Bioinspired laser-operated molecular locomotive

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Biomotors kinesin and dynein show us that robust track-walking is possible down to molecular scale. Here I design a laser-powered molecular locomotive that is able to do that on an easily constructed track. The core of the machine is its work cycle that periodically converts optical energy into mechanical work, which is further rectified into processive, directional motion. Thus the molecular locomotive is essentially beyond the famous design of molecular shuttles. Under automated laser operation, the locomotive can move a few μm per second comparable to its biological counterparts. However, this artificial motor is capable of conveniently switchable, dual directional motion in contrast to common unidirectionality of biomotors. The locomotive is also different from the big category of Brownian motors in the sense that move of the locomotive is not a result of biasing pre-existing fluctuations, rather it is directly and decisively driven by optomechanical strokes of the work cycle, generating a pulling force ten times greater than those of biomotors. Being a novel type of molecular motor as well as a powerful molecular engine, this machine will potentially enable automatic, forceful delivery of molecular building blocks with nanometer accuracy. Well within reach of established techniques, its implementation will be a significant advance in nanoscience and nanotechnology.

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I. INTRODUCTION

Recent progress in artificial molecular motors is fascinating [1–5]. Based on synthetic molecules such as rotaxanes and catenanes [6], controlled translocation has been demonstrated of a ring relative to a molecular chain which it encloses [7–12]. The ring, which can be regarded as a molecular train, is initially stabilized at a so-called station that is a binding site of the chain. A chemical stimulus or an absorbed photon modifies the electronic structure of the ring-chain system, and the energy input drives the train to a second, otherwise energetically disfavored location. A stimulus of opposite effect recovers the energy preference, and the train relaxes back to its initial station. This mechanism forms the basis for a variety of implementation of linear molecular shuttles [7–10]. Rotary systems are also developed where the chain forms a closed cycle and interlocks with the ring [11–13]. Controllable intramolecular rotation has also been realized in other systems [14,15]. These remarkable achievements, largely motivated by molecular motors ubiquitous in living organisms [16–18], are opening the door towards the new field of manmade molecular machinery.

Despite encouraging progress, the field is, however, still very much in its infancy [2]. From a fundamental point of view, basic guidelines for making molecular machines are still missing. While the bottom line for machine making at molecular level is, of course, drawn by fundamental laws of physics, practical lessons can be readily found in living organisms [19]. Biological motors [16–18], being tiny molecular compounds though, are not anonymous, random particles. Instead they function as genuine machines with unique "blueprints" (i.e., genetic code carried by DNA) and specific working rules (e.g., biochemical pumping by ATP and sophisticated regulation), revealing what is possible down to molecular world and how it is done.

In addition to molecular synthesis paramount in development of artificial molecular machines, there is currently also an emerging role of machine design. A prominent example is the idea of Brownian motors, which bias molecular fluctuations into directional motion [20]. Machine design at molecular scale should address the key issue of how to "convert" elusive microscopic particles into a robust union of unique mission, which can be certainly controlled so that energy is repeatedly pumped in and desired work rectified out. A good design should promise a reasonable level of working performance with a minimum level of technical demands, and allow for flexible implementation as well as future improvement. From a technical perspective, significant advances in chemical synthesis and in single-molecule detection and manipulation are offering real opportunities for fine designs that build imagination from the solid ground of technological details.

Automated, site-selective delivery of individual molecules is of great importance for nanoscience and engineering. For this task a molecular machine is desirable which is able to reach unlimited locations under a broad range of loads or through nontrivial obstacles, essentially beyond a couple of catch-and-return locations within a molecular shuttle system. In this paper I design a laser-operated molecular locomotive that is able to travel anywhere an easily constructed track reaches. The locomotive adopts an inchworm move mechanism, essentially mimicking some track-walking biomotors [21]. However, direction of the locomotive is conveniently tunable by laser pulses in contrast to common unidirectionality of biomotors. Distinctly different from the category of Brownian motors [20], the proposed machine actively and decisively drives its move with powerful optomechanical

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strokes, which are sufficient to overcome most noncovalent obstacles encountered in molecular transport in a variety of environments.

The article is organized as follows. In Sec. II a complete design of the locomotive will be presented. In Sec. III a set of theory is developed to facilitate quantitative analysis of the machine and its operation. Section IV examines characters and capacity of the proposed locomotive from molecular machinery perspective. The final section is perspective and outlook.

II. A LASER-OPERATED MOLECULAR LOCOMOTIVE

A. Constituents of the machine

For the molecular locomotive laser is used as an energy source and as an operational tool. Laser operation can be carried out a distance from the machine and its microenvironment, free of diffusive supply of chemical fuel or regulating chemical agents. Therefore, it is in principle possible for a laser driven machine to work in a variety of liquid or nonliquid environment under a broad range of thermodynamic conditions. Since electronic excitation upon photoabsorption and subsequent intramolecular relaxation are extremely fast, energy injection or state switching by laser can be regarded as an instantaneous process, presenting great advantages for control. Using ultrashort laser pulses and confocal optical microscopy setup, radiation field can be projected to a single macromolecule with great energy density in spatial as well as in temporal dimension, guaranteeing efficient driving, control and diagnosis of molecular machines [22–24].

The molecular locomotive is designed to have its main body as a linear polymer chain composed of repeated units. Each unit has within its backbone a double bond such as N═N, C═N or C═C, around which *cis-trans* isomerization can be triggered by laser irradiation. The other part of the backbone rectifies the laser-powered bond twist into sizable change of contour length of the unit. Thus each isomerizable unit acts as a working unit of the locomotive. Besides the optomechanical capable polymer, the locomotive contains other crucial parts. On either end there is a "head" group which, as being tuned by laser, can bind to or break from a track. A firm "docking" of the locomotive to the track preserves preceding steps of a directional motion, which would otherwise be easily lost because molecular world is dominated by thermal and quantum fluctuations [20]. To hold ground first is also necessary for making next move in a desired direction. The trailing end of the locomotive should also contain a linker group, which is devised to connect to a molecular cargo. A long, rigid linker is preferred to hold the cargo away from the locomotive to minimize interference with its operation. For transportation the cargo can be attached to the linker via a covalent bond, which can be subsequently photocleavaged to unload the cargo.

To meet the need of a molecular locomotive, a polymer molecule must be able to amplify light-initiated bond twist into sizable change in overall shape, and maintain robust configuration under mechanical load. In a recent, inspiring experiment Hugel *et al.* examined optomechanical capacity of a synthetic polymer of azobenzene units [25]. They observed that a polymer of contour length $L=88$ nm changes its length by $\Delta L=2.8$ nm when about 55% of the 47 azobenzene units in the molecule switch configuration upon laser irradiation. Significantly, this level of length change can be repeatedly achieved under an external force well above 200 pN inserted on the polymer backbone by an atomic force microscope cantilever, making possible a repetitive cycle for optomechanical energy conversion. The locomotive can be built from synthetic polymers such as those used by Hugel *et al.* [25]. A candidate for locomotive polymer should also possess large photoabsorption cross sections and high quantum yield for light-induced *cis-trans* configuration switching. For direction of isomerization to be controllable, resonance frequency must be sufficiently different from one direction to the other. There are plenty of synthetic polymers which meet these requirements [26,27].

The locomotive is to be adhered to a stable substrate for operation. There are a variety of possible candidates for the supporting platform. It can simply be a solid-state surface of macroscopic bulk material, or surface of a mesoscale particle that is sufficiently bigger than the locomotive. Another attractive choice is cylinder-shaped microtubule like those walked by many biomotors [16]. The locomotive together with its substrate can be either exposed in gas phase or placed in water. The present paper focuses more on the latter case where the locomotive works at a liquid-solid interface.

The interaction between a running locomotive and its ground should be strong enough to hold them together, yet not too strong to hinder lateral mobility. As proved by biomotors walking on microtubules [17], fluctuating forces of molecular world can do the job if they are properly regulated. A common intermolecular interaction is Van der Waals contacts which provide attraction over several Å of molecular separation with energy comparable to that of thermal motion, $\sim kT$ [28]. By site-specifically engineering hydrogen bonding groups to the locomotive and to the substrate, hydrogen bonds can be introduced into the locomotive-substrate interface. Normally stronger than a van der Waals contact, a hydrogen bond is of energy $2-20\ kT$ depending on atomic identity of the bonding partners and their relative orientation [28]. When hydrogen bonding groups of the substrate form multiple linear sequences which are parallel and within nanometers from each other, we essentially have a track for the locomotive because it is attracted by this hydrogen-bonding belt more than anywhere else on the substrate. Hydrogen bonding interaction is short-ranged: it turns on when a couple of partners touch each other, and is zero as soon as the contact is broken. Thus, a moving locomotive keeps breaking and forming hydrogen bonds with the track.

A processive biomotor such as kinesin or dynein decisively anchors itself to a microtubule via a major docking step enabled by electrostatic interaction [16–18]. Here covalent bonding is chosen for the task of docking to secure attachment of the locomotive to the track even under harsh working condition such as high potential energy barrier and strong fluctuations at high temperature. To enable covalent docking, a series of binding groups must be engineered into the track, further carving out a deep energy-minimum pathway for the locomotive. This narrow path is the route the

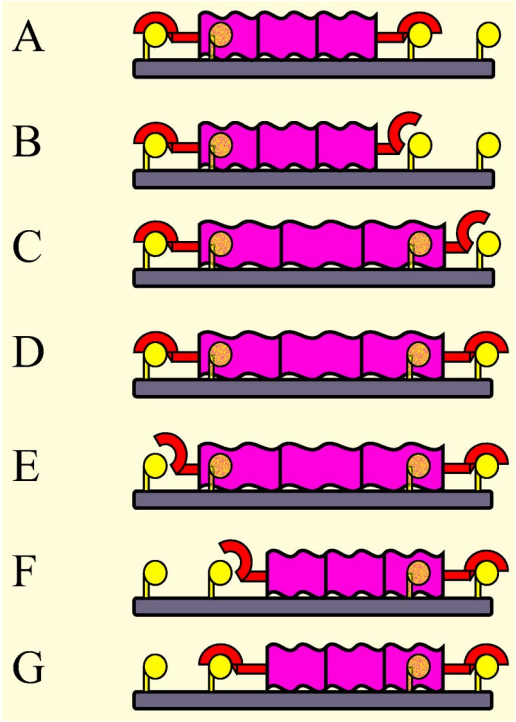

FIG. 1. Illustration of the work cycle. (A)–(D): Stretch step. A locomotive is initially in all-*cis* state with front and rear heads both docked to the track. Laser undocking of the front head is followed by laser-driven *cis*→*trans* isomerization, stretching the locomotive. Thermally activated or laser assisted docking of the forward-moving head at a new binding site anchors the extended locomotive to the track. (E)–(G): Contraction step. After the rear head is undocked, *trans*→*cis* photoisomerization pulls the locomotive ahead. Docking of the trailing head resumes the initial state of the locomotive, which now sits one binding site forward. Note that the locomotive is unrealistically shortened relative to distance between binding sites for illustrative purpose.

locomotive actually "walks" in the sense that the couple of heads make ground at these binding sites during locomotive movement. For easy operation of the locomotive the binding sites are better equally spaced along the track (Fig. 1).

Through this paper we assume contour length $l=2$ nm for a locomotive unit in *cis* configuration. Thus, a locomotive with $N=50$ units has a total contour length $L\approx 100$ nm. This value is usually larger than actual end-to-end distances of the locomotive chain unless all entropy is pulled out of the chain [29]. Assuming a modest size for side-groups, the average cross section of the locomotive is taken as $\pi r_0^2=12.56$ nm^2 with radius $r_0=2$ nm. The contour length change of a locomotive unit upon photoisomerization, Δl is taken as 0.2 nm. Thus, when 80% of the locomotive units switch configuration in the same direction, the whole locomotive will extend or shorten by 8 nm. The width of the track is taken as $w=10$ nm, and binding site period as $x_0=8$ nm.

B. Docking-undocking mechanism

I propose here a mechanism for self-contained docking and undocking (see Fig. 2). Suppose there are two major

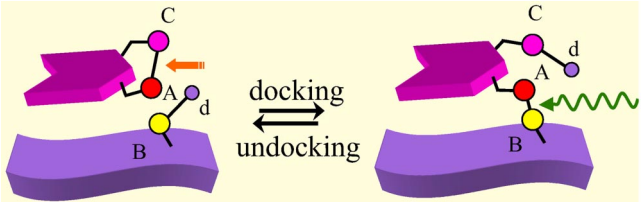

FIG. 2. Illustration of docking and undocking of a locomotive head. From left to right: Once a couple of docking units (AC) of the head diffuses into the interaction range of a couple of harboring units (Bd) sitting on the track, thermal motion or laser irradiation readily drives a bond switching $(A\text{-}C,B\text{-}d)\rightarrow(A\text{-}B,C\text{-}d)$, which eventually interlocks the locomotive and the track. From right to left: A laser beam breaks the A-B bond to engage the nearby C-d bond in a bond switching $(A\text{-}B,C\text{-}d)\rightarrow(A\text{-}C,B\text{-}d)$, setting the head free.

docking units A and C within a head group of the locomotive, and there is a major harboring unit B within a binding group on the path. Through covalent bonds A, C, and B are permanently fixed to their native groups, respectively. When the head is far from the binding site, A and C are bonded together, and B hosts a small chemical agent d. Assume that C, even when it is free of bonding with A, remains in the vicinity of A by steric constraints. The small agent d may hop between two hosts, i.e., B and C, depending on their chemical states. Suppose A,C and B,d are partners for a bimolecular reaction

$$AC + Bd \underset{\text{undocking}}{\overset{\text{docking}}{\rightleftarrows}} AB + Cd.$$

As is often the case, the reactants and the products are separated by a potential energy barrier, ΔG_{dc}. The docking-harboring groups should be chosen such that the docked state, i.e., the state of the reactive partners indicated on the right hand of above equation, has a much lower potential energy than the undocked state on the left hand. In the docked configuration the (Cd) unit remains close to the (AB) unit. Thus the undocking reaction readily proceeds when a laser beam breaks A-B bond linking the head and the binding site [30]. This is laser powered, sterically reinforced undocking. In the undocked configuration the docking unit (AC) keeps moving due to diffusion of the locomotive chain while the harboring unit (Bd) sits on the track. An ideal scenario is that thermal energy is already sufficient to activate the docking reaction. Then docking will be automatically accomplished once (AC) unit falls within the interaction range with (Bd) unit. If thermal motion alone is not sufficient, additional energy supply will be necessary. This can be done by introducing a laser beam that selectively excites the A-C bond [24,31]. Because of vibrational relaxation within the head group, repeated irradiation is necessary to guarantee that (AC) unit is prepared when it encounters (Bd). Thus, we have a diffusion controlled, thermally or laser assisted docking. Breaking of the A-C bond by the laser beam should be avoided, particularly before the docking-harboring partners get together. While selective excitation of the A-C bond alone likely accomplishes the docking, a better

laser docking scheme is to simultaneously optimize vibrational motion of both A-C bond and B-d bond. The laser pulse for the task can be determined by a closed-loop laboratory learning procedure that naturally takes into account the interaction between the reactive partners [24,31]. Such a pulse will have a maximum effect when A-C and B-d bonds are close. When they are separated, neither will be affected much. The optimal control scheme, being able to send energy flow in right direction and at right time, is ideal for the task of laser-assisted docking between moving partners.

The docking-undocking operation will be performed separately for the leading head and for the trailing head of the locomotive. To ensure at least one covalent connection between the locomotive and the track, one must be able to keep one while cutting the other. This requires two sufficiently different undocking frequencies, which can be achieved by using different main bodies for the two heads.

C. Work cycle

Here I shall establish for the molecular locomotive a work cycle, which is powered by laser and moves the locomotive and its cargo along the molecular track (see Fig. 1). I shall sketch the cycle before elaborating it in detail. Let us start from a state where both heads are bound to the track and the locomotive adopts an all-*cis* configuration. Send the first train of laser pulses to unlock the leading head, and shine the second series of pulses to power *cis*→*trans* isomerization of the locomotive. As the locomotive chain is extending and diffusing, the leading head randomly searches for a new binding site. When the docking and harboring groups meet, docking readily occurs with help of thermal motion or laser irradiation. These processes form stretch step of the work cycle. Completion of this step brings the locomotive to a double-docked, all *trans* state. In contraction step that follows, the fourth series of pulses frees the trailing head, and the fifth train of pulses powers *trans*→*cis* isomerization, pulling the locomotive and its cargo ahead. Settlement of the trailing head at a new binding site resumes the initial state of the locomotive. The full cycle moves the locomotive one binding site forward.

To start the stretch step intensity of the undocking beam should be high enough to guarantee the bond breaking within time duration, τ_{ud}, which is much shorter than the time, τ_{uso}, needed for a close-to-100% isomerization of the locomotive. Indeed, τ_{ud} can be made subnanoseconds [30], and τ_{iso} a few thousand ns. Consequently, undocking of the head is surely done before *cis*→*trans* transition.

Keep illuminating the locomotive with a laser beam suitable for *cis*→*trans* transition through τ_{iso} [see Fig. 3(A)]. We assume that an excited locomotive unit has a close-to-unit quantum yield for internal conversion (IC), and the IC path ends in either *trans* or *cis* configuration with equal chance. If a locomotive unit changes configuration upon its first absorption, it stretches and may not absorb another photon because the applied frequency (λ_C) is distinctly different from that for reverse transition (λ_T). Otherwise, the failed unit resumes its ability to absorb a second photon, the absorber again has 50% chance for *trans* configuration. By average 94 photons are absorbed for 46 of the 50 units to make *cis*→*trans* switching. The irradiation time, τ_{iso}, should be long enough to achieve close to 100% switching of the locomotive. The stretch step is free of the burden of cargo because the linker is close to the trailing end that remains fixed to the track during the step. Nevertheless, a certain amount of energy will be consumed by friction at the locomotive-track interface.

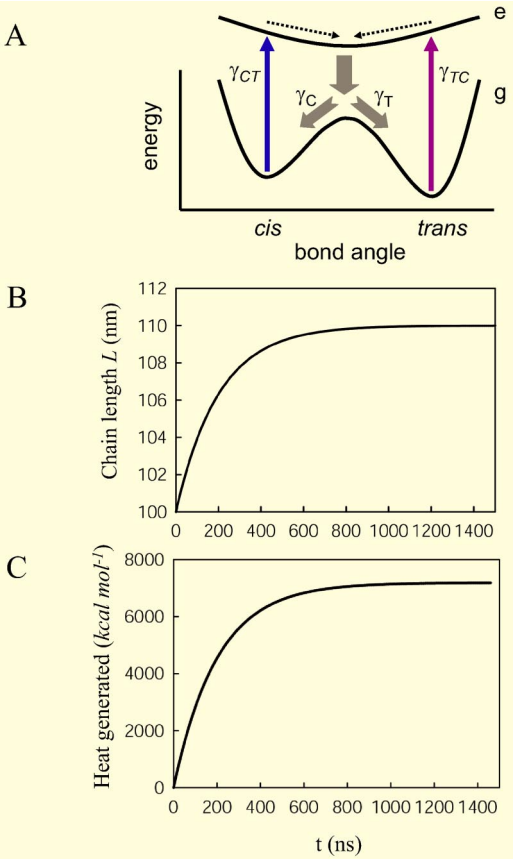

FIG. 3. Photoisomerization dynamics. (A) Schematic diagram of energy levels involved in *cis*-*trans* isomerization of a locomotive unit. $\gamma_{CT}(\gamma_{TC})$ is rate for laser excitation from *cis* (*trans*) configuration in ground state (g) to excited state (e). $\gamma_C(\gamma_T)$ is the internal conversion rate back to *cis* (*trans*) configuration in ground state. Through the paper we assume values: $\gamma_{CT}=\gamma_{TC}=0.01\ \mathrm{ns}^{-1}$, $\gamma_C=\gamma_T=10\ \mathrm{ns}^{-1}$. The wavelength of laser beam driving *cis*→*trans* transition is taken as $\lambda_C=404$ nm, and that for reverse transition as $\lambda_T=350$ nm. (B) Contour length of, and (C) amount of heat generated by a locomotive as it undergoes laser driven isomerization starting from an all-*cis* state.

It is designed that intrachain diffusion of a fully extended locomotive covers a sufficiently big area around the target binding site of the leading head. Search for a binding site is effectively guided by the hydrogen-bonding track. If necessary, additional groups may be engineered into binding sites to promote attraction for head groups. If laser assistance is necessary for docking, repeated laser irradiation must be performed close to the end of diffusive search period τ_{ran}.

During contraction step laser operations for undocking and for *trans*→*cis* isomerization can be done in the same manner as the stretch step, but at different frequencies. Un-

like the stretch step, the contraction step is under load of the cargo. Since the locomotive essentially walks a forced march with a fixed pace, energy in excess of mechanical work for cargo transport ends up as heat that must be thrown away. When the trailing head is in an undocked state, Brownian motion of the cargo, which may be much bigger than the locomotive itself, should help with heat release as well as diffusive search for the next binding site. One concern is whether or not heat will cause reverse *cis*→*trans* thermal isomerization. A heavy load, such as those caused by a potential energy barrier encountered by a forward moving cargo, might possibly make extended *trans* configuration energetically more favorable. However, as Hugel *et al.* found [25], thermal back isomerization turned out to be negligible even when their polymer molecules are under a persistent load up to 400 pN. As often is true, thermal isomerization is orders of magnitude slower than optical switching, making the former negligible in an optical operation.

III. THEORY OF THE MACHINE

I construct here a theory for the machine to facilitate quantitative analysis. Three key processes and their time scale will be examined in detail, which are photoisomerization, heat generation and release, and diffusive search for binding sites.

The whole process of photoisomerization consists of electronic excitation, internal conversion and subsequent intramolecular vibrational relaxation. The optoelectronic process lasts only femtoseconds; internal conversion and intramolecular relaxation are fast too, typically of subnanoseconds. Following the energy diagram and notations in Fig. 3(A), photoisomerization from *cis* to *trans* configuration can be described by the rate equations

$$\dot{n}_e = n_C\gamma_{CT} - n_e(\gamma_C + \gamma_T),$$

$$\dot{n}_C = n_e\gamma_C - n_C\gamma_{CT},$$

$$\dot{n}_T = n_e\gamma_T, \tag{1}$$

where n_i is population of locomotive units in ith state, with $i=e$ for the excited state, $i=C$ and T for *cis* and *trans* configuration in ground state. Population conservation requires $n_e+n_C+n_T=N$. The above equations assume a unit quantum yield for internal conversion. $1/\gamma_C$ or $1/\gamma_T$ is the average time for an excited unit to reach *cis* or *trans* state through internal conversion and vibrational relaxation to the extent that the unit is ready to be excited again. γ_C and γ_T are largely intrinsic molecular properties, while laser excitation rate from the *cis* or *trans* state, γ_{CT} and γ_{TC}, can be controlled by tuning laser power. With all of the locomotive units being in *cis* state initially, i.e., $n_C(t=0)=N$, the development of the *trans* population is solved out as

$$n_T(t) = 1 + \frac{1}{\gamma_+ - \gamma_-}(\gamma_- e^{-\gamma_+ t} - \gamma_+ e^{-\gamma_- t}), \tag{2}$$

where

$$\gamma_\pm = \frac{\gamma_{CT}+\gamma_C+\gamma_T}{2} \pm \sqrt{\left(\frac{\gamma_{CT}+\gamma_C+\gamma_T}{2}\right)^2 - \gamma_{CT}\gamma_T}. \tag{3}$$

Extension of the locomotive chain and the amount of heat generated can be readily obtained

$$L(t) = Nl_0 + Nn_T(t)\Delta l, \tag{4}$$

$$Q(t) = Nn_T(t)\left(\frac{\gamma_C}{\gamma_T}\Delta G_{CC} + \Delta G_{CT}\right). \tag{5}$$

Here ΔG_{CT} (ΔG_{CC}) is the amount of heat produced when internal conversion leads to *trans* (*cis*) configuration. We take $\Delta G_{CT}\approx\Delta G_{CC}\approx E_C$ (photon energy driving *cis*→*trans* transition). Equations (1)–(5) form the basis for analyzing the stretch step of the work cycle. Minor modifications lead to a similar set of equations for the contraction step.

Figures 3(B) and 3(C) show how the locomotive extends and heat is produced during laser-driven *cis*→*trans* isomerization. With $\gamma_{CT}=0.01$ ns^{-1}, the locomotive reaches maximum contour length within $\tau_{\rm iso}\approx 1000$ ns. The fastest extension occurs during the first 200 ns. Heat generation follows a similar time course.

Electronic transitions upon photon absorption are typically three orders of magnitude faster than nuclear motion. The gap of time between energy injection and dissipation might cause for the machine a problem of overheating, which could possibly make more often the occurrence of temporary loss of optical activity (e.g., blinking) of light-responding components of the machine, or even permanently damage their photophysical and photochemical capacity [22,23], and ultimately lead to instability of the locomotive-track system. By light absorption an energy quantum of the radiation is instantaneously injected into an isomeric unit, and heats it up upon internal conversion. Therefore, the instantaneous rate for heat generation within an individual unit is $E_C\times\gamma_C\approx 720$ kcal mol^{-1} ns^{-1} for *cis*→*trans* transition, independent of laser excitation rate. Here I estimate the time, $\tau_{\rm cool}$, for an isomeric unit to cool down to the extent that it resumes photoabsorption ability. I consider heat release through locomotive-water interface, which gives us an upper limit to $\tau_{\rm cool}$ because many direct contacts in locomotive-track interface are also efficient in transferring heat. According to classical heat diffusion theory, the rate for heat transfer driven by temperature gradient ΔT through a layer of cross section S and thickness Δx can be expressed as $\dot{Q}=\kappa S(\Delta T/\Delta x)$. Here κ is heat conductivity of the layer. The unit-water interface is taken as a cylinder surface of thickness $\Delta r=2$ nm and outer surface area $S=2\pi r_0 l$. Heat conductivity of the interface is difficult to estimate, and we take it as the value measured for bulk water [32] but multiplied by a reduction factor f. As a conservative choice, we take $f=1/50$. Considering fast distributing of vibrational energy within a unit, we have an initial, effective temperature for the unit: $kT_0\approx E_C/3N_B$. Taking the number of chemical bonds sharing heat as $N_B=20$ according to size of locomotive units, we have $T_0\approx 577$ K, which is several hundred Kelvin above room temperature assumed for surrounding liquid, i.e.,

$(\Delta T)_0 \approx 279$ K. Finally, cooling through the isomeric unit-water interface leads to exponential decay of temperature gradient over the interface

$$\Delta T = (\Delta T)_0 e^{-t/\tau_W}, \tag{6}$$

with $\tau_W \approx 0.018$ ns. The cooling time for an individual unit can be taken as $\tau_{\text{cool}} \approx 5\tau_W \approx 0.09$ ns, which is so short that overheating is unlikely a problem. If we assume a similar cooling efficiency for locomotive-track interface, the machine will be able to run in nonaqueous environment without any problem of overheating.

The average search time τ_{ran} can be estimated using the first passage time theory [33]. Approximating the random search as a two-dimensional intrachain diffusion of the locomotive over the track, we readily reach the result

$$\tau_{\text{ran}} = \frac{R^2}{D}\left[\frac{1}{2}\ln\left(\frac{R}{a}\right) - \frac{3}{8}\right], \tag{7}$$

where D is the intrachain diffusion coefficient, R is length scale of the search area, and a the distance over which a docking group and a binding group readily react. Consistent with assumed size of the locomotive-track, we take $a = 0.3$ nm. The available area for two-dimensional diffusion of a locomotive head can be estimated as follows. In dimension parallel to the straight path, the head diffusion is confined between maximum and minimum values for end-to-end distance of the locomotive chain, $x_{\max}$ and $x_{\min}$, as allowed by chain rigidity and locomotive-track interactions. According to the machine-track parameters adopted, the location of a target binding site x satisfies $x_{\max} - x \approx x - x_{\min} < x_0$ (x_0 is the period of binding sites). In the dimension vertical to the path the head diffusion is limited by the width of the track w. Drawing a circle of radius $R = x_0 (> w/2)$ from the target binding site, the enclosed area roughly defines the available space for the head diffusion. The typical value for intrachain diffusion of a linear polymer in water is $D = 10^{-8} - 10^{-6}$ cm^2/s [34]. Because of the friction caused by locomotive-track interactions, the diffusion occurs in a rugged potential landscape. The diffusion dynamics can be treated as in an averaged, smooth potential with a reduced, effective diffusion coefficient [35]. Taking $D_{\text{eff}} = 0.1 \times D$, we have $\tau_{\text{ran}} \approx 8.1\ \mu\text{s} - 0.81$ ms. It is clear that the random search is the slowest process in the work cycle of the machine. Since the docking probability is $p(\text{t}) = 1 - \exp(-t/\tau_{\text{ran}})$ [33], we take the maximum time needed for a successful docking as $(\tau_{\text{dc}})_M \approx 5\tau_{\text{ran}} \approx 40\ \mu\text{s} - 4$ ms.

IV. CHARACTER AND CAPACITY OF THE MACHINE

Since it is not difficult to arrange distinctively different undocking frequencies for the two heads, the direction of the locomotive move can be controlled with great certainty. Imagine a locomotive chain is brought to a track by an atomic force microscope tip. The attraction from the track easily detaches the chain from the tip to the track where both heads eventually settle down at a couple of binding sites. Applying either of the undocking frequencies and a *cis* $\rightarrow$ *trans* laser beam, we then have a nearly all-*trans* locomotive with both heads docked. Begin the first work cycle with a contraction step. The undocking frequency to be first applied will select the trailing head, and also a direction for locomotive move. Subsequent work cycles will maintain the chosen direction, leading a processive, unidirectional move of the locomotive and its cargo. If the direction is not desired, the locomotive can be stopped at an extended, docked state, and be turned back by resuming work cycles with the other undocking frequency than the one first used. Thus, the machine is capable of dual directional motion, unlike a biomotor which is normally destined for a unidirectional transport towards either of the polar ends of the molecular track [18]. While a biomotor seems to have a built-in mechanism for its fixed direction [18], direction of this artificial motor is to be controlled from a distance. The locomotive is essentially a polymer chain confined in an energy minimum path. The locomotive spans over 10 binding sites of the path, and moves a fixed pace of one binding site ahead each work cycle. A processive biomotor such as kinesin and dynein also walks a certain distance each ATP hydrolysis cycle, with step length determined by periods of basic building blocks of the biomicrotubule [17].

Diffusive search for docking determines the minimum time duration for a full cycle as $(\tau_{\text{cyc}})_M \approx 2 \times (\tau_{\text{dc}})_M < 8$ ms, because time scale of any other process involved in the cycle is at least three orders of magnitude shorter than τ_{ran}. The time actually spent by each cycle, τ_{cyc}, also depends on details of laser operation. To complete a work cycle six laser beams are needed, which must be arranged in a proper temporal order in order to accomplish an optimal τ_{cyc}. Suppose that a sequence of such six laser beams is automatically generated within time τ_{pul} $(\geqslant (\tau_{\text{cyc}})_M)$, and also suppose that the beam generation is repeated with a frequency $f_{\text{op}} (\leqslant 1/\tau_{\text{pul}})$, we will be able to run the locomotive continuously with an average speed of $r_0 f_{\text{op}}$. The optimal performance will be achieved when $f_{\text{op}} \approx 1/\tau_{\text{pul}} \approx 1/(\tau_{\text{cyc}})_M \approx 125\ \text{s}^{-1}$. Since laser pulse preparation at this level can be done by established technology [24], we will have an automated motor that makes 8 nm every 8 ms. The average speed will be 1 μm/s, comparable to those of biomotors [36,37].

A track-walking biomotor typically generates a force of several pN [18], which turns out to be already sufficient to move a molecular cargo many times bigger than the motor itself through viscous cytoplasm at maximum speed of typically several μm per second [36,37]. The stall force is usually no more than 10 pN [38]. As found by Hugel *et al.* [25] the synthetic polymers used in their experiment can be optically shortened against a load of more than 200 pN, and generate up to 40 pN nm mechanical work out of an isomeric unit per switching. These numbers can be reasonably taken as for the locomotive chain considered here. Output of mechanical work per step of a biomotor is limited by its energy supply, i.e., a single ATP hydrolysis that releases about 80 pN nm in free energy. Mechanical output per work cycle of the locomotive can be many times higher than those of a biomotor, because multiple isomeric units allow simultaneous injection of many energy quanta (photons). Since covalent docking readily rectifies stall force of the locomotive chain into maximum pulling force for the cargo, the machine likely affords up to 200 pN pulling power. Such an

amount of force easily breaks multiple hydrogen bonds, bridges between charged groups, or substantially loosens hydrophobic sticking between molecular surfaces. The machine is essentially a powerful molecular optical engine that has the ability to pull its cargo against many obstacles in the molecular world.

Not surprisingly, the artificial motor has an extremely poor energy efficiency compared to its biological counterparts, which routinely utilize a significant percentage of energy available from ATP hydrolysis [16]. Hugel *et al.* [25] found in their experiment that only 10% of the energy of an absorbed photon goes to mechanical work. If macroscopic laser power is considered, energy efficiency becomes as low as 10^{-18}. However, as Sadi Carnot, father of classic Carnot engine, cautioned more than 150 years ago [39], the economy of energy consumption is "only one of the conditions to be fulfilled" in designing a working engine. "In many cases it is only the secondary." The statement is vividly relevant for molecular machines, since molecular world is never short of energy [20]. Rather the challenge is how to turn a mess of tiny, restless particles into a union of partnership that submits to our guidance and does work to our benefit.

V. PERSPECTIVE AND OUTLOOK

We have completed the blueprint for a molecular locomotive system composed of locomotive, track, energy source, and operational means. These components are organized into a genuine machine by a work cycle that periodically converts optical energy into mechanical work, and further rectifies the mechanical work into directed, processive move. From a technical point of view, the task of realizing such a molecular machine is non trivial, although the core ideas for the machine and its operation have been developed essentially on the basis of available techniques. Here we outline concrete steps for ultimately accomplishing the proposed molecular locomotive:

(a) Fabrication of the track, and optomechanically capable polymers for the locomotive. Both can either be synthesized, or be made out of biological molecules through proper chemical modifications. One candidate for the locomotive can be the synthetic polymers used by Hugel *et al.* [25] in their optomechanical experiment. The molecular track can probably be produced by genetically engineering microtubules or filaments, which serve as tracks for biomotors.

(b) Integration of the locomotive with its track. This task can be conveniently accomplished in a variety of environment using established techniques for single-molecule manipulation such as atomic force microscopy (AFM).

(c) Laboratory testing of the machine and its work cycle. A combination of AFM instrument with confocal optics microscopy setup, such as achieved by Hugel *et al.* [25], can readily serve as a platform for testing of optomechanical capacity of the locomotive chain. In order to further test the work cycle and molecular locomotion, one needs more single-molecule techniques. In particularly, a technical means for monitoring the locomotive motion relative to the track is very desirable. One potential candidate for this purpose is the technique of single-pair fluorescence resonance energy transfer (Sp-FRET), which has been vigorously developed with great success in recent years [23]. For example, FRET between a couple of properly selected dye molecules, when they are chemically attached to a head of the locomotive and a binding site on the track respectively, will yield information on distance between them at nanometer precision.

(d) Refinement for real operation of the machine for various purposes. There is certainly big room for improvement over the present version. Two issues of particular importance are improvement of laser operation of the machine, and performance optimization at the level of the whole machine system. In these directions much experimental as well as theoretical work needs to be done in the future.

Major technical demands for realizing the machine, including laser operation procedures and fabrication of molecular modules, are within reach of established techniques. Core technologies, such as site-specific molecular engineering [2,4–6], and optical control of single molecules [22,24], keep advancing rapidly, promising a bright future for the proposed machine.

The molecular locomotive proposed here has the capacity of delivering molecular cargo wherever the track reaches. The spatial resolution is largely determined by size of the track, which is several nm. The pulling power is great, readily overcoming resistance as high as a few hundreds pN. Importantly, laser operation of the machine can be automated [24]. With many adjustable parameters the work cycle can be implemented rather flexibly, offering the possibility for a specific transport task to be programmed into an automatic operational scheme. As far as bottom-up nanofabrication is concerned, decisive, forceful and automated delivery of individual molecular building blocks with high spatial resolution has great advantage over random diffusion. With help of the machine nanofabrication can be done in a variety of environment where molecular mobility is reduced, or reaction is prevented by high potential energy barriers or steric obstacles. Realization of the machine will be a significant step towards Feynman's vision of "a physical way to synthesize" "absolutely anything" [19].

From design perspective, the machine proposed here represents a new category of molecular motors other than molecular shuttles and Brownian motors. By optomechanical strokes of its work cycles the locomotive actively generates mechanical work, which then forces a decisive move into a chosen direction. Therefore, the locomotive is not only a molecular motor, it is also well qualified as a molecular engine, which may be used for power-demanding tasks other than cargo transportation. For example, there let be a folded protein molecule with one end of its polypeptide chain grasped by a locomotive linker and the other end attached to a substrate. Running the locomotive away from the substrate will be able to unfold the protein molecule.

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