and detaching of ligands, and so it obeys the second law of thermodynamics. Here we will examine a model that creates state change (vertical movement in Fig. 1) coupled with energy consumption (transition to lower state) from state transition (Fig. 1: Direction of the *y*-axis). The coupling does not have to be between energy consumption and movement, but we will do so in order to examine the mathematical and physical model under conditions that obey the laws of physics. In examining the movement (over time) of particles that function under conditions of thermal noise, we will use the Langevin equation[6] to simulate the movement of the functional particle (changes in state and position over time), based on the precondition that we will use methods that are not physically impractical. Changes in the external environment and internal state of the functional particle are also taken into account in designing the model, so the simulation will be carried out in discrete state potentials under the assumption that each different internal state of the functional particle will have a different potential. To simplify things, the basic conditions we set for the model we designed were two state potentials (Fig. 1: Potential (*D*: Detached state) & (*A*: Attached state)) resulting from a difference in the internal state of the functional particle, and the state potential under a ligand-detached state (Fig. 1: Potential (*E*: Empty state)) to simulate the attachment and detachment of ligands (e.g., energy supply molecule).

Here is a simple mathematical and physical explanation for the above simulation. If we were to record only the changes in state over time, we would use a kinetic model based on chemical kinetics, in which case a differential equation would be the most appropriate way of expressing this[7]. However, we need to consider not only the changes in state over time, but also the movement over time relative to the potential, which is dependent on the internal state. So we used an extended kinetic model for recording this state and movement over time[5][8]. Moreover, the signals are not necessarily the same all the time in biomolecular machines such as proteins[2]–[4], and in the case of our functional particle this means it moves in both negative and positive directions randomly. To account for this randomness of signal output, the transition rate of changes in the state differs depending on the position in our model.

We will not delve into the details here, but in our model the positions at which state changes occur, and reaction rates, have been adjusted to generate movement in both directions. To explain this using Fig. 1, a general kinetic transition process would appear as a vertical shift from the top of the graph toward the bottom. What we added to this was the generation of movement in real space (Fig. 1: Horizontal direction along the *x*-axis) in accordance with one state potential when the functional particle is in one particular internal state. The transition rate of the state transition is set to be dependent on the position along the *x*-axis. In other words, the transition rate changes depending on the position of the functional particle, and the particle is moved by a different potential force that is dependent on the position where the state transition occurred, resulting in movement in both directions. The movement of the functional particle within one state potential can be expressed as a differential equation using the Langevin equation, and it is a Brownian motion regulated by the size of the functional particle, the temperature, the viscosity coefficient of the solvent, and the state potential force [1]. The periodic potential is defined by the entire system involving the interaction between the internal structure of the functional particle and the rail structure. We limited our study to three state potentials shown in Fig. 1. Furthermore, to simplify things we assumed each of the state potentials to be flat (zero inclination overall) as shown in Fig. 1. Assuming that transition between state potentials occurs in succession, the simple transition rates of k_{ED}, k_{DA1}, k_{DA2}, k_{AE1}, k_{AE2} of potential (*En*) → (*Dn*), (*Dn*) → (*An*), (*An*) → (E_{n-1}) ⋯ will be the parameters for the settings (Fig. 1 explanatory notes), and k exp (-Δ E/k_BT) will become the opposite transition rate (k_B: Boltzmann's constant, T: Absolute temperature)[9]. However, Δ E is the difference in energy between state potentials at the positions where state transitions occur, and they are in detailed balance. Recording the movement of the functional particle (over time) as a state transition in accordance with the Langevin equation and detailed balance allowed us to realize a physically consistent model. The difference in energy between the potentials here is to regulate the transition between states in the opposite direction in accordance with the detailed balance, and it is not the essence of this model. If the difference in energy is large, the transition rate in the opposite direction (Fig. 1: From the bottom to the top) becomes small, so that transition occurs mostly in one direction only (Fig.1: From the top to the bottom). In this model, the three state potentials undergo successive

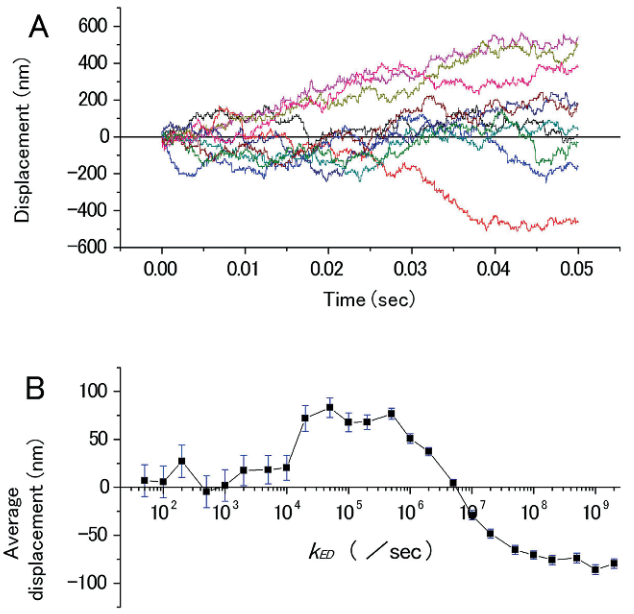


Fig. 2 A: The distance moved in 50 msec in the case of the transition rate from (*En*) → (*Dn*) being k_{ED}= 5.0 × 10^5. It is a random process so the displacement shows distribution. The different line colors indicate different traces (shows 10 traces).
B: Profile of the average value of the amount of displacement generated when the ligand concentration-dependent transition rate (k_{ED} the transition rate from (*En*) → (*Dn*)) is changed. Horizontal axis: The ligand concentration-dependent transition rate (In Fig. 1: Transition rate from (*En*) → (*Dn*) [/sec]) Vertical axis: Amount of displacement in 50 msec [nm]. Black squares indicate average amounts of displacement. Blue vertical lines indicate standard errors.

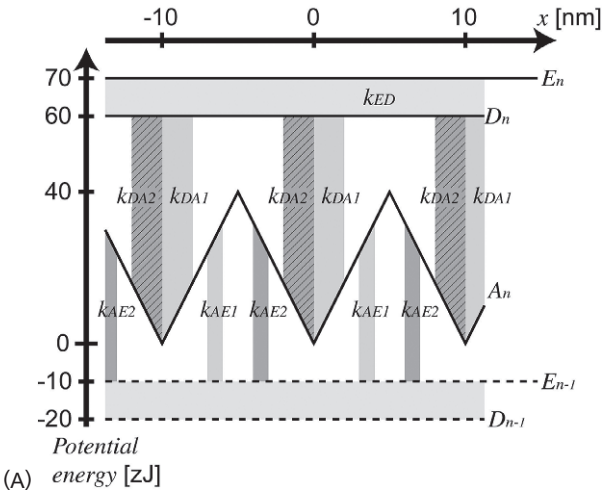
transition over time. There is a fixed amount of energy between all the state potentials, and a difference in speed is observed in the transition rate from the top to the bottom, and from the bottom to the top that is dependent on energy differences. This difference in rate is equivalent to the energy consumption, and transition reactions occur autonomously in this model in the direction of energy consumption (from the top to the bottom). In addition, all state potential shapes have been made symmetrical or flat to simplify the model. For this reason, unidirectional movement is not observed along the *x*-axis by only one potential. Directional movement is produced upon the generation of a bias in the position distribution of functional particles, through the repeating of the transition process between states at limited positions while consuming energy. The state potential (*En*) and transition process to (*Dn*) were included to take account of the transition rate, which is dependent on the variable quantity of ligand (signaling molecules, energy supplying molecules, etc.) concentration in this model. (*En*) → (*Dn*) represents

the transition of a ligand from a detached state to an attached state, and the value is the same at any point along the *x*-axis. The (*En*) → (*Dn*) transition rate is set between 50−2 × 10^9[/sec] in accordance with the set ligand concentration, and the movement generated is calculated for each value. Simulation calculations are carried out every 0.2 nsec, and the distance moved along the *x*-axis in 50 msec after relaxing from the initial state is calculated. Furthermore, the reaction speed of the state transition is regarded as a probability in accordance with the 0.2 nsec intervals between calculations in the simulation, and it is a stochastic process in which random transitions are attempted for every calculation.

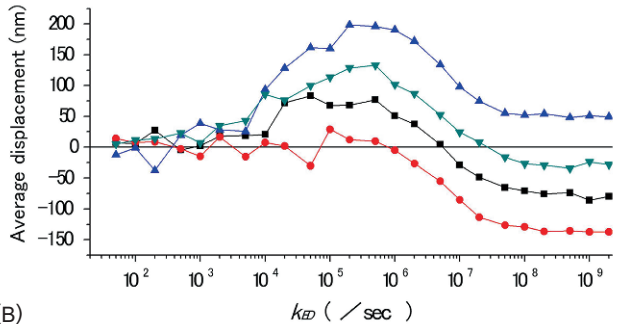
3 The results from the model

3.1 The results of calculations in the simulation

Below are the results of calculations. Time evolution of particle movement is a stochastic process, so individual movements are widely distributed (Fig. 2A). The average amounts of displacement are calculated statistically (Fig. 2B: average ± standard error (vertical blue lines)). Discussions below will be based on these average values. The internal processes remained the same (the internal state transition and Brownian motion remained the same), and the transition rate (probability of transition) between the different states in the ligand attachment step (transition step (*En*) → (*Dn*)) were changed to 50−2 × 10^9[/sec]. Figure 2B shows the results of calculating the movement of functional particles under the various conditions. The results of calculations in the simulation show that the output can be changed autonomously in accordance with the reaction speed of the ligand attachment step (ligand concentration). To simplify things here, no limitations were imposed on the location of state transitions (transition step (*En*) → (*Dn*)) as the result of ligand attachment, while other transitions between state potentials were limited to a certain range (Fig. 1). In consideration of the movement of the functional particle within the state potential (*An*), we made it so that a transition would be possible to the state potential (E_{n-1}) near the point where the potential peaks, and not where it dips. So far to this point, the functional particle is moving against the potential force, driven by fluctuations from the thermal noise. In other words, the overall unidirectional movement of the functional molecule here is being generated as the result of the selection of unidirectional thermal noise (rectification of the thermal noise) from what is essentially random in direction, through the interrelationship with the shape of the state potential. Our results are from simulations under these conditions of rectified thermal noise, and ligand concentrations being expressed as transition rates. The results show that the speed of particle movement changes and the direction of movement reverses depending on the transition rate (transition probability) of the step in which transition progresses (Fig. 1: The (*En*) → (*Dn*) step) due to ligand attachment. In other words it is a simple model, but it autonomously adjusts the speed of movement in accordance with external environmental conditions, and realizes a mechanism for switching the



(A)



(B)

Fig. 3 A: State potential graph showing partially changed transition rate. A part of the transition rate (k_{DA2}, diagonal lines) is changed (modified) from the values used in Fig. 1, 2.0 × 10^6 [/sec].
B: Changes over a time interval of 50 msec are calculated, and the average amounts of displacement are plotted on a graph. The transition rates k_{DA2} (diagonal lines) are changed (different colors), and average amounts of displacement (along the vertical axis) relative to the transition rate k_{ED} (equivalent to ligand concentration) are plotted on a graph. The graph shows the dependence of the distance moved on k_{ED}. The values of the transition rates k_{DA2} (diagonal lines) are 2.0 × 10^6 (black line as in Fig. 2B), 1.0 × 10^6 (red line), 3.0 × 10^6 (green line), and 5.0 × 10^6 (blue line) [/sec]. It can be seen that the particles continue to function even after the transition rates k_{DA2} (diagonal lines) have been changed (modified).

direction of movement through rectification of noise.

3.2 The Characteristics of the Model

The essence of noise rectification by the functional particle discussed here is the inclusion of a function in the mechanism for transition between states for selecting a single direction from opposing positive and negative directions in potential movement. External environmental conditions are regarded in terms of their probability, and the processing of the probability is changed through the internal processing mechanism (transition between the states and Brownian motion). This allows the changing of the output in accordance with the conditions. Furthermore, in the case of this kind of noise-rectifying random movement mechanism, the driving force is essentially random, so the results of processing are always outputted. In summary, the interaction between noise (here it is movement in random directions) and the internal structure of the machine leads to rectification of directional movement from the noise. In this movement-rectifying process, the external environment is considered in terms of probability, and the output is controlled autonomously in accordance with the conditions (through the reversal of direction). This is the kind of machine that will be created.

In conditions under which numerous random phenomena are observed on nanoscales and in biological phenomena, there is a high possibility that this kind of design algorithm that functions by rectifying noise instead of simply removing it, will be very effective. This kind of control mechanism may also be effective in the autonomous control of numerous machines. It is hoped that this will result in the realization of overall functions that are well-balanced, in which individual machines function randomly in accordance with the external conditions in their immediate surroundings.

This noise-rectifying design has its merits and demerits, of course. A merit is that it is designed to function randomly, so it is resistant to noise disturbances and it functions with stability. It is also resistant to irregular incidents. Examples of this may include the appearance of a displacement that changes the shape of the potential, or a change in the transition rate between potentials. Here are the results of calculations (Fig. 3B) after a part of the transition rates changed (Fig. 3A). The profile of the response to the external environment (ligand concentration) has changed, and the autonomous direction switching function sometimes weakens (is lost). If the change is small (k_{DA2}= $2.0 \times 10^6 \rightarrow 1.0 \times 10^6$: Black line in Fig. 3B $\rightarrow 3.0 \times 10^6$: Green line), the switching function that responds to changes in the external environment remains, but its speed response profile changes. If the change is large (k_{DA2} = $2.0 \times 10^6 \rightarrow 5.0 \times 10^6$: Blue line in Fig 3B), the switching function is sometimes lost in the zone where the value of k_{DA2} is large. Incidentally, even when a function (switching) is lost in this way, a characteristic of functional particles is that its other functions are not lost. In other words, even when the internal structure is changed (modified), because its movement is random it does not suffer a dramatic loss of its original functions. Because the movement is random to begin with, changes (modifications) in the internal structure often results in unpredictable outputs. Some people are of the opinion that the generation of unpredictable outputs may cause damage, but from the perspective of creating new functions, it is possible to think of it as a mechanism for autonomous improvement or addition of functions. What we need to consider is a way of designing that can make use of such new functions. In the future, we must think of designs that adapt this random movement type mechanism to the output demanded.

Lastly, noise itself shows complicated behavior. It would be believed to be easier to selectively pick up what is needed from the variation of complicated behaviors, rather than to try and create the complicated behavior itself. In this paper, we reported on (one-dimensional diffusion) a simple example of a model (algorithm) in which a functional particle generates a signal output (the size and direction of movement in this case) through the selection and use of an overall unidirectional movement from noise including movement in both directions, in accordance with external environmental conditions (ligand concentration in this case). The model fulfills physical requirements so in theory it can be turned into a real device for which there are high expectations. Expectations are also held for its development for application in systems that include chemical reactions, through the use of reaction coordinates as coordinates, and not just its movement.

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