An in-silico walker

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The paradox of biomimetic research is to perform bio-functionality, usually associated with sophisticated structures optimized by nature, with minimal structural complexity for the ease of fabrication. Here we show that a three-particle trimer can exhibit kinesin-like autonomous walk on a track via reactive molecular dynamics simulations. The autonomous motion is due to imbalanced transitions resulting from exothermic catalytic reactions, and the spatial asymmetry from the track. This molecular design can be realized by reproducing the particle-particle interactions in functionalized nano- or colloidal particles. Our results open up the possibility of fabricating bio-mimetic nano-systems in a minimalist approach.

Keywords: nanomotor; kinesin; molecular dynamics; biomimetic; self-motile.

Through billions of years of evolution, biological systems exhibit a wide range of fascinating functionalities including sensing, actuation, catalysis, self-healing, and self-replication. Producing these bio-functionalities in artificial systems at comparable length scales is extremely challenging, yet highly beneficial ¹⁻⁵. The first approach is to synthesize substances identical or structurally similar to those in nature from bottom-up. This “clone-the-nature” approach ranges from copying atom-by-atom as in total synthesis ⁶ to reproducing only the essential microstructural features as in artificial bones ⁷. Once the desirable structure is obtained, the associated functionality will emerge due to structure-property relations. This biomimetic approach is limited by synthesis, interfacing with other components, and physiological working conditions. More importantly, the design by nature is not always perfect, for instance, the recurrent laryngeal nerve. The alternative approach is to utilize available yet tunable nanomaterials as building blocks (very much like pseudo-atoms), such that the assembly of these building blocks exhibits functions similar to those in biosystems. Colloidal particles, nanoparticles, and macromolecules have all been exploited as pseudo-atoms, with their interactions tuned by the charge, coating, shape, among other factors ⁸⁻¹⁵. However, this “pseudo-atoms” approach is rather Edisonian, due to poor mechanistic understanding of biofunctionality, and the lack of prediction of how the assembly of pseudo-atoms behave. Moreover, it is desirable to reduce the structural complexity of the functional assembly for the ease of fabrication, yet it is unknown whether there exists a minimum complexity in structure to produce biofunctionalities.

Among different biofunctions, self-motility is arguably the most intriguing as it represents one important characteristic of living things. Kinesin catalyzes the reactions of ATP to ADP, converts the released chemical energy into mechanical work, and propels itself into a

forward step-wise motion on a polar track ¹⁶. Biomotors are essential in almost all important biological processes which provides actuation, active transport and assemble/disassemble biological structures ¹⁷. Remarkably, the motor efficiency of kinesin has been estimated as high as 50% ¹⁸, indicating a strong chemomechanical coupling. Significant research efforts have been devoted in synthesize artificial nanomotors both powered by chemistry as well as non-chemical energy sources. Autonomous motion has been observed in a variety of nanomotors such as, macromolecule-based motor², DNA-based walkers ^{19,20}, bimetallic nanorods ²¹⁻²³, Janus colloidal particles ²⁴, and thermosensitive polymer motor ²⁵. However, these artificial nanomotors suffer from various drawbacks from lack of persistent motion and poor motor performance.

Here, we demonstrated that, by using reactive molecular dynamics (MD) simulations, “kinesin-like” self-motile motion can be achieved by a three-particle trimer. This minimalist’s model walker incorporates key features of a kinesin: catalytic chemical reactions, conformational changes and an asymmetric track. Importantly, the trajectory generated in MD simulations can in principle be reproduced in real world by matching the initial positions and velocities, as well as the inter-particle interactions. In other words, this model kinesin can be experimentally fabricated using the “pseudo-atom” approach.

The simulation system consists of an asymmetric track, a walker and a fuel/product gas environment as shown in Figure 1. For simplicity, a two-dimensional system was investigated here. The asymmetric track consists of two rows of immobile atoms. The lower row attracts the trimer while the upper row is repulsive to all other species. The lateral shift between those two rows leads to the track asymmetry (polarity). The trimer consists of a catalyst atom in the middle and two inert head atoms. The catalyst atom catalyzes the exothermic combination reaction of two monatomic reactant molecules into one diatomic product molecule. The track attracts the

two head atoms, while repels the catalyst (for bare walker without absorbed fuel or product molecules). Thus, the isolated walker prefers to stay in the dangling state rather than the docking state. However, once the catalyst binds with a fuel atom (either a monatomic fuel or a diatomic product), the catalyst-track repulsion weakens, thus allows the bending-down of the walker and the dangling-to-docking transition. In other words, the binding of fuel atoms induces a shape (conformational) change of the walker from a linear trimer to a bended trimer. Therefore, this model system possesses kinesin-like properties: catalytic reactions, conformational changes and an asymmetric track, all necessary for autonomous walking. The formulation and parameterization of the force field can be found in the Supplemental Materials.

The system is coupled to a thermostat of 580 K to dissipate the released heat from exothermic reactions. Moreover, a Monte-Carlo operation is invoked periodically that converts products (diatomic fuel molecules) to fuel (monatomic fuel molecules) away from the walker. In this way, both the temperature and the fuel concentration were kept constant. The self-motile behavior reported below was acquired under thus-maintained steady-state thermochemical environment.

The walker moves along the track via consecutive transitions between docking states and dangling states (i.e., rolling motion instead of shifting laterally, as shown in Figure S1). The trimer walks both left and right, with a slight bias to the left. Figure 1(a) shows a sequence of snapshots a left-ward motion of the walker during the MD simulation, involving adsorption/desorption/reaction. Representative walker trajectories are shown in Figure 1(b). The average displacement after ~86 ns is about 13.8 nm, or a velocity of ~0.16 m/s. The distribution of the final displacement from 100 independent nanowalkers is shown in the inset of Figure 1(b), resembling a shifted Gaussian distribution. A large number of parallel samples are necessary to

demonstrate the autonomous motion, as the Brownian motion of the nanowalker is significant. The walking direction is determined by the asymmetry of the track (the first row of the track is shifted slightly to the left relative to the second row of the track). Walker behaviors with different track symmetries can be found in the Supporting Materials. As shown in Figure S2, the directional displacement vanishes as the track becomes symmetric. Moreover, the net displacement reverses direction as the track tilts to the opposite way.

Next, the walker was coupled to a constant external force to examine its response to mechanical load (Figure 1c). The average drift velocity decreases as the external force increases. Consider force balancing in the steady-state, and assume a linear drag force with respect to the drift velocity v , one has,

$$f_{propulsion} + f_{ex} - \gamma v = 0 \quad (1)$$

Here $f_{propulsion}$, f_{ex} and γ is the chemical propulsion force, external force and the drag coefficient, respectively. From linear fitting, the chemical propulsion force is estimated to be 1.3 pN, and the drag coefficient is estimated to be 7.49E-9 kg/s. Together with the rate of the chemical reaction (7.8 ns^{-1}), one can estimate the Stokes efficiency²⁶ of the walker to be 4.7E-5. This efficiency is quite low compare to that of biomotor kinesin, but on par with other model molecular motors^{27–29} and much higher than bimetallic nanorods³⁰.

To understand the autonomous motion of the walker, the elementary transitions of the walker among its different residing states were shown in the kinetic cycle diagram (Figure 2). Despite a minimalist's construction of a nanowalker, there are eight distinctive states the walker can reside.

The horizontal motion of the walker is contributed mainly by three types of transitions: the docking transition with one fuel atom $4 \rightarrow 6$ and $5 \rightarrow 4$, with about 10 net rightward

halfsteps), the undocking transition with two fuel atoms ($2 \rightarrow 1$ and $2 \rightarrow 3$, with about 15 net left - ward halfsteps), the undocking transition without any fuel atom ($7 \rightarrow 8$, with about 40 net left - ward halfsteps). It is clear that the third type accounts for the majority of the autonomous motion, while the first two types almost cancel each other out. As the combination of a docking halfstep and an undocking halfstep constitutes the repeating unit of the track (0.6 nm), thus a halfstep moves the walker by 0.3 nm. We can estimate the walker moves to the left by 12.0 nm (87% of the observed net displacement of the walker) due to 40 left-ward halfsteps of $7 \rightarrow 8$ transitions. Thus, the net displacement for the duration of ~ 86 ns is,

$$\Delta L \approx (N_{7 \rightarrow 8}^R - N_{7 \rightarrow 8}^L) \cdot \frac{d}{2} \quad (2)$$

Here, ΔL , $N_{7 \rightarrow 8}^R$, $N_{7 \rightarrow 8}^L$, and d is the net displacement, the number of $7 \rightarrow 8$ transitions to the right, the number of $7 \rightarrow 8$ transitions to the left, and the length of the repeating unit of the track (0.6 nm), respectively.

The preceding section establishes that the autonomous motion mostly comes from the asymmetric docking-to-dangling transitions of isolated walker (i.e., the $7 \rightarrow 8$ transitions that bias towards left). We will now focus on the $7 \rightarrow 8$ transition to understand the asymmetry and the energetics from free energy landscape analysis.

To simplify the analysis, only an isolated walker on the same track was considered to calculate the free energy profile along the horizontal direction. We employed the weighted histogram analysis method (WHAM),^{31,32} a minimum-variance estimator of the density of states that relies on several simulations under different conditions. The free-energy profile was reconstructed at 580 K from simulations at temperatures ranging from 436 to 639 K. A bootstrap analysis of the data provided error bars. The resulting free energy profile is shown in Figure 3.

There is a free energy drop ($\Delta F_{7 \rightarrow 8}$) of about 0.003 eV for the isolated walker during docking (state 7) to dangling (state 8) transition, which provides the driving force for the walker motion. Moreover, the docking to dangling transition is evidently asymmetric, with a ~ 0.04 eV barrier for left-ward transitions or a ~ 0.07 eV barrier for right-ward transitions.

The biased $7 \rightarrow 8$ transition alone cannot lead to sustained autonomous motion. For instance, under thermodynamic equilibrium, detailed balance must be maintained such that the reverse $8 \rightarrow 7$ transitions will bias to the right. Thus there is no net motion under equilibrium. It is the non-reversible combination reaction that breaks the thermodynamic equilibrium and the detailed balance. Importantly, the reaction is localized near the walker (the middle atom of the walker is the catalyst), exothermic (thus providing the energy source), and coupled to the walker motion (the attachment of the fuel atom cause the conformation change of the walker, i.e., bending down and docking).

For a simple propulsion model, we assumed all transitions other than $7 \rightarrow 8$ transitions are unbiased. Thus, the processes of $8 \rightarrow 6 \rightarrow 4 \rightarrow 2 \rightarrow 7$ and $8 \rightarrow 6 \rightarrow 4 \rightarrow 2 \rightarrow 7$ continue to produce walkers in state 7 (no net horizontal motion due to symmetry), while producing one diatomic product molecule. Thus, one can calculate the chemical propulsion force, as the total free energy change during the course of the simulation ($\Delta F \approx (N_{7 \rightarrow 8}^R - N_{7 \rightarrow 8}^L) \cdot \Delta F_{7 \rightarrow 8}$) divided by the total horizontal displacement (Eq. 1),

$$f_{propulsion} \approx \frac{\Delta F}{\Delta L} = \frac{\Delta F_{7 \rightarrow 8}}{d/2} \quad (3)$$

Here d is again the length of the repeating unit of the track. The estimated propulsion force is around 2.0 pN, which is close to 1.3 pN measured in Figure 1. Note that only the free energy changes coupled to the horizontal movement of the walker need to be considered for the

calculation of the propulsion force. For instance, ~~86~~ transitions are not associated with net walker motion in the horizontal direction, thus the associated free energy change will not contribute to chemical propulsion.

In simple terms, it is the catalytic chemical reaction breaks the detailed balance and drives the system through directional loops among its phase space. Thus, the walker alternates with zero, one or two fuel atoms due to catalytic reactions. Moreover, the binding of the fuel with the catalyst modified the originally asymmetric barriers (due to the polar track) to symmetric barriers, somewhat analogous to the flashing potential energy landscape in a Brownian motor ³³. It should be noted that, only one out of five catalytic chemical reactions triggers a dangling-to-docking transition due to imperfect coupling. The asymmetry will lead to about 1:3 bias towards left, which leads to roughly a quarter step for every dangling-to-docking transitions. Therefore, it took about twenty catalytic chemical reactions to drive the walker one step to the left. In addition, only a tiny fraction of the chemical energy release of the combination reaction is stored to drive the 7→8 transition (0.003 eV out of 0.88 eV). The above two issues need to be addressed in future optimization of the nanowalker design.

In principle, this *in silico* walker described above can be implemented in experiments by fabricating nanoparticles as “pseudo-atoms” with tunable particle-particle interactions. Significant progress has been made recently: the interaction can be tuned by DNA/polymer grafting on the surface ^{8,34}, electric charge ³⁵, patches ³⁶, and shape ¹¹.

In summary, a minimalist’s nanowalker consisting of three particles have shown kinesin-like autonomous walking behavior on a polar track driving by catalytic chemistry. It was shown that the autonomous motion of the walker is due to the asymmetric docking-to-dangling transition of the walker, an imbalance sustained by irreversible chemical reactions. This

minimalist nanowalker can in principle be manufactured in experiments using pseudo-atoms with tunable interactions.

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Figure 1

Figure 1. (a1-a6) Snapshots of the sequence of a kinesin-like walking gait of the nanowalker during one MD simulation (the animation can be found in the Supplementary Materials). The head, catalyst, fuel atoms are colored green, yellow and blue, respectively. Two rows of track atoms are colored purple and gray. This sequence is $8 \rightarrow 6 \rightarrow 4 \rightarrow 2 \rightarrow 7 \rightarrow 8$, according to Figure 2. (b) The displacement as a function of time for 16 independent walkers. The inset shows the statistics of the final displacements of 100 independent walkers after 86 ns, showing the walkers move to the left (negative displacement).

Figure 2

Figure 2. The kinetic cycle diagram of the nanowalker. The walker resides in a specific state depending on the position relative to the track (docking or dangling), the chemical state (0/1/2 attached fuel atoms), and the side of the fuel atoms (left or right), if any. One hundred independent walker trajectories with high time resolution (every 1.7 *ps*) have been used to calculate the average number of transitions for one typical simulation duration (86 *ns*). The transitions from one state to another are represented by red, blue and gray arrows, indicating right-, left- and no-motion in the horizontal direction, respectively. The green loops represent catalytic reactions that are not coupled to walker motions (8→1→8, 8→5→3→8 and 7→4→2→7). Please note that transitions with very low flux were omitted for clarity.

Figure 3

Figure 3. The free energy profile as a function of the x-position of the catalyst for a nanowalker on the track with no fuel environment at a temperature of 580 K. The docking to dangling transition of 7→8 is energetically favorable, with a lower barrier to the left. The inset graph shows the autonomous left-ward motion can be accomplished by 7→8 transition, followed by 8→6→4→2→7 or 8→5→4→2→7 (assumed to be symmetric in the simple propulsion model, thus there is no free energy change coupled to the walker motion in the horizontal direction), then repeat.

https://en.wikipedia.org/wiki/Kinesin#/media/File:Kinesin_cartoon.png