A Minimal 2D Model of the Free Energy Surface for a Unidirectional Natural Molecular Motor

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Abstract A schematic model of a natural molecular motor is proposed. It uses the change of the free energy surface to an effective surface as long as the enzyme is active. This effective surface acts as a trapdoor and explains the power stroke in biomotors, as well as its unidirectional movement. Then a thermal relaxation can do the energy transduction of the motor. The model uses Newton trajectories to explain the movement of stationary points on the effective surface.

Keywords Natural molecular motor · Effective free energy surface · Newton trajectory · Barrier breakdown point · Unidirectional movement

1 Introduction

A natural molecular motor requires an energy-consuming catalyst for its cyclic movement [1]. It converts the chemical energy into mechanical work [2]. To work in the defined kind, the movement has to be unidirectional. There are natural [3–7] as well as artificial examples of molecular motors [8–19] where the latter are still more interesting toys, in comparison to the former. Natural motor proteins generate mechanical work from the chemical energy of adenosine triphosphate (ATP). They are included in nearly all aspects of the living world. We make the important assumption that the catalytic force, $\mathbf{f}$, which initializes the chemical reaction of the motor molecule, is mainly of an electrostatic character [20–25]. Interesting studies [23, 26] show that to calculate the direction of $\mathbf{f}$ for a motor enzyme remains a difficulty. The free energy surface (FES), V, of the motor molecule changes under the force, which means that the minimums and the saddle points (SPs), thus the barriers in-between change [2, 27–33]. Therefore the reactivity is either enhanced or suppressed [34], and especially enzymes achieve an extraordinary rate acceleration and specificity [26, 35]. The extent of the barrier modification depends on the direction and on the magnitude of the external force, the loading rate [32, 33]. At all, "one can think of the enzyme as exerting a force on the substrate that catalyzes the reaction."[2] The resulting effective FES, $V_{\mathbf{f}}(\mathbf{x})$, is obtained for a force, $\mathbf{f}$, via the linear approximation [2, 29, 31, 36–41]

$$V_{\mathbf{f}}(\mathbf{x}) = V(\mathbf{x}) - \mathbf{f}^T \cdot \mathbf{x} \tag{1}$$

where the superscript T denotes transpose, and $\mathbf{x}$ is the vector of the internal coordinates of the motor molecule. The symbolic point between $\mathbf{f}$ and $\mathbf{x}$ means the scalar product.

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This is explained elsewhere [42]. If $|\mathbf{f}|$ is zero then Eq.(1) reduces to the pure 'thermal limit'. The disturbance of the stationary points on the effective FES, $V_{\mathbf{f}}(\mathbf{x})$, is described by Newton trajectories (NT) if only the loading rate of $\mathbf{f}$ variates [32,33,43–47]. In Section 2 we shortly describe the background necessary to the application of NTs. In Section 3 we introduce a test FES and propose the new molecular motor model.

2 Application of Newton Trajectories

The stationary points on the effective potential have to satisfy the condition, $\nabla_{\mathbf{x}} V_{\mathbf{f}}(\mathbf{x}) = \mathbf{0}$. Since $V_{\mathbf{f}}(\mathbf{x})$ is the one given in Eq.(1), it follows that its minimums and SPs should satisfy the vector equation, see also reference [48]

$$\nabla_{\mathbf{x}} V_{\mathbf{f}}(\mathbf{x}) = \mathbf{g}(\mathbf{x}) - \mathbf{f} = \mathbf{0} \ . \tag{2}$$

One searches a point where the gradient of the original FES, $\mathbf{g}(\mathbf{x})$, has to be equal to the force, $\mathbf{f}$. This is the definition of an NT in the case that the force $\mathbf{f}$ changes its magnitude in a continuous way but its direction remains a constant unit vector. Thus, the NT then describes a curve of force displaced stationary points (FDSPs) under different load [32,33, 43–47].

Eq.(2) can be written in a projector form [43,44]

$$\left(\mathbf{U} - \mathbf{l}\mathbf{l}^T\right)\mathbf{g} = \mathbf{0} \tag{3}$$

where $\mathbf{U}$ is the unit matrix and the $\mathbf{l}$-unit vector is the direction of $\mathbf{f}$. The equation means nothing else that $\mathbf{g}$ and $\mathbf{l}$ are parallel. If we differentiate the projector Eq.(3) with respect to the parameter that characterizes the curve, s, we obtain [44,46]

$$\left(\mathbf{U} - \mathbf{l}\mathbf{l}^T\right)\mathbf{H}\frac{d\mathbf{x}}{ds} = \mathbf{0} \ . \tag{4}$$

This is an expression of the tangent of the FDSPs curve. Eq.(4) is a way to generate the FDSPs curve.

If one uses a given fixed unit vector of the direction, $\mathbf{l}$ of $\mathbf{f}$, and if one goes along the corresponding FDSPs curve then the magnitude of the force, $|\mathbf{f}|$, starts with zero at a stationary point, and ends with zero at the final next stationary point. In between there has to be a maximum of $|\mathbf{g}|$, according to Eq.(2). Here holds the condition [31,32,34]

$$Det(\mathbf{H}(\mathbf{x})) = 0 \tag{5}$$

with the Hessian of the original FES, $V(\mathbf{x})$. The case is the point where the square of the gradient norm achieves a turning point, and the effective $V_{\mathbf{f}}(\mathbf{x})$ along the FDSPs path here achieves a shoulder [31,32,34]. The point on the FDSPs curve is referred to as barrier breakdown point (BBP) [32,34]. The barrier of $V_{\mathbf{f}}(\mathbf{x})$ decreases from the original FES barrier to zero at the BBP. The kind of points is discussed also elsewhere [49].

3 Model FES for a motor molecule

We use the following test function for a 2D-section of the full FES of the motor molecule

$$V(x,y) = 5\,Exp[-x^2 - (y+1)^2] + 0.5\,Exp[-x^2 - 0.1(y-1)^2]$$

$$+ 40\,Exp[-1.5(x^2 + y^2)] + 3\,(y+1)^2 + 10\,(x/3)^4 + 0.2\,x^3 \ . \tag{6}$$

We describe why the test function is used, see also Fig. 1a where we show the surface by its
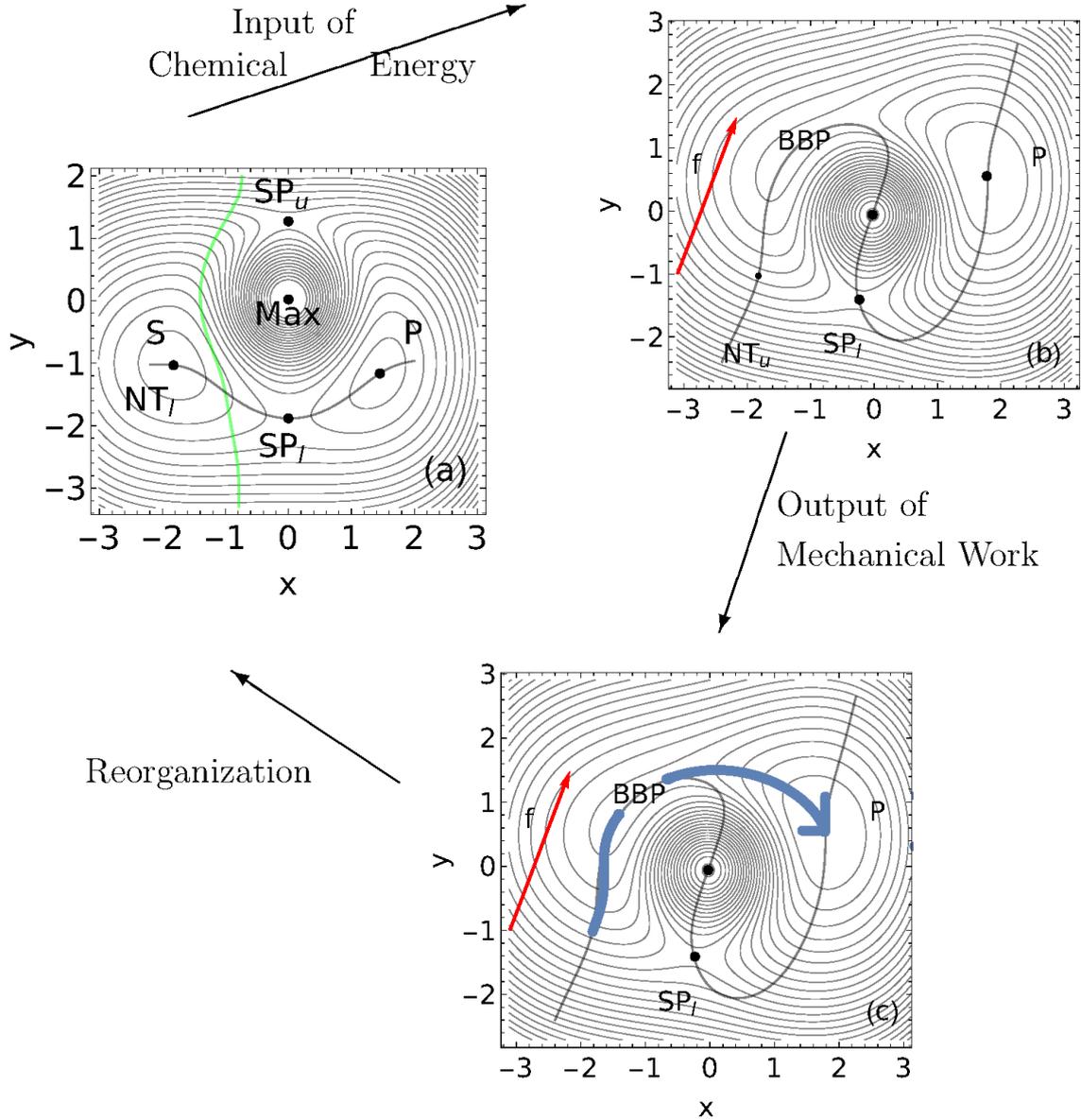
Fig. 1 Minimal scheme of a molecular motor cycle. (a) The ground state may be at S. A line of BBPs between S and the SPs is thin and green. (b) The enzyme (red arrow) enforces the transformation to an effective surface up or near a BBP on NT_u. (c) Relaxation induces the reaction $S \to P$ over the upper pathway. It is depicted here by a steepest descent (bold, blue). Then a back-reaction, or reorganization leads to the startpoint, S, in panel (a) over the lower pathway. It is depicted by another NT_l in the valley $P \to S$.

contours. The two minimums are slightly different: the stable substrate, S, is deeper than the unstable state, P, of the molecule. However, the two competing reaction pathways over the two transition states (TSs), SP_l and SP_u, are quite different. The upper way over the SP_u is so high that a thermic reaction may be excluded. The lower pathway is depicted by an NT_l. In Fig. 1a additionally included is the line (thin, green) of the BBPs [32–34] on the substrate side. The curve is characterized by the condition of Eq.(5).

Our aim is to broadly reproduce the case of the F_1-ATPase motor where two minimums and two SPs are reported on a least FES path [23]. The first step in solving complex questions is to articulate precisely what needs explaining. The surface of Eq.(6) is a minimal model of the case with two minimums and two SPs. Here we can try to explain the

main process of a natural motor molecule like the F_1-ATPase. Note that Adachi et al.[50] achieved in 2007 a comprehensive mechanochemical characterization of this ATPase.

It is known that different directions of an outer force can change the kind of the reaction path [2,32,33,38,51–53]. We use this for the proposal of a new minimal model of a molecular motor. We assume that the substrate, S, is already bound by the enzyme [54], and we assume that the force works mainly by the electrostatics of the enzyme [21,22,25] which is actuated by the chemical energy of a fuel molecule being usually ATP.

Step one

This may be step one of the motor model shown in panel (b) of Fig.1. By a certain molecular configuration a fuel molecule enters the catalytic side of the enzyme [55]. There it releases its energy, and the enzyme is able to apply its catalytic force, here in Fig.1b $f = 9.5\,(0.35,\,0.94)$ (in units of the surface of Eq.2) in direction to the upper SP_u. Then we get an effective surface: the energy of the former minimum S is risen up along the NT_u, and the former SP_u is lowered along the same NT_u, and both can collapse at a BBP at least. A ground state destabilization [56], as well as a transition state stabilisation (TSS) [56,57] happen here, but possibly in their final form. The new effective FES in panel 1b forms a third, but instable state for the motor molecule, besides S and P.

Step two

The difference of the free energy, $\Delta V_{\mathbf{f}}$, between the former states S and P is inverted in panel (b), compare Fig.1 of Ref.[2]. Now step two occurs. The molecule will relax along the given minimum energy pathway (bold, blue) of Fig.1c with a thermodynamic downhill direction. The effective FES acts like a one-way trapdoor. Many research workers name it power stroke [2,20,26,58–62], to name a few. But there are also other opinions [63]. The molecular environment can harvest the energy in form of work, a mechanical translation, or rotation [3,20]. The phase ends in the region of state P. It can be expected that step one and step two somewhat overlap. Note that the way over the former lower SP_l is inhibited in the two steps. The SP_l is moved uphill by the force $\mathbf{f}$ in direction to the maximum on the NT_u.

Step three

The next step will be the reorganization, or the recovery stroke [58,64–66]. If the fuel molecule is taken to pieces, the catalytic force ends and the motor molecule is again in the thermal limit. By a usual thermally activated relaxation from P to S along an NT_l, like in Fig.1a, the cycle finishes. The thermodynamic equilibrium between S and P will appear. A further output of mechanical work is possible. It would explain the partition of the elementary rotational work of 120° in two substeps for the F_1-ATPase [67–70]. A release of the reaction products of the fuel may be included [71] and a binding of a new fuel molecule to the catalytic side near the start position S [4]. Often the velocity of the motor depends on the fuel concentration [2,65,72].

Then the cycle can start again. The three steps are illustrated in Fig.1. The proposed new model is an information ratchet, as well as an energy ratchet [11,73]. The first one applies because of the directed action of the enzyme which gives priority to one of the possible reaction pathways. The second one applies because the TSS by the enzyme acts directly as the energy ratchet for the motor molecule. Thus one obtains a natural unidirectional cyclic behavior.

Note that the information ratchet acts over an excitation by visible light [14], or ultraviolet light [73,74] in many artificial molecular motors. The excitation path then goes over another electronic surface [74,75] which replaces the electrostatic force, $\mathbf{f}$. The trapdoor for the unidirectional movement is a transition from an electronic excited surface back to

the ground state surface. It also acts as a power stroke [63]. A one-dimensional profile of the FES is reported [74, 75] which also contains 2 minimums and 2 TSs like our model. An orthogonality of the trajectories of the thermal and the photochemical pathways [15, 75] is conjectured which again is a hint to the intrinsic two-dimensional character of the FES part of the motor problem.

To select the intrinsic two coordinates, (x, y), out of the full dimension of the motor molecule can be a difficult task. The FES is periodic if angular coordinates are used [23]. Note that both dimensions, (x, y) in Fig.1, of the FES should belong to the motor molecule and still not to the enzyme. There are other proposals to understand the matter by one dimension for a chemical coordinate of the motor molecule, and one dimension of a conformational coordinate for the catalyst [23]. Such a treatment is appropriate in any case because the enzyme will also come in many conformations. In our case, a conformational coordinate would be a further, additional dimension behind the used two. In this additional dimension could be, in another plane, so to say lifted by the force $\mathbf{f}$ over the ground state of Fig.1a, the effective FES of the trapdoor state Fig.1b.

In other dimensions orthogonal to the minimal model of Fig.1, the input of the chemical energy [26], as well as the output of mechanical translation [3] will be governed by other FESs [23, 71]. These processes will also be of cyclic kind, and they will also be enforced by corresponding parts of the enzyme. Note that in some natural molecular motors the direction of the energy transduction is reversible [2, 3, 20, 76, 77]. However, this is not discussed here in our minimal model.

4 Discussion

The proposed model for the action of a natural molecular motor explains in a very simple kind the unidirectional way of the movement of the motors found in nature. The key is that there is no single ground state FES of the motor. In contrast, there is a periodically changing effective FES which drives the unidirectional motion by a trapdoor state. The new model says that the power stroke is not the reverse of the recovery stroke, as it is assumed in former work [78], and one needs a time-dependent modulation [19]. Interestingly, the step one of Fig.1b is connected for a combined direction of the conformational and the chemical coordinate in F_1-ATPase with a jump over an upper SP_u on the Mukherjee-Warshel surface [23]. The unidirectionality of this step is claimed, however, it is not explained in reference [23], and it is not explained in later papers of these authors, see reference [63]. A valley of a ground-FES cannot lead to a unidirectional movement because of the reversibility of chemical reactions [19]. Such a unidirectional movement would be like the waterfall of M.C.Escher. On a usual FES there is missing the 'pawl', the ratchet for a unidirectional movement. The ratchet emerges in our play by the force displaced trapdoor state of Fig.1 b.

Our new model also explains the two substeps in many natural motors, the substeps of 40° and 80° rotation in the 120° full step of one third of the F_1ATPase motor cycle, for example, or the power stroke and the recovery stroke in myosin. The two substeps in the F_1ATPase motor are already given by the existence of two minimums on the FES ground state, A/C and B in [23] in Fig.2A being here in Fig.1 the points P and S. However the directionality over the two very different SPs between the two minimums remains unclear. On the other hand, the recovery stroke in myosin does not require ATP hydrolysis [79], thus it does not need the fuel. It could be a thermal relaxation like in Fig.1a along the way back from P to S. This recovery stroke is understandable by a minimum energy pathway over mild barriers along a usual reaction coordinate [78, 80].

There are at least two simplifications in model Eq.(1).
(i) The electrostatic force of the enzyme acts on the dipole moment of the included sub-

groups of the motor molecule. So one should use $-\mathbf{f}\cdot\mathbf{d}_e(\mathbf{x})$ in Eq.(1) with the corresponding vector of the dipole moment function, $\mathbf{d}_e$ [81]. Then Eq.(1) is a first approximation of the reality. Usually it is difficult to determine $\mathbf{d}_e(\mathbf{x})$ already for small molecules [82].

(ii) The direction of the force of the enzyme, $\mathbf{f}$, may not be totally constant under the attac of the enzyme. Then we can imagine to follow a changed direction a corresponding changed NT. But if the new NT remains in the corridor of NTs which belong to SP_u [33], then a final effective FES will emerge with a shape shown in Fig.1b.

5 Conclusion

The proposed cyclic molecular motor model needs

 (i) an FES section with two competing reaction valleys, one from substrate, S, to product, P, over a lower TS, and one from S to P over an upper TS. One can assume that the upper way is not available for usual thermic Brownian noise.
 (ii) An enzymatic electrostatic force acts in the selected direction of the upper TS. It absorbs the chemical energy of the fuel. It leads to a TSS and enforces the transition $S \rightarrow P$ over the upper reaction path by an instable trapdoor state, but the lower pathway is inhibited.
(iii) Then the relaxation part facilitates an output of mechanical work, the transduction task of the motor.
(iv) If the fuel energy is over, then a back-reaction by the given balance of substrate and product is enforced by usual Brownian noise along the lower pathway over the lower transition state. It again will be an output of mechanical work.
 (v) There is an outer exchange of the reaction products of the fuel, by another cyclic process.

If conditions (i) to (v) are given then it may work.

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