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Directed motion of periodically driven molecular motors: A graph-theoretical approach

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We propose a numerical algorithm for calculation of quantized directed motion of a stochastic system of interacting particles induced by periodic changes of control parameters on the graph of microstates. As a main application, we consider models of catenane molecular motors, which demonstrated the possibility of a similar control of directed motion of molecular components. We show that our algorithm allows one to calculate the motion of a system in the space of its microstates even when the considered phase space is combinatorially large ($\sim 1 \times 10^6$ microscopic states). Several general observations are made about the structure of the phase diagram of the systems studied, which may be used for rational design and efficient control of new generations of molecular motors.

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I. INTRODUCTION

Molecular machines and motors are widespread in nature, comprising a large list of membrane proteins and enzymes, supra-molecular complexes such as bacterial flagellum and many others.^{1–5} High efficiency and robustness of such biological objects are well known. They attracted an interest of many researchers in an effort to create artificial analogs with similar properties.^{6–16} There have been many theoretical insights into mechanisms and properties of molecular machines and artificial molecular rotors and motors.^{17–42}

Experimentally, the possibility to induce an unidirectional rotation of molecular systems by periodic perturbations has been observed in catenane systems.^{14,43} The catenane molecules are made of molecular components that are bound together topologically rather than by covalent interactions.^{14,43,44} They usually consist of a big organic ring which is interlocked with the smaller ones, as shown in Fig. 1. A catenane molecule made of N rings can generically be called N -catenane. Unidirectional driving may be induced by periodically adding some chemicals to the solution or by changing the solution pH, thus changing kinetic rates that characterize transitions between different metastable states of the molecule. Upon the periodic perturbation the smaller rings can move along the larger one in a directed (clockwise or counterclockwise) fashion on average. This directed motion happens on the background of random thermally induced jumps of smaller rings between stations. Obviously, without driving of parameters, thermally induced transitions would not lead to any directed motion on average.

The experimental progress toward synthesis of artificial non-autonomous molecular motors raised new theoretical challenges. Anticipating future applications of synthetic molecular motors in nanomechanical devices, it is important to know how one should control these systems in order to produce desired motion of the smaller rings efficiently. Even if metastable states of the molecule are identified and transition rates are determined, finding the response of a molecule to a large external perturbation is a complex problem for a molecule with a large phase space.

The dynamics of the $(M + 1)$ -catenane systems, such as one shown in Fig. 1(a), as well as many other molecular motors, is fully described in terms of the corresponding graph G of microstates (Fig. 1(b)). In this graph, each microstate corresponds to one configuration of the smaller rings on the bigger one, and links represent allowed elementary transitions. For example, in catenanes, each link in the microstate graph corresponds to a jump of one of the smaller rings to an unoccupied neighboring station at fixed positions of other rings.

The dynamics of the system in the space of graph microstates merely substitutes a many-body problem by a mathematically equivalent model of motion of a single particle on the graph G . The analysis of kinetics in this space can reveal fundamental properties, such as existence of fluctuation relations, energy exchange between cycles of the microstate graph, etc.²⁹ However, only relatively simple kinetic models of molecular motors can be analyzed on the level of a microstate graph. The reason is a quickly growing complexity of the space of microstates. While for a simple catenane molecule in Fig. 1(a) the space of microstates consists of only $|V| = 6$ states, the number of possible microstates, between which the transitions are allowed, is growing as $N!/(N-M)!(M-1)!$ with the number of the stations N and

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FIG. 1. (a) Schematic representation of the $M + 1$ -catenane system with the number of smaller rings $M = 2$ and the number of physical nodes is $N = 3$. (b) In the microstate phase space, this system is represented as a graph G with 6-nodes and 6-edges.

the number of smaller rings M , occupying these stations. For example, for $N = 6$ and $M = 3$, we have $[V] = 60$ microstates, and for $N = 15$ and $M = 7$ we already have $[V] = 45\,045$. Such large graphs are not only hard to visualize, it is challenging to perform numerical studies of the kinetics on such graphs.

Hence, our goal is to design an efficient approach to quantify a directed motion of a molecule that emerges in response to periodic changes of parameters of the graph of microstates. In this work, we propose such a graph-theoretical approach to quantify the control of a catenane molecule by performing computation with a combinatorially large phase space of microstates. Our algorithm describes the behavior in a specific but important limit when the periodic driving of parameters is adiabatically slow, so that a system has time to explore its phase space by performing random transitions before substantial changes of control parameters happen. The perturbation of parameters is also assumed to be large in the energy scale in comparison to the temperature scale. Mathematically, this regime corresponds to taking the limit of low temperature after assuming adiabatic approximation. This regime is important for operations of many molecular motors, including catenane molecules.³¹

Our method is based on a recent theoretical insight^{45–47} that related the calculation of a molecular response to an adiabatic periodic driving with finding the minimum spanning trees (MSTs) of the microstate graph that represents the kinetic model. Finding MSTs is the most computationally expensive part of our algorithm, which determines the scaling for the overall method. Efficient MST search algorithms exist and are described in the literature.⁴⁸ They are known to scale as $[V]\log[V]$. Hence, the performance of our numerical algorithm for finding the response to a periodic driving of parameters also scales as $[V]\log([V])$ with the size of the phase space $[V]$.

The structure of our article is as follows. In Sec. II, we define the general model of stochastic motion of rings in a catenane molecule. In Sec. III, we review previous theoretical results and provide the motivation and an explanation of the idea of our algorithm. In Sec. IV, we test the speed of our algorithm on models of a complex molecule assuming periodic driving protocols. In Sec. V, we apply our algorithm to study global characteristics of the sensitivity field for currents on the graph of microstates of several catenane molecules. While the primary goal of this article is to test our numerical approach, in this section we also observe several features of the sensi-

tivity field that always appear in our numerical results. One of such observations is that the flux lines of the sensitivity field, in the case of the integer quantization, carry only unit fluxes. We prove this fact rigorously in Sec. VI, but we leave other observations, reported in Sec. V, as conjectures. Section VII summarizes our findings.

II. KINETICS ON THE GRAPH OF MICROSTATES

We study the $(M + 1)$ -catenane systems, which consist of one big ring and M smaller rings topologically interlocked with the bigger one, so that they may jump along the bigger one from one station to another (Fig. 1(a)). We will refer to the smaller rings as the particles that make random transitions among stations of the larger ring.³¹ Such particles interact with each other due to repulsive interactions which forbid two or more particles to appear on the same station simultaneously. At the thermodynamic equilibrium, the detailed balance constraints on kinetic rates result in the absence of a directed motion on average, while purely thermal random jumps from one state to another are possible.^{31,49} The application of the external control is equivalent to making kinetic rates of the model explicitly time dependent, changing according to a prescribed driving protocol.

Each particle may interact with a given station differently from other particles; different particles may also interact differently with the different stations. In Fig. 1(a), this is reflected by different colors of smaller rings and stations. Transition rates can be parameterized by state energies and barrier sizes.^{31,50} According to this parameterization, ε_j^i in Fig. 1(a) has the meaning of the interaction energy (affinity) of the i th particle with the j th station, $w_{jk}^i = w_{kj}^i$ is the energy barrier for the i th particle to move from the j th station to one of the neighboring unoccupied stations k . The mentioned quantities ε_j^i and $w_{jk}^i = w_{kj}^i$ are defined such that $\varepsilon_j^i - w_{jk}^i$ has a meaning of the energy barrier for transition of i th particle (small ring) from the station j to the station k in the standard chemical kinetics sense. Although the barriers w_{jk}^i are equal for forward and backward transitions, the energies of the states j and k are different in general. This makes the transition barriers in the chemical kinetics sense to be different for different directions. If a station is occupied by a particle, transition rates of other particles to this station are set to zero. Detailed balance constraints correspond to restricting kinetic rates to have the so-called Arrhenius form $k_{jk}^i = e^{-\beta(\varepsilon_j^i - w_{jk}^i)}$, where $\beta = 1/(k_B T)$ is the inverse temperature and k_{jk}^i is the kinetic rate of transition of the i th particle from the station j to the station k when the latter is unoccupied by another ring.

In the space of the microstates, the system may be described by an undirected graph $G = \{V, L\}$, where V is the set of the vertices/nodes and $L = \{(v_1, v_2) | v_1, v_2 \in V\}$ is the set of the links connecting nodes (Fig. 1(b)). Each node represents a distinct microstate of the system, i.e., a distinct configuration of catenane rings on the stations, and has the energy equal to the sum of energies of all occupied stations (which also depends on the type of the particles that reside on it)

$$E_I = \sum_{j=1}^M \varepsilon_{c_j}^j, \quad (1)$$

where $I = (c_1 c_2 \dots c_M)$ is the index of the given microstate (the coefficient c_i has the meaning of the index of the station on which the i th particle resides).

For a given molecule, there are restrictions on configurations of rings that can be valid microstates. Any pair of smaller rings in a catenane molecule cannot occupy the same station simultaneously. It is also impossible to squeeze one smaller ring through the other, so only cyclic permutations of smaller rings can be connected by kinetics. Restrictions on the links of the graph G follow from the fact that the elementary transitions among microstates must differ by no more than one transition of a smaller ring between the stations in the physical space. Only such microstates are connected by links in G . This observation implies that the number of links of the graph of microstates is growing almost linearly with the number of microstates when the latter is combinatorially large.

Links in the space of microstates are characterized by their own weights, $W_{IJ} = W_{JI}$, (energy barriers to hop from the microstate I to another microstate J or vice versa) that can also be used to parameterize the kinetic rates of a model with detailed balance

$$k_{I \rightarrow J} = e^{\beta(E_I - W_{IJ})}. \quad (2)$$

We require that the kinetic rates are the same in both descriptions – in the particle-station or in the microstate phase spaces. This leads us to the set of equations from which we define the barriers for transitions between microstates in the corresponding phase space

$$\exp\{\beta(E_{IJ} - W_{IJ})\} = \exp\{\beta(\varepsilon_{i_k}^k - \omega_{i_k \tilde{i}_k}^k)\}. \quad (3)$$

Here, we used the following notation: the initial state was $I = (i_1 i_2 \dots i_k \dots i_M)$ and the final state was $J = (i_1 i_2 \dots \tilde{i}_k \dots i_M)$ meaning that the k th particle moved from the station i_k to one of the adjacent stations $\tilde{i}_k$. Taking into account that $E_I = \sum_{j=1}^M \varepsilon_{i_j}^j = \varepsilon_{i_k}^k + \sum_{\substack{j=1 \\ j \neq k}}^M \varepsilon_{i_j}^j$ we obtain

$$W_{IJ} = \sum_{\substack{j=1 \\ j \neq k}}^M \varepsilon_{i_j}^j + \omega_{i_k \tilde{i}_k}^k. \quad (4)$$

Examples of explicit conversions between the two parameterizations for 3-catenane molecules can be found in the previous works.⁵⁰

III. NUMERICAL APPROACH

Our goal is to develop a computational approach that allows one to study the response of a kinetic model on a graph, such as G with kinetic rates given by Eq. (2), to the action of imposed adiabatically slow periodic changes of a subset of parameters. In addition, we consider only the low temperature limit, which corresponds to setting $\beta \rightarrow \infty$ in Eq. (3), or alternatively, assuming the limit of large amplitude of the parameter changes in comparison to $1/\beta$ in the energy scale. Specifically, we concentrate on the time integrated (average) currents on the graph of microstates G . This is the average number of transitions a particle makes through the links of the graph during the period of the driving protocol. We will assume that all

links have imposed directions so that “the number of transitions” through a link of G is the number of transitions along the direction of this link minus the number of transitions in the opposite direction through the same link. This problem was recently studied theoretically.^{46,47} We will formulate our numerical algorithm using the results of these studies.

A. Averaging formula

Recent theoretical studies^{46,47} showed that in the adiabatic limit followed by the low temperature limit, there is a simplified procedure to determine quantized currents in response to periodic changes of parameters in the kinetic model of motion of a single particle on a graph. The currents integrated over the period of a driving protocol were shown to be fractionally quantized and explicitly given by the averaging formula

$$Q_a = \sum_{k=1}^T \frac{1}{N_{\text{MST}}(t_k) N_I(t_k) N_F(t_k)} \times \left[\sum_{n=1}^{N_{\text{MST}}} \sum_i^{N_I} \sum_f^{N_F} j_b(n, V_i \rightarrow V_f, t_k) \delta_{ab} \right], \quad (5)$$

where Q_a is the average (per period of the driving) current through the link a , k runs over all the moments t_k when the set of the minimal energies of the graph G undergoes a change during the periodic driving of parameters, T is the number of such moments, $N_{\text{MST}}(t)$ is the number of the minimum spanning trees (MST) at a given time t , and $N_I(t_k)$ [or $N_F(t_k)$] is the number of nodes with the minimal energy at time $t_k - dt$ [or $t_k + dt$] where dt is infinitesimally small. For more detailed definition of the MST, we refer reader to the Appendix. The summations are performed over all possible equivalent MSTs; for each of them all initial and final vertices with the minimal energy are taken into account. The quantity $j_b(n, V_i \rightarrow V_f, t)$ is the integer-valued current generated on the link b by changing parameters during the time interval $[t_k - dt, t_k + dt]$ that belongs to the n th equivalent MST. It has unit value if the link b belongs to the shortest path on this MST from one of the initial minimal energy vertices V_i to one of the final vertices V_f with minimal energies at the end of the time interval.

Considerable simplifications in the averaging formula can be made when the original model has no permanent symmetry of parameters. In this case, the currents per period of the driving were shown to have integer values. This follows from the quantization theorem.⁵⁰ In case of catenanes, the permanent degeneracy can arise when some of the small rings or stations or both can be considered identical, i.e., having identical values for energies and barriers that parameterize kinetic rates, in addition to instantaneous pairwise degeneracies that can happen during periodic driving of parameters. If the permanent degeneracy conditions are not imposed, the quantization theorem guarantees that there is always a single MST at each sufficiently small time interval, which corresponds to the change of minimal energies during parameter driving between only a pair of minimal energy microstates, i.e., we would always have $N_{\text{MST}}(t_k) = 1$, $N_I(t_k) = 1$, and $N_F(t_k) = 1$.

FIG. 2. (a) The construction of integer quantized current Q as a sum of piece-wise integer currents (red arrows) defined on minimum spanning trees (parts (b)–(d)). The path in the control parameter space can be split into overlapping intervals. Intervals of the first type have an unchanging node with the lowest energy, while intervals of the second type correspond to transitions between nodes but having the minimum spanning tree unchanged.

As an example of application of the averaging formula in the integer quantization regime, consider the graph in Fig. 2(a). The red arrows show the cyclic path that is generated by some periodic protocol at low temperature. Assume that a particle starts at the minimal node 1 having the largest barriers along the links connecting nodes $\{3,4\}$, $\{1,6\}$, and $\{2,4\}$. Suppose that by the time when this configuration of largest barriers changes, the node with the lowest energy becomes the node 3. The average current during this time interval can be computed by assuming that a particle goes deterministically from the node 1 to the node 3 via the path indicated by red arrows in Fig. 2(b) along the corresponding MST. After this, the protocol proceeds with a time interval during which a particle stays at the node 3 until the barrier configuration is such that the minimum spanning tree is the one shown in Fig. 2(c). We then repeat our arguments until the protocol completes one period and the particle returns to the node 1. After the motion along the MSTs illustrated in Fig. 2, parts (b)–(d), a unit integrated over time current will be generated on average through links $\{1,2\}$, $\{2,3\}$, $\{3,4\}$, $\{4,5\}$, $\{5,6\}$, $\{6,1\}$, and zero current will pass on average through links $\{1,4\}$ and $\{2,4\}$.

B. The algorithm for obtaining quantized response to periodic driving

The averaging formula suggests a simple numerical procedure to obtain the quantized current generated by driving parameters along a closed contour:

- (i) Split the driving contour into sufficiently small time intervals of control parameter variation. Sizes of intervals should be such that only one pair of minimal energy states on the microstate graph may experience the degeneracy at each time interval.
- (ii) At each time interval, check whether the set of lowest energies is different at the end points of this interval.
- (iii) If this set does not change, then the generated current at this interval is set to zero. If lowest energy set changes, determine the set of minimum spanning trees and calculate currents at this interval generated by paths that connect pairs of nodes with minimal energies along the minimum spanning trees.

FIG. 3. An example of a driving contour to test the algorithm performance: T is the driving period.

- (iv) Sum up the contributions of all intervals, sets of the minimal energies, and MSTs, with proper weights according to the averaging formula, to obtain the total current passed through any link of the graph.

In such an approach, the central part of the calculations is the finding of all equivalent MSTs. The powerful algorithms for finding MSTs are the Kruskal or Prim algorithms which scale as $[V]\log[V]$ in our systems. A detailed description of the original Kruskal algorithm and its generalizations on the case of degenerate graphs are presented in the Appendix.

IV. SCALING PROPERTIES OF THE ALGORITHM

We developed a numerical code that combines the Kruskal algorithm with the steps described in Sec. III in order to obtain the quantized currents. In order to evaluate the performance of our algorithm, we applied it to a series of models with increasing size of the phase space. We considered cyclic contours in the space of control parameters, such as shown in Figure 3. We periodically varied the energies (ε_i^r , ε_j^r) of two stations i and j for a given smaller ring/particle r

$$\begin{aligned}\varepsilon_i^r(t) &= \varepsilon_i^{r,0} + f_1(R, t, T), \\ \varepsilon_j^r(t) &= \varepsilon_j^{r,0} + f_2(R, t, T),\end{aligned}\quad (6)$$

where f_1 and f_2 are the periodic functions (to produce a cycle in parameter space) with the amplitude R and the period T . The point in the phase space ($\varepsilon_i^{r,0}$, $\varepsilon_j^{r,0}$) determines the center of the contour (Fig. 3).

For each tested model of a catenane molecule, we created a graph of microstates and calculated the currents, induced on this graph by periodic driving. To prove that the algorithm complexity scales as $[V]\log[V]$, where $[V]$ is the number of microstates, we showed the linear relation between this quantity and the central processing unit (CPU) time for corresponding calculations (Fig. 4(a)). We also considered the number of the links in the graph as the complexity parameter, similar to the number of states. Similar scaling of the algorithm was found as function of the number of the edges (links) of the graph, as shown in Fig. 4(b). The calculations for all cases take quite reasonable time on a typical personal computer machine because of the good scaling properties of

FIG. 4. Scaling properties of the algorithm: CPU time vs. (a) $V \log V$ and (b) $E \log E$, where V is the number of graph vertices (states), E is the number of links in the graph of microstates. The description of the parameters and the simulation setup used is given in the main text.

the algorithm. Direct numerical solution of the master equation would scale at least as $[V]^2$, so that the required CPU time would be of the order of $\sim 10^5$ times of the time used in our calculations.

In our calculations, the system size of up to $\sim 5 \cdot 10^6$ microstates were considered. To vary the number of states, we kept the number of smaller rings fixed, $M = 3$, and systematically increased the number of stations on the bigger ring from $N = 10$ (360 states) to $N = 100$ (485 100 states). In each simulation, the energies of the stations for all rings ε_i^r were set to random values in the interval $[-1, 1]$ except for the energies of the first ring on two of the stations ε_1 and ε_2 , which were considered as the control parameters. The barriers for transitions between adjacent stations for all rings ω_{ij}^r were set to random values in the interval $[-1, 1]$. In addition, we checked that the energies of all stations and all barriers are distinct by at least 10^{-9} to avoid permanent degeneracies to this accuracy. Parameters of the microstate graph were calculated according to Eqs. (1) and (4).

V. APPLICATION: THE MAP OF THE SENSITIVITY FIELD

A. Sensitivity field

In our previous studies, we argued that the current through a link a , induced by adiabatic periodic driving of parameters, can be characterized by the “sensitivity field,” $\vec{F} = \vec{F}(\{E\}, \{W\})$, which has similar properties to a magnetic field but acting in the space of control parameters.^{45,50,39,51} If this field is known as a function of control parameters, then the average number of transitions Q_a through the link a , generated by periodic changes of control parameters, is given by the flux of this field through the area S_c enclosed by the contour c that the driven parameters make in the control parameter space

$$Q_a = \iint_{S_c} \vec{F} \cdot d\vec{s}, \quad (7)$$

where $d\vec{s}$ is the element of the surface in the control parameter space inside the contour.^{52,53} If there are only three parameters available for control, then the sensitivity field is generally

concentrated in tubes, with the temperature-dependent widths in parameter space. The widths of the tubes shrink to zero in the low temperature limit. The flux of this field in any tube remains constant and quantized, i.e., it has been proven to be an integer or a rational number even in the limit of zero temperature.^{46,47,50}

In our previous work,³⁹ we demonstrated that the plot of the sensitivity field ($\vec{F}$) can be a useful tool to visualize the controllability of a current through a specific link. For example, by choosing the driving protocol along a contour in the control parameter space that encloses areas with large values of $\vec{F}$ we can achieve a substantial current through a considered link of a graph by such a driving protocol. Conversely, if a contour does not enclose substantial values of $\vec{F}$, the system will not produce a directed motion on average via the given link of the graph of microstates.

Figure 5 shows an example of the distribution of the sensitivity field at low temperature for a 3-catenane model that was worked out analytically in Ref. 50. It illustrates the fact that the sensitivity field for this molecule is concentrated in four tubes with a unit flux tube splitting into three tubes carrying the fractional fluxes of a magnitude $1/3$.

Figure 5 can be used in practice as a phase diagram that classifies quantized (fractionally) currents induced by time

FIG. 5. Sensitivity field flux lines (red) in a 3-catenane molecule with three identical stations and different mobile rings. The model is described in Ref. 50, and the phase diagram is recalculated by the algorithm based on the averaging formula.

evolution of the control parameters along arbitrary contours in the parameter space. For example, if a contour encloses only one of the tubes in Fig. 5, then the resulting current through a link of the graph can be either 1 or $1/3$, depending on the particular choice of the driving contour. A more complex contour that encloses several tubes and, possibly, winds many times around them generates the current that is merely the sum of the fluxes in each tube multiplied by the number of windings around them. Such quantized currents are robust, i.e., it was shown previously^{46,50} that they do not change upon distortions of contours that do not lead to crossings of the flux lines.

Generally, the dimension of a phase diagram is equal to the number of parameters available for control. Hence, if complexity of a model increases, the visualization of the phase diagram as function of all possible parameters becomes a complex problem. In most practical applications, however, only a few parameters, such as temperature, pH-level, etc. are available for control. Therefore, in this work, we restrict to the practically interesting situation when only 3 parameters (i.e., 3 arbitrary combinations of energies and barriers) are controlled directly and other parameters are set constant or evolve proportionally to directly driven control parameters. In this case, the phase diagram can be represented as a 3D plot of the sensitivity field.

At finite temperature, the tubes with essentially nonzero sensitivity field have finite widths of the order of $k_B T$ in the energy scale, but they shrink to one-dimensional (1D) lines when the temperature decreases.^{45–47} This observation suggests that in order to visualize the phase diagram, such as in Fig. 5, it is sufficient to obtain the sensitivity field in the low temperature limit. Such a diagram, although not giving details at finite temperature, still contains a lot of important information about the global properties of the sensitivity field, i.e., positions of the lines around which the sensitivity field is concentrated and the fluxes carried by these lines.

To construct the three-dimensional plot of the sensitivity field, we grade the control parameter region of interest with small intervals (Fig. 6), so that the set of minimal energies changes not more than once per each interval. Subsequently, we obtain currents generated at each link of such a grading according to the averaging formula. Finally, we find circulation

of such currents through each plaquette of the grading. The plaquettes with nonzero circulation of currents correspond to places that are crossed by flux lines, with the flux equal to the corresponding current circulation around a plaquette.

Note that the problem of finding the quantized current reduces to the calculation of the MSTs at a set of intervals of control parameters. The size of such intervals should be chosen carefully to avoid the events of missing important intervals with changing sets of minimal energies. Fortunately, during our numerical studies, we found that, generally, the complexity of the phase diagram does not scale with the size of the phase space, i.e., the number of flux lines does not increase quickly with the increasing complexity of the model. Therefore, the size of the interval for numerical application of the averaging formula in our studies can usually be chosen to be a numerical factor 10–100 smaller than the typical energy differences of states in the considered region of parameters. Also, in practice, missing such important events in calculations usually leads to clearly observable irregularities of the phase diagrams, such as planes rather than lines of the sensitivity field, which cannot be physical, and which can be fixed by decreasing the size of the interval in a problematic region.

Summarizing, the phase diagram, obtained by the described method, is a set of 1D flux lines imbedded in 3D space of control parameters. A periodic driving of parameters, which is represented by a contour that encloses any of the flux lines, induces some unidirectional motion through some links on the graph of microstates. The size of the flux line corresponds to the total average number of induced transitions through some links of the graph. If a contour in the space of control parameters does not enclose any of the flux lines, this contour does not produce any unidirectional motion in the graph of microstates.

As a practical application of the method developed, we identified flux lines in calculations, applied to microstate graphs of various $(M + 1)$ -catenane models with different suppositions about types of the particles and the stations. The study of the specific physical manifestations of the directed motion that each flux line represents is beyond the objective of this work, which focuses on the principal possibility to identify flux lines and geometry of such lines on the phase diagram.

FIG. 6. (a) Parameter space is graded with a finite grid step. (b) A 2D slice of the phase diagram. If parameters are varied along links ab or ef a unit current is generated (black arrows show the convention for the positive direction of currents). Other shown links correspond to zero generated current. Flux line (red) crosses the plaquette $abcd$. This is inferred from the fact that the sum of currents along the boundary of $abcd$ is 1. In contrast, although currents through links of $aefb$ -plaquette are not all zero, their circulation along $aefb$ is zero, meaning no flux line going through this plaquette.

B. Reproducing phase diagram of a 3-catenane

First, to test our algorithm, we reproduced the phase diagram for the model, which was explained and solved previously.⁵⁰ In this model, we have $M = 2$ smaller rings on a bigger ring with $N = 3$ stations. We assume same symmetries of parameters as in Ref. 50. Control parameters here are the interaction energies ($\varepsilon_1, \varepsilon_2, \varepsilon_3$) of one of the smaller rings with each of the three stations. The energies are distinct for each particle. Both particles are considered to be different. Since in this case $M = N - 1$, the number of transitions through a link on the graph of microstates corresponds also to the number of rotations of the molecular components around the center of the larger ring because the graph of microstates is cyclic (Fig. 1(b)).

FIG. 7. Flux lines of the sensitivity field in the integer quantization regime of a 3-catenane system, $M = 2$, $N = 3$. Choice of parameters: $\varepsilon_i^1 = c \cdot \varepsilon_i^0$, $\forall i = 0, 1, 2$, where $c = 1.733$, and ε_i are the control parameters. The barriers are: $\omega_{01}^0 = 1/7$, $\omega_{01}^1 = 0$, $\omega_{02}^0 = -1/2$, $\omega_{02}^1 = 1/2$, $\omega_{12}^0 = 1/4$, and $\omega_{12}^1 = -1/11$. Integer numbers denote the current induced in the system by driving the control parameters along the contour enclosing a corresponding line.

The particular case in Fig. 5 corresponds to zero values of all barriers in the physical space and degeneracy of coupling of one of the rings to three stations. Therefore, we obtain the graph with permanently degenerate values of some parameters, resulting in more than one MST at some regions of the control parameter values. This leads to non-integer current quantization with values of $1/3$ as well as a unit quantization (Fig. 5). This result is in agreement with previous calculations of the same phase diagram, which was reported in Ref. 50.

Next, we considered the previously unstudied case of a 3-catenane system with 3 stations in the integer quantization regime. The initial setup and driving protocols were chosen such that all coupling energies of rings to the stations, as well as all the barriers, can be considered distinct. Three control parameters are the coupling energies of the first ring on the three stations. The phase diagram for the sensitivity field is shown in Fig. 7. It consists of the distinct lines which all have the flux of the sensitivity field equal to 1. That is, if one drives the energies in the contour enclosing one of the lines, the resulting current will be equal to $+1$ or -1 , depending on the direction of the driving along the contour. If the driving con-

tour encloses several lines and goes the same direction, the currents will sum up.

C. Sensitivity fields for complex models

The developed algorithm allows one to study more complex systems, such as higher order catenane molecules. For example, Figure 8 shows the phase diagram for a sensitivity field for the graph of microstates of a catenane molecule with $M = 3$ and $N = 6$, with all stations and rings different (integer quantization regime). The size of the phase space is $[V] = 60$. Each flux line in Figure 8 represents a set of parameters whose enclosure by a closed contour induces nonzero current through at least one of the links of the microstate graph. The size of the flux represents the number of uncompensated transitions generated through links with nonzero current generated by driving the system along an infinitesimal contour that encloses the flux line.

By studying many such examples of phase diagrams for complex molecules with integer and fractional quantization of responses, we made several general observations about the structure of the flux lines of the sensitivity field that describe currents through links of the graph of microstates as described in the following:

- The number of the flux lines, representing currents through a specific link of the graph of microstates, usually does not increase fast with the size of a phase space. For the case in Fig. 8, for example, we have only two flux lines, which is even less than in the case of Fig. 7 despite the 10 times difference in the number of microstates and the fact that the graph of microstates for $N = 6$ and $M = 3$ is not a simple cycle. Instead, the structure of the flux lines becomes more complex, i.e., they more often experience sharp twists and turns, when complexity of the model increases.
- In the case of the integer quantization regime, we always observe that the flux lines do not branch, unlike the case of the fractional quantization, shown in Fig. 5. For the case of a fractional quantization, if a flux line branches into several lines, the total flux at the branching point is conserved as in Fig. 5.
- We never observe situations when the flux lines suddenly terminate at finite values of control parameters.

FIG. 8. (a) Flux line positions in a non-degenerate system with $M = 3$, $N = 6$. (b) Zoom of the same figure at the region with complex behavior of the lines. Choice of parameters: $\varepsilon_i^r = c_{ri} \cdot \varepsilon_i^0$, $\forall i = 0 \dots 5$, $\forall r = 1, 2$, where $\varepsilon_i \equiv \varepsilon_i^0$ are the control parameters and c_{ri} are the coupling constants, chosen randomly in the range $[-1.5, 1.5]$, but to be distinct from each other.

Also, we never observe a case when the flux lines are created as finite size loops in the parameter space. One can say that, in all our tested models, the sensitivity field lines originate and disappear at infinite values of parameters in the control parameter space.

- (d) It is common that some of the flux lines propagate parallel to each other but at a finite distance from each other in the parameter space. Hence, a small but finite sized closed contour may enclose two or several such flux lines. This observation implies that at a finite temperature, when these lines transform into tubes with finite widths, flux tubes in a bundle may substantially overlap with each other and the whole bundle of flux tubes may look like a single tube carrying a non-unit flux. However, at sufficiently low temperature, those tubes become distinguishable.
- (e) In all our simulations, the integer quantization case produces only the flux lines carrying unit fluxes. In Sec. VI, we prove that this is actually the only possibility in this regime. In the case of a fractional quantization, with permanent parameter degeneracies, there is no such universality. Generally in the fractional quantization regime, we observed several flux lines carrying different non-integer fluxes with values equal or below unity, but we never observed flux lines with higher than unit fluxes.
- (f) A special important example of a permanent parameter degeneracy is the case when smaller rings of a catenane molecule are identical, but stations are not, that is, $\omega_{ij}^0 = \omega_{ij}^1 = \dots = \omega_{ij}^{M-1}$ and $\varepsilon_i^0 = \varepsilon_i^1 = \dots = \varepsilon_i^{M-1}$ for all i . It has been shown previously⁴⁷ that a 3-catenane molecule with two identical small rings produces fractional $\frac{1}{2}$ -valued quantization of the response. We explored a number of $(M + 1)$ -catenane systems with M identical small rings (Fig. 9). This corresponds to the case of the motion of M identical particles on a cyclic graph with exclusion interactions. All particles interact with any given station with the same energy, but this energy may be different for different stations. In this case, there is more than one MST at any moment, which leads to a fractional quantization of currents. In all our samples of models of this kind, we found only flux lines carrying a flux $1/M$ (Fig. 9), where M is the number of identical small rings.

VI. UNIT FLUX OF SENSITIVITY FIELD LINES IN INTEGER QUANTIZATION REGIME

Our observations in Sec. V are based on a restricted set of kinetic models. At this stage, we cannot exclude the possibility of counterexamples. In this section, we will explain only one of these observations, while we leave the study of the others for future research. Here, we prove the statement that the flux lines in the sensitivity field diagram that represent the current through any link of the microstate graph in the integer quantized regime carry only unit fluxes.

FIG. 9. Fractional quantization for M identical particle motion on a ring with three controlled node energies. (a) $M = 2$, $N = 3$, with parameters: $\omega_{01}^i = \frac{1}{5}$, $\omega_{02}^i = \frac{3}{10}$, $\omega_{12}^i = -\frac{1}{10}$ for all i , $\varepsilon_i^1 = \varepsilon_i^0$ for all i ; (b) $M = 3$, $N = 4$, with parameters: $\omega_{01}^i = \frac{1}{5}$, $\omega_{03}^i = \frac{4}{10}$, $\omega_{12}^i = -\frac{1}{10}$, $\omega_{23}^i = \frac{3}{10}$ for all i , $\varepsilon_i^2 = \varepsilon_i^1 = \varepsilon_i^0$ for all i ; (c) $M = 4$, $N = 5$, with parameters $\omega_{01}^i = \frac{1}{5}$, $\omega_{04}^i = -\frac{9}{20}$, $\omega_{12}^i = -\frac{1}{10}$, $\omega_{23}^i = \frac{3}{10}$, $\omega_{34}^i = \frac{4}{10}$ for all i , $\varepsilon_i^3 = \varepsilon_i^2 = \varepsilon_i^1 = \varepsilon_i^0$ for all i . In all cases, $\varepsilon_i = \varepsilon_i^0$ are the control parameters. In all cases, graph of microstates is a simple cycle with sensitivity field representing identical currents through all links of the graph.

- (i) First, we note that we can calculate the flux through any line by calculating the quantized current generated by a control contour that winds once around this line and does not wind around any other flux line. Any such contour can be continuously deformed, without crossing any flux line, into a trivial infinitesimally small contour that encloses the considered flux line, as we show in Fig. 10. According to Refs. 45–47, such deformations do not change the current that is induced by the protocol. Hence, calculating quantized current through infinitesimal closed contour that encloses it is sufficient to determine the flux.
- (ii) Consider a catenane without any permanent degeneracy of parameters, i.e., with all distinct energy levels and barriers and a unique MST for all values of control parameters, except for accidental pairwise degeneracy during the time-dependent driving. A pairwise degeneracy, such as $W_{IJ} = W_{KL}$, corresponds to a linear constraint, so the

FIG. 10. A line with integer flux (red) and an infinitesimal contour in the parameter space that encloses it.

FIG. 11. A 2D cross-section of the parametric space with flux line crossing this cross-section. The red line corresponds to the cross-section of the degenerate minimum energy plane and blue lines correspond to cross-sections of some pair of degenerate barriers planes. It is generally impossible for three such curves to intersect simultaneously in the cross-sectional plane. The green contour represents an arbitrary small periodic protocol. When this contour is sufficiently small, it encloses only the simple intersection of two degeneracy planes.

points with this constraint in 3D space of control parameters generally lie on a 2D plane. Higher orders of degeneracies may appear only along the intersections of these planes. The theory in Refs. 45–47 showed that points on a flux line correspond to parameter values at which at least two lowest energies are degenerate simultaneously with a degeneracy of, at least, two barriers. Moreover, for the regime of integer quantization, higher order degeneracies do not happen, so that flux lines correspond, in this case, to a simultaneous degeneracy of exactly two node energies and exactly two link barriers, i.e., flux lines lie at intersections of two degeneracy planes which explains why they are 1D-manifolds if there are 3 parameters available for control.

- (iii) The infinitesimal contour, which is shown in Fig. 11 as a (green) square, can then be chosen to consist only of four intervals: two intervals with a pairwise degeneracy of energies on the graph of microstates happening at some parameter values (let them be intervals ab and cd , while barriers remain non-degenerate at all points on ab and cd). On another pair of intervals, bc and da , two barriers on the graph of microstates become degenerate at some values of parameters but lowest energies remain non-degenerate. Figure 11 illustrates that this follows from the fact that the simultaneous degeneracy line can typically appear at an intersection of degeneracy planes – one plane with degeneracy of two lowest energies and one plane with degeneracy of two barriers. Intersection of more than two planes at a single line is impossible in the integer quantization regime because they require the assumption of an additional symmetry in the system. Hence, we can choose intervals ab , bc , cd , and da so that each of them crosses one of the two intersecting planes.
- (iv) According to Refs. 45–47, a current is induced through some links of the graph of microstates only when the lowest energy nodes change. In the contour $abcda$, this happens at intervals ab and cd and the movements take place along the corresponding MSTs. Because the contour $abcda$ intersects just one plane of barrier degeneracy (see Fig. 11), the two MSTs can differ by an exchange of just two links – the pair whose barriers become degenerate on this plane.

FIG. 12. A 6-state graph with two non-cyclic paths between states 1 and 5. (a) Given the red path, the blue path is unacceptable as the other path of current in a generic small periodic protocol. (b) This pair of non-cyclic paths, red and blue, is acceptable for a small contour.

- (v) According to (iv), the motion on the full graph of microstates, when parameters are driven along the infinitesimal contour $abcda$, is always restricted to the sub-graph, which consists of a tree and a single extra link. This can be the MST at interval ab plus the link that appeared on the new MST during the interval bc . According to the Euler formula, such a sub-graph has only one cycle. Figure 12 illustrates this conclusion. It shows a 6-state graph. Assume that states 1 and 5 are the lowest energy nodes that exchange their order of magnitude during intervals ab and cd of the infinitesimal contour. At ab the system should go from 1 to 5 along one noncyclic path and at cd it should return along another noncyclic path. Figure 12(a) shows a pair of paths that cannot be induced by infinitesimal driving protocol because the resulting graph contains two cycles. Figure 12(b) shows a pair of paths between 1 and 5 that are allowed. Their combination creates only one cycle 3-4-5-3.
- (vi) Only links on a single cycle can sustain nonzero current as a result of driving parameters along the $a-b-c-d-a$ protocol. Other links of the graph, such as links 1-2 and 2-3 in Fig. 12 can be passed by a closed path only even number of times so that numbers of transitions in positive and negative directions are equal, so that the net current through those links is zero.
- (vii) We conclude the proof by showing that the cyclic path that is induced by the protocol $a-b-c-d-a$ can wind around the cycle of the sub-graph only one time. Consider the two links which become degenerate during intervals bc and da . Both these links must belong to the cycle of the sub-graph because the latter becomes a MST in absence of any one of them. Equivalently, each of these links should belong to exactly one of the two MSTs at intervals ab and cd . Unit nonzero currents are induced along these MSTs in their respective intervals. So the two links, by which two MSTs are different, can carry only unit currents during the whole protocol $a-b-c-d-a$. As the links in any cycle carry equal current, this implies all links in the cycle of the sub-graph carry a current equal to unity.

Thus, we showed that all currents induced through links of the microstate graph by an infinitesimal protocol that encloses the flux line in the control parameter space have either zero or unit values, which proves our original statement.

VII. CONCLUSIONS

We developed and tested the numerical approach to study the stochastic transport induced by periodic changes of parameters in a graph of microstates of a nonautonomous molecular motor. Using efficient algorithms for finding (MST) of the graphs, we were able to obtain global properties of the sensitivity field at the cost of CPU time which scales as $\sim[V]\log[V]$, where $[V]$ is the size of the phase space of the model. This makes the calculation of the response to a periodic driving protocol, for a complex system up to $\sim 10^6$ states, possible to produce with a single desktop within reasonable time.

In this work, we focused on the currents through links of the graph of microstates. We note that, generally, such currents do not coincide with some valuable characteristics, such as the number of rotations of smaller rings around the center of the larger ring. However, having currents on the graph of microstates, it is straightforward to obtain such characteristics without a cost for the scaling of the algorithm performance. We leave the study of such important characteristics of catenane molecules an open research direction.

Our numerical results suggest that currents on the graph of microstates may follow laws that can be formulated in terms of constraints on the properties of flux lines in the sensitivity field diagram. Theoretical investigation of all these properties would lead us far beyond the scope of our goals. We explained only one of such observations, leaving the others as conjectures for the future investigation.

Our algorithm will help to plan operation and control of various nanoscale devices and synthetic motors that employ ratchets and stochastic pump effects. Many-body interactions in such systems have always been underrepresented in theoretical studies due to the complexity of their kinetic models. Our numerical approach provides a non-standard direction to understand such many-body systems.

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APPENDIX: MINIMUM SPANNING TREES

Consider an undirected connected graph $G = \{V, E\}$ with the edges marked by some weights (costs). It is then required to find the connected sub-graph $G' = \{V', E'\} \subset G$ of the original graph which will contain all the vertices of the graph G (thus $V' = V$), but will not contain any cycles (thus $E' \subset E$) and will minimize the total sum of the weights of all included edges. The first two conditions mean that the sub-graph G' has a tree structure. Such trees which include all the vertices of the original graph are known as spanning trees. The spanning trees with the minimal cost (sum of the weights on all its edges) are known as minimum spanning trees (MST).

One of the most popular algorithms of finding the MSTs is a Kruskal algorithm. The Kruskal algorithm is performed in several steps. First, the edges of the initial graph G are sorted on the basis of their weights (costs). The first edge with the smallest weight becomes an initial MST. One then adds more and more edges of the original graph in the order they are sorted but skipping all those edges which would create cycles in the MST. For simple cyclic graphs this procedure is effectively equivalent to cutting the initial graph on its edge with the biggest cost (Fig. 13(a)). The same approach of cutting edges with maximal weights may be used if there are many equivalent edges (Fig. 13(b)). In this case one just has to create a list of the edges with the maximal weights and cut each of them to obtain a separate MST. This way one may obtain all equivalent MSTs almost without any additional computations.

However, such a simplistic approach to find all equivalent MSTs is not applicable for more general case (Fig. 14). If one

FIG. 13. Finding the MST in a special case of the cyclic graph. The numbers shown represent the weights of the graph edges. (a) Non-degenerate case, there is only a single edge with the maximal weight; (b) degenerate case, there are several edges with the same (maximal) value of the edge weight.

FIG. 14. Some of the 9 possible MST for general case graph.

starts adding minimal edges to form the MST, then there are 3 possibilities to choose first 2 edges with minimal weights (2), after that there is only 1 possibility to choose next smallest edge with weight 3. Finally there are 3 ways to choose one of the 2 edges with the next smallest (actually the biggest) weights (5). Overall, there are 9 possible MST with the total cost of 17.

Thus, the more general way to find all MSTs is the following. First, one has to group all edges into groups of equivalent edges, which have the same weight. Then one creates all the permutations of the edges within all groups. This defines in which order the edges within the group will be picked up for MST construction. Finally, one has to concatenate all permutations for all groups, starting with the group of edges with smallest weights. If all edges are grouped into m such sub-groups, each of which contains $n_1, n_2, \dots, n_m$ edges correspondingly, the total number of all possible variants will be $\prod_{i=1}^m n_i!$, which is considerably smaller than $(\sum_{i=1}^m n_i)! = E!$. The latter result is simply enumeration of all possible sequences of the edges, the brute-force approach.

To get the feeling of how these methods are different from each other consider the example on Fig. 14. With the grouping of edges into equivalency groups we will obtain $3! \cdot 1! \cdot 3! = 36$ which will produce only 9 really distinct MST with the same cost. On the other hand, the brute-force would result in $(3 + 1 + 3)! = 7! = 5040$ combinations. Although the method described is not yet optimal, it gives a significant speed up in comparison to the brute-force approach. It should be noted that even the group-based method produces the identical sequences of the edge pickup orders. Thus, after the procedure is done one still needs to check for identical (repeating) MSTs and leave only unique MSTs.

The efficiency of the method described depends strongly on the number of groups of equivalent edges and on their size. In degenerate cases one may encounter the situation when this approach is not longer practical. Imagine for example 2 groups of 9 equivalent edges in each. This already gives 131681894400 combinations. The case when we have 9 groups of 2 equivalent edges in each gives much smaller number of combinations, but already of the order of 1000 (512).

For our studies we thus used only the simplest version of the Kruskal algorithm for finding all MSTs, based on cutting of the edges with the biggest weights. Such approach is validated by the additional requirements on the transitions between states and the occupation number of the stations as well as by the preserving the initial ordering of the particles on the big ring. This simplifies the topology of the corresponding transitions network, allowing for faster algorithm to be used.

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