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Optimizing rotary processes in synthetic molecular motors

Edzard M. Geertsemaa,1, Sense Jan van der Molenb, Marco Martensc, and Ben L. Feringaa,2

aStratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands; bKamerlingh Onnes Laboratory, Leiden University, Niels Bohrweg 2, 2333 CA Leiden, The Netherlands; and cInstitute for Mathematical Sciences, State University of New York at Stony Brook, Stony Brook, NY 11794-3651

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We deal with the issue of quantifying and optimizing the rotation dynamics of synthetic molecular motors. For this purpose, the continuous four-stage rotation behavior of a typical light-activated molecular motor was measured in detail. All reaction constants were determined empirically. Next, we developed a Markov model that describes the full motor dynamics mathematically. We derived expressions for a set of characteristic quantities, i.e., the average rate of quarter rotations or “velocity,” V, the spread in the average number of quarter rotations, D, and the dimensionless Péclet number, Pe = V/D. Furthermore, we determined the rate of full, four-step rotations (Ωeff), from which we derived another dimensionless quantity, the “rotational excess,” r.e. This quantity, defined as the relative difference between total forward (Ω+) and backward (Ω−) full rotations, is a good measure of the unidirectionality of the rotation process. Our model provides a pragmatic tool to optimize motor performance. We demonstrate this by calculating V, D, Pe, Ωeff, and r.e. for different rates of thermal versus photochemical energy input. We find that for a given light intensity, an optimal temperature range exists in which the motor exhibits excellent efficiency and unidirectional behavior, above or below which motor performance decreases.

Markov model | unidirectional rotation

The development of nanoscale molecular devices that exhibit controlled movement upon energy input advances progressively (1–11). In the past decade, a spectrum of ingeniously designed molecular structures, ranging from artificial muscles (12) to molecular cars (13), was introduced. In the B.L.F. group, chiroptical switches have evolved into unidirectionally rotating molecular motors (14–17). In fact, an internal, 360° rotation was induced in one specific direction (i.e., clockwise or counterclockwise) upon input of photons and thermal energy. On the road toward applications, it was shown that the phase of liquid crystals can be controlled when doped with small portions of optically enriched molecular motor, and micro objects can be moved (18–20). In addition, molecular motors were recently grafted on gold (21) and quartz surfaces (22).

The general concept of these molecular motors is visualized in Scheme 1 (16, 17). The rotor consists of a lower part (“stator,” red) and an upper part (“rotor,” blue). The rotation takes place around a central double bond (“axle,” black) in four stages, i.e., through transitions between four isomers.

All four conversions in Scheme 1 are in principle reversible (i.e., equilibria are involved). For example, motor molecules with R = OCH3 have photochemical equilibria of 14/86 and 11/89 for the concentration ratios A/B and C/D, respectively. Importantly, the thermal conversions from unstable to stable forms are quantitative (i.e., 100%). Previous research focused on attempts to optimize molecular rotation kinetics through chemical design (24–27). However, it focused on single, thermal reaction steps only. Full and ongoing rotation of individual motor molecules can be realized when both light of appropriate energy (hv) and thermal energy (denoted as Δ) are supplied simultaneously. We therefore envisioned that quantification and optimization of continuous four-stage rotation should be the next challenge to take on. Remarkably, a proper approach to quantify the rotational dynamics and efficiency of synthetic rotational motors is lacking. This is in contrast to the situation for biological molecular motors, generally defined as Brownian motors (28–34) or steppers (35–38), which have been the inspiration of numerous studies.

Scheme 1. General concept of molecular motors. R denotes the stereochemistry of the stereogenic center at the 2-position of the rotor. P and M denote helicity of the entire molecule (23). Cis and trans denote whether the naphthalene part of rotor is at the identical (cis) or opposite side (trans) as the R-substituent of the stator.

Results and Discussion

Empirical Results. Several experiments were necessary to fully characterize the rotation dynamics of the synthetic molecular motor (Scheme 1) upon simultaneous input of photons and heat. Next, all empirically determined reaction constants were inserted in a mathematical model based on the theory of Markov processes. Finally, we show how the model can be used to optimize rotational behavior (i.e., efficiency) of existing molecular motors.


The authors declare no conflict of interest.

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1Present address: University of Edinburgh, School of Chemistry, The King’s Buildings, West Mains Road, Edinburgh EH9 3JU, United Kingdom.
2To whom correspondence should be addressed. E-mail: b.l.feringa@rug.nl.

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nm) and heated (55.5 °C) to induce rotation of the motor molecules. See supporting information (SI) for details. The development of concentrations of all four isomers in course of time was monitored by $^1$H NMR spectroscopy (Fig. 1). Care was taken to ensure that light intensity and temperature were identical and constant throughout both experiments.

When pure A was irradiated and heated, a relatively fast cis-trans isomerization into B was observed. The fraction of A decreased from 1.00 to 0.10 in 1.3 $\times$ 10$^3$ s, passing through a shallow minimum. The fraction of B reached a maximum of 0.59 at $t = 6.6 \times 10^3$ s and then slowly decreased to a final value of 0.43 at equilibrium. The third isomer in the cycle (C) was formed next, and its fraction reached a final value of 0.17. The fourth isomer (D) was not observed during the first 1.2 $\times$ 10$^3$ s of the experiment and from that moment, fraction D slowly increased to a final magnitude of 0.28. The order of formation of isomers is in line with the unidirectional rotation behavior of this system. The observation that the third isomer (C) initially developed faster than the fourth (D), although its final fraction value at equilibrium is significantly lower (0.17 versus 0.28), is especially notable.

A similar result was observed when the other stable isomer, C, was taken as starting material (experiment 2). In final equilibrium, equal fraction values of A, B, C, and D were expected for both experiments ([A]$_{eq}$ = 0.12, [B]$_{eq}$ = 0.43, [C]$_{eq}$ = 0.17, [D]$_{eq}$ = 0.28). This was indeed the case, within the measurement error of the NMR method (=3%). It demonstrates that we were able to keep experimental input parameters, most notably the illumination intensity, constant in both experiments.

From Fig. 1, we determined a first set of reaction rates, namely $k_{AB}$ (27.4 $\times$ 10$^{-5}$ s$^{-1}$), $k_{AC}$ (1.4 $\times$ 10$^{-5}$ s$^{-1}$), and $k_{AD}$ (not observed). For this, a first-order exponential fit of the decay of transitions (denoted by arrows) in our motor system is depicted.

Cross-conversions of A into C and B into D and vice versa are split in positive (+, clockwise) and negative (−, counterclockwise) rotational movements because these conversions can take place in either direction.

To characterize the system, we note that motor rotation is a stochastic process. The dynamics of a given molecule will be a random walk through Scheme 2, which is an example of a Markov process. The basic property of a Markov process is that every next step is dependent only on the present state of the system, i.e., it does not depend on its history. This assumption is certainly valid for synthetic molecular motors such as shown in Scheme 1. A quarter rotation, once the motor is excited, happens on the scale of tens of picoseconds (27, 39–42), whereas the interval between two jumps (i.e., two quarter rotations) typically ranges from seconds to hours. Due to the huge ratio of both time scales (>10$^6$), we can safely conclude that in between two quarter rotations, a molecular motor will have lost its memory. There is extensive literature on Markov processes (43, 44). Their dynamics are controlled by probabilities, which are, in our case, related to the motor’s reaction constants. The fact that we typically have 10$^{19}$ molecules in a container, fully justifies a stochastic approach.

To model reaction dynamics, we first defined a time-dependent row vector $X(t) = [A(t), B(t), C(t), D(t)]$. Its elements equal the normalized concentration, or fraction, of the four isomers of the molecular motor, at a time $t$ (see Fig. 1). Next, a 4 $\times$ 4 matrix $P_0$ was determined from Scheme 2. This matrix governs how $X$ changes in a small time interval $\Delta t$ by the collection of all reactions, i.e.:

$$X(t + \Delta t) = X(t) \cdot P_0$$

The elements of $P_0$ are related to the probabilities $p_{KL}$ in Scheme 2 (with $K, L \in \{A, B, C, D\}$). They are given by

$$p_{KL} = k_{KL} \cdot \Delta t$$

(2a)

$$p_{KK} = 1 - \sum_{L \neq K} p_{KL}$$

(2b)

Modeling the Evolution of the Molecular Fractions. We proceed by deriving a Markov model for molecular rotation dynamics. In Scheme 2, a schematic overview of all mathematically possible transitions (denoted by arrows) in our motor system is depicted.
The matrix $P_0$ was determined for our specific molecular system, using Eqs. 2a and 2b and the 12 empirical reaction constants. Making use of standard linear algebra after letting $\Delta t \to 0$, we solved Eq. 1 for the initial conditions in experiments 1 and 2 (see SI). The calculated isomeric fractions for experiment 1 are visualized as solid lines in Fig. 1. The motor system finally reached a dynamic equilibrium. This implies that $X(t \to \infty) \to W = [w_A, w_B, w_C, w_D]$. The elements $w_K$ of $W$ form the equilibrium fractions of the four isomers. From Eq. 1, it follows directly that

$$W \cdot P_0 = W$$  \[3\]

Thus, $W$ is a left-side eigenvector of $P_0$ with eigenvalue 1. We calculated $W$ from Eq. 3 and the reaction constants; $W = [w_A = 0.13, w_B = 0.43, w_C = 0.17, w_D = 0.27]$.

The correspondence between model and empirical data are very accurate, given the considerable standard error of NMR ($\pm 3\%$) and the experimental challenge of keeping the input of photons and heat constant during the experiments. This result establishes that the matrix $P_0$ and the empirically determined reaction constants adequately describe the fraction development of experiments 1 and 2, once again justifying our approach. We note that matrix $P_0$ is easily modified to be applied to rotational motors with any number of cyclic stages as well as nonrotational (i.e., linear) motors (45).

**Rotation Dynamics.** The Markov process described by $P_0$ is appropriate for studying the development of the fractions of isomers A, B, C, and D in time. However, it does not allow one to determine all dynamic parameters. It is essential to realize that in dynamic equilibrium, the motor system finally reached a vector $W$, according to: $X(t \to \infty) \to W = [w_A, w_B, w_C, w_D]$. The elements $w_K$ of $W$ form the equilibrium fractions of the four isomers. From Eq. 1, it follows directly that

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10^6 s (black). These distributions have the shape of spiked Gaussians, with well-defined, global V and D values. The spiky appearance is due to the prefactor cK(Φ) which differs for each isomer as cK(Φ) ≈ wK. Therefore, the Gaussians in Fig. 2 are modulated periodically, with a period of four quarter rotations. For example, isomer B, with wB = 0.43, is responsible for the large spikes. The local minima, on the other hand, are due to the isomers A and C, with their lower equilibrium concentrations wA and wC. This is illustrated in Fig. 2 Inset, which zooms in on the curve at t = 10^6 s.

We stress that the full dynamics of the equilibrium motor system is captured in Eq. 7-10. As an independent check, we also numerically calculated μK(Φ) from the four-variable differential equation that describes the evolution of A, B, C and D. For large times, like in Fig. 2, the simulations are indistinguishable from the curves calculated with Eqs. 7-10.

Optimizing Motor Dynamics. Interestingly, it is possible to adjust motor performance by tuning the two types of energy supplied to the system: heat and light. Reaction constants kBC, kCB, kAD, and kDA describe the thermally activated jumps from the unstable to the stable forms. Hence, they follow the relation k = (kT exp(−ΔG^‡/RT))/h. On the other hand, the rates kAB, kAC, kBA, kBD, kCA, kCD, kDB, and kDC scale with the illumination intensity. Obviously changes in the reaction rates result in different rotation dynamics, via Eqs. 2 and 4. This triggers the question if temperature and light intensity can be tuned in such a manner that the motors rotate optimally.

To substantiate on this interesting issue, we calculated V (see Fig. 3A) and D (see Fig. 3B) in the temperature range 250 < T < 370 K, for the specific motor used in our experiments. We considered two different illumination intensities. The first (solid curves) equals the value in our experiments whereas for the second (dashed) we assume a light input that is 10 times smaller. The temperature dependent rates were determined by using empirical values: ΔG^‡ (B → C) = 25.6 kcal mol^-1, ΔG^‡ (C → B) = 30.3 kcal mol^-1 and ΔG^‡ (D → A) = 25.3 kcal mol^-1, ΔG^‡ (A → D) = 30.0 kcal mol^-1.

As can be seen from Fig. 3A, V increases both with increasing T and increasing light input (black vs. red curves). At higher temperatures, V reaches saturation. The saturation value depends on the light input (it differs a factor 10 for the two curves), because the light-induced steps are rate limiting in this temperature region. At lower T, however, the thermal steps become rate limiting, so that V decreases dramatically. Because the light input is not dominant any longer, the two curves approach each other. As for the temperature dependence of D, we observe two S-shaped curves. At higher T, saturation similar to the one for V is seen. At lower T, however, D also reaches a plateau value, unlike V. The reason for the latter is that D is not limited by the ever slower thermal steps, because it takes all possible jumps into account (see Eqs. 9 and 10). Hence, the light-induced steps also determine D at low T, as confirmed by the factor of 10 between the curves with high and low light input.

Péclet Number. A measure giving insight in motor performance is formed by the dimensionless Péclet number Pe. It is defined as (taking a quarter rotation as a unit step) (35, 38):

\[ Pe = V/D \]

Thus Pe, which originated in fluid dynamics, quantifies the ratio of directed motion and diffusive spreading. For molecular motors, Pe is optimal if all forward rate constants are matched (i.e., equal) and the backward rate constants are small. Indeed, if the forward rates have very dissimilar values, “traffic jams” (or pile up of a certain isomer) will limit the rotation efficiency so that Pe is small. The spikes in Fig. 2 are the signature of such “piling up.” Nevertheless, even for optimized synthetic molecular motors, under continuous irradiation, Pe is limited to unity, i.e., |Pe| = 1. This is a direct consequence of the stochastic nature of the rotation process. It illustrates the fundamental difference between synthetic molecular engines and daily-life macroscopic engines. The latter have Pe >> 1 because their movement (work) is tightly coupled to distinct quantities of supplied energy.

As shown in Fig. 3C, Pe reaches a maximum value of 0.75 at ≈340 K for the motor and light intensity used in experiments 1 and 2. This fact can be understood as follows. At low T, the rates of the thermal steps are much smaller than the light-induced rates, i.e., the forward rates are not matched at all, and Pe is small. Upon increasing T, the temperature-dependent rates increase until values close to the light-sensitive rates are reached. At that point, Pe arrives at a maximum. As T increases further, the thermal rates start to dominate the light-induced rates, and Pe
may have a low in contrast to the case of etc.) in the forward direction that contains no backward jumps in. A similar definition holds for diastereomeric excess that describe selectivity in asymmetric catalysis (49) and chiral resolution (50). We define:

\[ \text{r.e.} = 100\% \frac{\Omega_+ - \Omega_-}{\Omega_+ + \Omega_-} \]  

Here, \( \Omega_+ \) denotes the number of full forward rotations per unit time. The definition of \( \Omega_+ \) is much more stringent than that of \( \Omega_- \). We define a full forward rotation as a rotation from \( A \) to \( A \) (or \( B \) to \( B \), etc.) in the forward direction that contains no backward jumps in between. A similar definition holds for \( \Omega_- \), which describes the rate of full backward rotations. If the motor is fully unidirectional, we have \( \Omega_- = 0 \), and \( \text{r.e.} = 100\% \). If there are as many forward as backward rotations, the motor does not rotate on average and \( \text{r.e.} = 0\% \).

A calculation of \( \Omega_+ \), requires knowledge about the exact sequence of partial rotations. As soon as a backward jump takes place, a rotation should be disregarded. To take this into account, we adapt our Markov approach. Intuitively, it works in the following way (a mathematically adequate description can be found in SI). First, we define five mathematical “graphs” similar to Scheme 2. Four of these are used as “counters” for full forward rotations: \( G_A, G_B, G_C, \) and \( G_D \). The fifth graph, \( G_e \), acts as a pool of molecules that rotated backwards in their last attempt. To intuitively explain the function of “subgraphs” \( G_A, G_B, G_C, \) and \( G_D \) as well as of \( G_e \), let us suppose that a molecule has just jumped backwards from state \( B \) to state \( A \). Therefore, it is by definition part of graph \( G_e \). Next, the molecule rotates forward by a quarter turn to become \( B \). At that point, it is transferred to graph \( G_A \), which follows molecules that started as isomer \( A \) and are “trying” to make a full forward rotation. Indeed, if the molecule keeps rotating forward only, without going backwards at all, it stays within \( G_A \). Upon completion of a full turn, we add one full rotation (1) to our counter. In other words, a backward rotation takes place before the full rotation is completed, the complete rotation attempt is disregarded. This is done by transferring this molecular state to \( G_e \) again. From there, another attempt can be made for a full rotation, etc.

By properly connecting the subgraphs \( G_A, G_B, G_C, G_D, \) and \( G_e \), a complete graph is formed that describes the Markov problem fully. From this extended graph, a \( 20 \times 20 \) matrix \( P^* \) was derived, which serves as the basis for our calculations of \( \Omega_+ \). The method we use to actually compute \( \Omega_+ \) is related to the way we calculate \( V \) above. An analogous procedure is used for \( \Omega_- \).

In Fig. 4A, we show the rate of full forward rotations (\( \Omega_+, \) black) and full backward rotations (\( \Omega_-, \) blue), as well as their difference (\( \Omega_{\text{eff}} = \Omega_+ - \Omega_- \), red), calculated versus temperature. Again, we assumed two light intensities: the photon input of experiments 1 and 2 (solid lines) and 1/10 of that (dashed lines). Remarkably, a clear optimum in \( \Omega_{\text{eff}} \) is found in both cases. The maximum value of \( \Omega_+ \) scales with the light input: It is 10 times higher for a 10-times-higher intensity (1.1 × 10^{-4} and 1.1 × 10^{-5} full rotations per second, respectively). Moreover, the temperature at which the maximum occurs also depends on light input. It is located at \( \approx 370 \) K for the standard light intensity and at \( \approx 350 \) K for 1/10 the intensity. Finally, for high temperatures (\( T > 450 \) K), \( \Omega_{\text{eff}} \) is \( \approx 100 \) times smaller for the lower light input than for the higher intensity.

We explain these interesting results in the following way. At temperatures below \( 310 \) K, the thermal rates are much slower than the photochemical rates (\( k_A \ll k_{\text{th}} \)). The thermal rates are therefore rate determining and inhibit relatively fast full rotations to take place. For this reason, \( \Omega_{\text{eff}} \) is basically the same for both light inputs. When the temperature rises, the thermal rates increase and \( \Omega_{\text{eff}} \) increases correspondingly. A maximum is reached when the thermal and light-induced rates match, such that each forward quarter rotation can be followed by another step forward. However, as the temperature increases further, the thermal rates become dominant. Moreover, the probability of a backward thermal step becomes larger than the probability of a light-induced forward jump. At that point, \( \Omega_{\text{eff}} \) will start decreasing due to our stringent demands: only uninterrupted rotations are included. For a lower light input, this point is reached for a lower temperature, explaining the shift of the maximum in Fig. 4A. Once again, this shows the importance of an accurate balance between photon and heat input to achieve the highest rate of total rotations (i.e., motor efficiency).

In Fig. 4B, the r.e. of the motor studied is plotted versus temperature, for the two light intensities considered. At temperatures <275 K, r.e. is close to 0%. In the region at \( \approx 300 \) K, a steep rise to >99% is observed, after which, r.e. flattens off to a value >99.8% for higher temperatures. Once more, the curves for different light intensities are shifted over the temperature axis. These observations are rationalized by the fact that the thermal
motors are almost perfectly unidirectional. The point is reached at lower temperatures, explaining the shift in Fig. 4B. We conclude that for temperatures that are high enough, these motors are almost perfectly unidirectional.

**Optimal Conditions for the Motor Studied.** Having calculated $V$, $D$, $Pe$, $\Omega_{\text{eff}}$, and $r.e.$, we can finally investigate the question at which conditions the motor studied rotates optimally. We assume the light intensity in experiments 1 and 2. Fig. 4 reveals that the highest motor efficiency is achieved between 345 and 370 K, because at these temperatures, $\Omega_{\text{eff}}$ is near its maximum and $r.e.$ is $>99\%$. Furthermore, Fig. 3 shows that the $Pe$ is near its maximum, whereas $V$ has practically reached its saturation value. Hence, the motors are both very efficient in their rotations (high $Pe$), as well as almost perfectly unidirectional ($r.e. = 1$). Remarkably, it is not useful to raise the temperature further. Motor rotation becomes neither faster nor more efficient at higher temperatures. This, at first sight, counterintuitive result, forms one of the main conclusions of our Markov study.

**Summary**

We applied the theory of Markov processes to quantify the general reaction dynamics of synthetic molecular motors. A specific unidirectional four-stage rotating motor was completely characterized by a temperature and photon-cycled experimental routine based on $^1$H NMR spectroscopy. All its relevant reaction rates were determined empirically. By using Markov theory, the probability density of observing a certain number of quarter rotations at time $t$ was calculated. Spiked, drifting Gaussians were obtained. Next, expressions were found for the quarter rotation velocity $V$ and rotational spread $D$. This allowed us to determine the $Pe$, $(V/D)$, $0 \leq Pe \leq 1$, for rotational motors, which is a measure for motor performance. Furthermore, we defined the quantity $r.e. \leq r.e. \leq 1$, as the relative ratio of the rate of full forward rotations ($\Omega_+$) versus the rate of full backward rotations ($\Omega_-$). The effective rate of full rotations is given by $\Omega_{\text{eff}} = \Omega_+ - \Omega_-$. We demonstrated that $V$, $D$, $Pe$, $\Omega_{\text{eff}}$, and $r.e.$ can be optimized by tuning the temperature and light input, thus achieving maximum efficiency and unidirectionality.

Remarkably, there is an optimal temperature range for motor rotation at a given light intensity. Increasing the temperature beyond that range reduces motor performance.

Our work presents a pragmatic and powerful combination of theory and experiment for optimization and control of molecular motor performance. This provides a pivotal step forward toward possible nanoscientific applications.

**Matlab Routines**

Matlab routines to calculate Figs. 3 and 4 are included in SI.

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7. van Delden RA, ter Wiel MKJ, Koumara N, Feringa BL (2003) In control of the reaction dynamics of synthetic molecular motors. A specific unidirectional four-stage rotating motor was completely characterized by a temperature and photon-cycled experimental routine based on $^1$H NMR spectroscopy. All its relevant reaction rates were determined empirically. By using Markov theory, the probability density of observing a certain number of quarter rotations at time $t$ was calculated. Spiked, drifting Gaussians were obtained. Next, expressions were found for the quarter rotation velocity $V$ and rotational spread $D$. This allowed us to determine the $Pe$, $(V/D)$, $0 \leq Pe \leq 1$, for rotational motors, which is a measure for motor performance. Furthermore, we defined the quantity $r.e. \leq r.e. \leq 1$, as the relative ratio of the rate of full forward rotations ($\Omega_+$) versus the rate of full backward rotations ($\Omega_-$). The effective rate of full rotations is given by $\Omega_{\text{eff}} = \Omega_+ - \Omega_-$. We demonstrated that $V$, $D$, $Pe$, $\Omega_{\text{eff}}$, and $r.e.$ can be optimized by tuning the temperature and light input, thus achieving maximum efficiency and unidirectionality.

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