Autonomous free-energy transducer working under thermal fluctuations

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1 Introduction

Biological molecular machines such as ion pumps, molecular motors (myosin, F1 motor, etc.) or signal transducers (G-proteins) have attracted a lot of interest among physicists as well as biologists (Alberts et al., 1998). The molecular machines work under thermal fluctuations, where the latter serve as an energy source (Sekimoto, 1997) for the free energy transduction (Eisenberg and Hill, 1985)2 as well as for the thermal activation (Wong et al., 1997). Moreover, the cycle of free-energy transduction in a single molecular machine requires no external control. As many of these molecular machines share highly conserved three-dimensional structural modules, it is widely believed that they have been

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1 On leave from Université Louis Pasteur, Strasbourg, France.

2 Upon a single ATP hydrolysis reaction in vivo, about 70% of the maximally available work (20kT with kBT ≃ 4pN·nm) is ascribed to the change of the mixing entropy.
evolved from a common ancestors (Kull et al., 1998). This fact suggests that such molecular machines may be composed of a few modular structures each of which bears some elementary functional role. With recent rapid development of nano-biology and the structural biology, the biologists have begun to look for such modular structure-function relationships within a single molecular motors (Higuchi and Endow, 2002; Nitta et al., 2004; Tsiavaliaris et al., 2004).

From the theoretical physicists side, there is no surprise about the mere fact that a molecular machine without any special forward-backward symmetry can move in one direction under non-equilibrium conditions (e.g. under the ATP hydrolysis), as stated in the Curie’s principle (Curie, 1894)\(^3\). With this in mind, the question of our interest is how we can construct, in combining well-defined simple functional modules, an autonomously controlled system that can work under thermal fluctuations. Since the early works by Feynman et al. (1966) and Büttiker et al. (1987), several models of autonomous free energy transducer have been proposed, and their improvements through the incorporation of a “gate” have been proposed (Sakaguchi, 1998; Derényi and Astumian, 1999) (see also the review by Reimann (2002)). These models were, however, rather ad hoc and the modular nature of the construction was not clearly visible. In the present paper, we would construct a free energy transducer with being more conscious about the modules and taking the object oriented approach (Sekimoto, 2000). We start by introducing the concept of “semi-detectors”, the detectors that can perceive a certain external state, but not all, with arbitrary sureness despite the thermal fluctuation (§ 2). We then combine these semi-detectors together with the gates, under the designing concept that we call the “bidirectional control”, to realize an autonomous particle transporter (§ 3). Because of the limited space of this special issue, the extensive discussion on the possible relations to the real biological molecular machines will be given elsewhere.

2 semi-detectors in the fluctuating world

The detector is the mechanism that correlates the states of the outside to those of the inside of the system in question. We focus on the case where the detection site admits a single ligand particle coming randomly from the outside. We will limit ourselves to the energetically “neutral” detections, involving no change of the total energy. Let us define the mapping from a state of the outside, \(x\), to a subset of the states of the inside, \(\Phi(x)\). In the discrete representation, the states of outside consists of \(\text{IN}\) (i.e. a ligand particle is on the

\[\text{“Lorsque certaines causes produisent certains effets, les éléments de symétrie des causes doivent se retrouver dans les effets produits.”}\]
detection site) and OUT (otherwise), while those states inside consist of ON and OFF. The perfect detector would establish the mapping, \( \Phi(IN) = \{ON\} \) and \( \Phi(OUT) = \{OFF\} \). But these correspondences are too stringent to realize under thermal fluctuations. We will show below that there can be the physical mechanisms which assure either one of the above correspondences. We will call the mappings corresponding to such mechanisms the semi-detectors.

**Semi-detector of absence:** This module functions as the mapping \( \Phi_{ab}(x) \) that prohibits only the output of OFF under the input of IN. That is,

\[
\Phi_{ab}(IN) = \{ON\}, \quad \Phi_{ab}(OUT) = \{ON, OFF\}. \tag{1}
\]

Then the OFF surely indicates the absence of the particle (OUT). Such aspect is useful for repressive processes like the suppression of DNA transcription by a repressor (Lewin, 2003). In the continuum representation, one may define \( x \) as the position of a ligand particle in a half space \( 0 \leq x < \infty \), where \( x = 0 \) corresponds to the detection site (see Fig. 1 **Left**). The state of the inside, \( a \), is assumed to be bounded, say, in the region of \(-1 \leq a \leq 0\) without losing generality. The semi-detector of absence may be realized by the steric repulsion between the ligand particle and a movable object (thick bars in Fig. 1 **Left**). The total energy of the ligand-detector system, \( U(x, a) \), is written as \( U(x, a) = 0 \) for \( x \geq a + 1 \) and \( U(x, a) = \infty \) otherwise. OFF and ON states correspond, respectively, to \( a \geq -1 + \delta \) and \(-1 \leq a < -1 + \delta \) with a small \( \delta > 0 \).

**Semi-detector of presence:** This module functions complementarily to the former semi-detector. The mapping \( \Phi_{pr}(x) \) that it defines prohibits only the output of ON under the input of OUT. That is,

\[
\Phi_{pr}(IN) = \{ON, OFF\}, \quad \Phi_{pr}(OUT) = \{OFF\}. \tag{2}
\]

Then the ON surely indicates the presence of the particle (IN). Such aspect is useful for active processes like the uptake of ATP by a molecular motor. In

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**Fig. 1.** **Left:** Schematic representation of the semi-detector of absence in a continuum representation. The movable object (thick bar) and the ligand particle (thick dot) are sterically excluding with each other. \( a \) represents the coordinate of the left extremity of the object. \( x = 0 \) is the detection site. **Right:** The shadowed region on the \((x, a)\)-plane indicates the accessible phase space, where \( U(x, a) = 0 \).
the continuum representation, the semi-detector of presence may be realized by the compensation of a strong restoring potential for the movable object, $M\phi(a)$ ($M \gg k_B T$), by the strong attractive interaction energy, $-M\phi(a-x)$, between the ligand particle and the movable object (see Fig. 2 Left). Here $\phi(z)$ is defined on $-\infty < z \leq 0$ so that $\phi(z) = 0$ for $z \leq -1$ and that $\phi(z)$ increases monotonically from $\phi(-1) = 0$ to $\phi(0) = 1$. Energetically, this movable object can take the value $a \geq -1 + \delta$ only when the particle is near the binding site, that is $0 \leq x \leq \delta$ with a small $\delta > 0$ so that $M\phi(\delta) \lesssim k_B T^4$. Therefore ON and OFF correspond, respectively, to $a \geq -1 + \delta$ and $-1 \leq a < -1 + \delta$. The compensation mechanism similar to the one discussed here has been discussed and called induced fit by Koshland (1973) in the context of the ligand binding by enzymes.

The above two semi-detectors establishes the correlations between the outer world of the detectors and the detectors themselves in the way that the semi-detectors represent certain error-free information despite the thermal fluctuations. If the state variables of two semi-detectors of presence, say $a_1$ and $a_2$, respectively, are coupled energetically with each other, the resulting system might function to realize the “cooperative binding” (Monod et al., 1965; Koshland et al., 1973) or the “exchange of binding” (Eisenberg and Hill, 1985), depending on the nature of the coupling.

3 Free-energy transducer based on the semi-detectors of presence and the gates

In order to focus on the subject of the autonomous control, we would like to avoid energetic aspects as far as possible. To this end, we will construct a pump of the ideal “load” (L) gas particles from a dilute reservoir, $(L, l)$, to a

![Fig. 2. Left: Schematic representation of the semi-detector of presence. $a$ and $x$ represent, respectively, the position of the movable object (filled square) and that of the ligand particle (thick dot). Unless the particle is within the proximity of the detection cite ($0 \leq x < \delta$) with small $\delta$, the movable object is constrained at $a \simeq -1$ even under thermal agitations. Right: The accessible phase space is indicated as a shadowed region, where $U(x,a) \sim k_B T$.](image-url)

4 One can verify this by drawing $M\{\phi(a) - \phi(a-x)\}$ vs $a$ for various values of $x$. 


dense reservoir, \((L,h)\), at the expense of the diffusion of the ideal “fuel”\((F)\) particles from a dense reservoir, \((F,h)\), to a dilute reservoir, \((F,l)\), see Fig 3. If we denote the chemical potentials of these reservoirs by \(\mu_{L,l}\), \(\mu_{L,h}\), \(\mu_{F,h}\) and \(\mu_{F,l}\), respectively, then the decrease of the total Gibbs’ free energy in the course of the transport of \(\Delta N_{L,l\rightarrow h}\) of the load particles at the expense of \(\Delta N_{F,h\rightarrow l}\) of the fuel particles is \((\mu_{F,h} - \mu_{F,l})\Delta N_{F,h\rightarrow l} - (\mu_{L,h} - \mu_{L,l})\Delta N_{L,l\rightarrow h}\). Below we will present a completely symmetric model in which the roles of the fuel and the load are totally exchangeable depending on the relative magnitude of \(\mu_{F,h} - \mu_{F,l}\) and \(\mu_{L,h} - \mu_{L,l}\)\(^\text{5}\).

The cyclic process in the above mentioned pump requires at least two internal degrees of freedom\(^6\). To construct such pump with using the semi-detectors of presence as constituent modules, the most natural way would be to put one semi-detector on the fuel side (with the variable \(a_F\)) and the another one on the load side (with the variable \(a_L\)), and to have them to control the access of the particles on the opposite sides, via allosteric couplings (Monod et al., 1965), see Fig. 4. We would call this scheme “bidirectional control”. We will describe in three steps the details of the model which implements this scheme:

**Step-1: Introduction of the “reaction” coordinates \(\tilde{x}_L\) and \(\tilde{x}_F\).** Being inspired by Fig. 2, we introduce the convenient coordinate \(\tilde{x}\) \((0 \leq \tilde{x} < \infty)\) which

\[
J_{L,l\rightarrow h} = L_{\text{asy}} \Delta \mu_{\text{asy}} - L_{\text{sym}} \Delta \mu_{\text{sym}}\]

and

\[
J_{F,h\rightarrow l} = L_{\text{asy}} \Delta \mu_{\text{asy}} + L_{\text{sym}} \Delta \mu_{\text{sym}}.\]

Here \(L_{\text{asy}} \geq 0\) and \(L_{\text{sym}} \geq 0\) are the kinetic coefficients, and \(\Delta \mu_{\text{asy}} \equiv \mu_{F,h} - \mu_{F,l} - \mu_{L,h} + \mu_{L,l}\) and \(\Delta \mu_{\text{sym}} \equiv \mu_{F,h} - \mu_{F,l} + \mu_{L,h} - \mu_{L,l}\). This pump can work almost reversibly near the stalled condition, \(\Delta \mu_{\text{asy}} = 0\), if \(L_{\text{sym}}\) is sufficiently small.

\(^5\) Under this symmetry, the currents of the active transport of the load particles, \(J_{L,l\rightarrow h}\), and that of the passive diffusion of the fuel particles, \(J_{F,h\rightarrow l}\), are given in the linear non-equilibrium thermodynamics as \(J_{L,l\rightarrow h} = L_{\text{asy}} \Delta \mu_{\text{asy}} - L_{\text{sym}} \Delta \mu_{\text{sym}}\) and \(J_{F,h\rightarrow l} = L_{\text{asy}} \Delta \mu_{\text{asy}} + L_{\text{sym}} \Delta \mu_{\text{sym}}\). Here \(L_{\text{asy}} \geq 0\) and \(L_{\text{sym}} \geq 0\) are the kinetic coefficients, and \(\Delta \mu_{\text{asy}} \equiv \mu_{F,h} - \mu_{F,l} - \mu_{L,h} + \mu_{L,l}\) and \(\Delta \mu_{\text{sym}} \equiv \mu_{F,h} - \mu_{F,l} + \mu_{L,h} - \mu_{L,l}\). This pump can work almost reversibly near the stalled condition, \(\Delta \mu_{\text{asy}} = 0\), if \(L_{\text{sym}}\) is sufficiently small.

\(^6\) This statement does not contradicts with the fact that the existing models of heat engine (Feynman et al., 1966; Böttiker et al., 1987) have assumed only one rotational degree of freedom to lift a load, since such degree of freedom corresponds to two bounded degrees of freedom.
describes a ligand particle and a semi-detector of presence: 
\[ x = \max(\tilde{x} - 1, 0), \quad a = -\min(\tilde{x}, 1). \]
Then we extend this definition of \( \tilde{x} \) to the case of two particle reservoirs: We assume that the high-density [low-density] reservoir occupies the half space \( x > 0 \) [\( x < 0 \)], respectively. We redefine the mapping \( \tilde{x} \mapsto (x, a) \) so that \( \tilde{x} \) can take the values on the entire axis, \( -\infty < \tilde{x} < \infty \), with:
\[ x = (\tilde{x}/|\tilde{x}|) \max(|\tilde{x}| - 1, 0), \quad a = -\min(|\tilde{x}|, 1). \]

A ligand particle is on the detection site if \( |\tilde{x}| \leq 1 \), in the high-density reservoir if \( \tilde{x} > 1 \), and in the low-density reservoir if \( \tilde{x} < -1 \). We interpret \( \tilde{x} \) so that the region of \( |\tilde{x}| \leq 1 - \delta \) with small \( \delta > 0 \) corresponds to the state ON of the semi-detector, while \( |\tilde{x}| > 1 - \delta \) corresponds to the state OFF. Finally we apply this type of mapping for both the load side (\( \tilde{x}_L \)) and the fuel side (\( \tilde{x}_F \)). The coordinate plane (\( \tilde{x}_L, \tilde{x}_F \)) can then represent the positioning of one representative load particle and the one fuel particle together with the states of the semi-detectors of presence, \( a_L \) and \( a_F \).

**Step-2: Definition of the gates’ action.** For the fuel particles, we construct the gate which allows the access of the particles exclusively from one of their reservoirs at a time. In the Top of Fig. 5, the potential barrier (the height \( \gg k_B T \)) is established at \( \tilde{x}_F = 1 + \epsilon \) with a small \( \epsilon > 0 \), so that the access of the fuel particles from the high-density reservoir is blocked at a distance \( \epsilon \) off the detection site (\( |\tilde{x}_F| \leq 1 \)). The same architecture is defined for the load particles. Similarly the gate represented in the Bottom of Fig. 5 blocks the access of the fuel particles from the low-density reservoir at the distance \( \epsilon \) off the detection site.

**Step-3: Coupling of the semi-detectors to the gates.** We define the bidirectional control by the following symmetric rules:

[Control by \( a_F \)] If a fuel particle is detected, i.e. if \( |\tilde{x}_F| \leq 1 - \delta \) (Top-Left of Fig. 6), only the load particles in the low-density reservoir (\( \tilde{x}_L < -1 \)) can access to their detection site. If a fuel particle is not detected i.e., if \( |\tilde{x}_F| > 1 - \delta \) (Top-
Fig. 5. *Top:* Potential profile of the gate that opens to the fuel particles in their low-density reservoir. *Bottom:* Similar to the above but the accessibility is for the high-density side. The thick horizontal bars indicate the detection site for the fuel particles.

Fig. 6. *Top:* The control of the load particles by the detection of the fuel particles. *Bottom:* The control of the fuel particles by the detection of the load particles. The J-shaped symbol in, for example, the Top-Left indicates the exclusive accessibility from the low-density reservoir of the load particles, as indicated in the Top of Fig. 5. The other cases would be understood similarly.

Right), then only the load particles in the high-density reservoir ($\tilde{x}_L > -1$) can access to their detection site.

[Control by $a_L$]: If a load particle is detected, i.e. if $|\tilde{x}_L| \leq 1 - \delta$ (*Bottom-Left* of Fig. 6), only the fuel particles in the low-density reservoir ($\tilde{x}_F < -1$) can access to their detection site. If a load particle is not detected, i.e. if $|\tilde{x}_L| > 1 - \delta$ (*Bottom-Right*), then only the fuel particles in the high-density reservoir ($\tilde{x}_F > -1$) can access to their detection site.

The consequence of these simple and symmetric combination of the semi-detectors and the gates is immediately seen by the graphical representation in Fig. 7. There, the potential barriers of the gates are indicated by the thick horizontal or vertical bars. For example, the short horizontal bar at $\tilde{x}_F = 1 + \epsilon$ in the range of $|\tilde{x}_L| < 1 - \delta$ represents the blockade of the access of the fuel particles from their high-density reservoir. We see how the combination of those bars organizes a broad passageway joining the second and the forth quadrants on the $(\tilde{x}_L, \tilde{x}_F)$-plane. This passageway corresponds to the diffusion of a single fuel particle from its high-density reservoir to the low-density one.
In the \((\tilde{x}_L, \tilde{x}_F)\)-plane, the thick horizontal and vertical bars represent the presence of the potential barriers either for the \textit{fuel} particles (the horizontal bars) or for the \textit{load} particles (the vertical bars). The shaded regions are where the bidirectional control prohibits to access except for a small “leak” due to the finite values of \(\epsilon\) and \(\delta\). See the text for the details. The dashed curve shows one representative process (cf. the footnote on the multiplication of the state points). \(B-E\) on the curve correspond roughly to those in Fig 4.

accompanying the active transport of a single \textit{load} particle from its low-density reservoir to the high-density one. Therefore, if we could neglect the small gaps between the bars due to the finite values of \(\epsilon\) and \(\delta\), this pump would work tightly with \(\Delta N_{F,h \rightarrow l} = \Delta N_{L,l \rightarrow h}\), whose mean flow direction is determined by the sign of \((\mu_{F,h} - \mu_{F,l}) - (\mu_{L,h} - \mu_{L,l})\). Actual autonomous pump seems not be able to avoid the “leak” due to the above mentioned gaps, but this leak would be of importance only near the stalled state \((\mu_{F,h} = \mu_{F,1} = \mu_{L,h} = \mu_{L,1})\) as far as \(\epsilon\) and \(\delta\) are small\(^8\).

How would the pump thus constructed looks like for an observer who can survey only the \textit{load} particles? Let us suppose that \((\mu_{F,h} - \mu_{F,1}) - (\mu_{L,h} - \mu_{L,1})\) is positive and enough greater than \(k_BT\). As long as the detection site of the \textit{load} particle is empty, this site is almost always accessible from the low-density reservoir of the \textit{load} particle (\(B\) along the dashed curve in Fig. 7). When a \textit{load} particle arrives at the detection site and is detected (\(C,D\)), the gate is very likely to reverse its accessibility so that the \textit{load} particle on the detection site can leave now for the high-density reservoir (\(E\)). Then as soon as the \textit{load} particle quits the detection site (\(F\)), the gate comes back to the initial conformation (\(B\)). Thus the pump behaves as if it responded by itself to the arrival and the leave of the \textit{load} particle.

\(^8\) In the context of the the linear non-equilibrium thermodynamics, we expect that \(L_{sym}/L_{asy}\) is at most of the order of \(\epsilon\) and \(\delta\).
4 Discussion

We have constructed theoretically an autonomous system that works under thermal fluctuations. The errors of the detection was avoided by introducing what we call the semi-detectors. The concept of the semi-detectors on mesoscopic scale might also be of interest in the context of the mesoscopic devices (Imry, 1997). The cyclic process was enabled by what we call the bidirectional control. The latter idea is applicable also to the macroscopic autonomous processes. For example, in the operation protocols of vending machines or of pay-phones, the gate on one side (taking up the money) and that on the other side (rendering goods or services in exchange) are controlled by their respective detectors on the opposite sides.

The biological molecular motors are not as simple as we have discussed. Still, the present analysis might help as a reference frame when we look for the structure-function relationship in those systems. For example, we might ask if the hydrolysis reaction of ATP (fuel) in a molecular motor corresponds to changing the accessibility from the reservoir of the ATP to that of the ADP and the inorganic phosphate \([\text{P}_i]\). Also we might wonder if the putative Pi-sensors ("switch loop" etc., Vale (1996); Brendza et al. (2000)) can be compared to the semi-detector of the ligand in our model. As for the kinetics of the interaction between the molecular motor and its counterpart filament (load), we might ask if the motors have a degree of freedom to detect its own mechanical strain (Tsiavaliaris et al., 2004; Sekimoto, 2000), in addition to the degree of freedom to control the binding to the filament (Nitta et al., 2004). As a qualitative prediction, we might mention the possibility of the "mutants" in which the degree of freedom related to the detection of, say, the load particles, \(a_L\), is immobilized, as shown in Fig. 8. In this case, the rate of passive diffusion of the load particles should depend on the density of the (non-consumed) fuel particles in their high-density reservoirs.

\[ \begin{align*}
\tilde{x}_F \\
\tilde{x}_L \\
\end{align*} \]

"Wilde-type"

\[ \begin{align*}
\tilde{x}_F \\
\tilde{x}_L \\
\end{align*} \]

"Mutant"

Fig. 8. The pump of the "wild-type" (left, see Fig. 7) and a "mutant" with blocked fuel reactions (right). See the text.
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