Upper bounding the average residence times in partially observed steady-state Markov jump processes

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Several types of stochastic dynamics can be modeled as a continuous-time Markov jump process among a finite number of sites. Within such framework, we face the problem of getting an upper bound on the average residence time of the system in a given site β (i.e., the average lifetime of the site) if what we can observe is only the permanence of the system in an adjacent site α and the occurrence of the transitions $\alpha \to \beta$. Supposing to have a long time record of this partial monitoring of the network under steady-state conditions, we show that an upper bound on the average time spent in the unobserved site can indeed be given. The bound is formally proved, tested by means of simulations, and illustrated for a multicyclic enzymatic reaction scheme.

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I. INTRODUCTION AND SETUP

Several types of stochastic dynamics can be likely modeled as a Markov jump process among a finite number of physical states which we call "sites". The markovian character lies in the fact that the future evolution of the system only depends on the actual state regardless of the past history. For instance, several examples can be found in the (bio)chemical ambit [1], where the discreteness may be intrinsic or could derive from a coarse-graining procedure. It is worth mentioning the conformational motions of complex molecules [2], the discrete representation of molecular motors and machines [3,4], the stochastic kinetics in the configurational space of the numbers of molecules [5], and the jumps of tagged molecular moieties from species to species due to the occurrence of chemical reactions [6–9]. Discrete Markov models also lie at the heart of the so-called "statistical kinetics" whose aim is making inferences on the kinetic mechanism from the statistical analysis of the single-molecule behavior [10]. Markov jump processes also constitute the best platform to develop and test connections between kinetics and thermodynamics, such as the "thermodynamic uncertainty relations" [11–13] and the "kinetic uncertainty relations" [14] for systems in nonequilibrium steady states. There is also an increasing interest for the thermodynamic inferences that can be made for fully observed [15,16] and partially observed [17,18] networks on the basis of the waiting time distributions of specific transitions.

Within such a broad context, here we face a specific problem of pure kinetic type. First, let us fix the physical setup. Let us consider a network constituted by a finite number of sites. Each site fully specifies the actual state of the system, meaning that no hidden variables affect the dynamics. The system can jump among the sites according to the available site-to-site connections, and the dynamics is a Markov jump process. Some site-site connections may be absent whereas, if two sites are directly connected, the transition can be either unidirectional or bidirectional. Let us assume that the jumps are instantaneous and let $k_{i\to j}$ be the jump rate constant from site i to site j (possibly equal to zero, if this transition is not allowed). In the case of multiple channels for the $i \to j$ transition, it is meant that $k_{i\to j}$ is the cumulative rate constant given by the summation of the rates of the single processes. There might be also "neutral jumps" in which the system does not change site. A jump of this type, say $i \to i$, would be associated with a rate constant $k_{i\to i}$. Such neutral jumps, if present, are irrelevant in our discussion. We assume that the jump rate constants are fixed, and that the dynamics admits a unique stationary distribution with occupation probabilities $p_i^{ss} > 0$. This requires that the network is "irreducible" (strongly connected), meaning that each site can be reached from any other site through at least one pathway [19,20]. The stationary state can be either a thermal equilibrium state (with reversible transitions and fulfillment of detailed balance) or a nonequilibrium steady state. Looking at the system's evolution, what we would see is an erratic dynamics because the time at which the next jump takes place is a stochastic variable and because the arrival site can be one among the reachable sites.

Let us consider the "average residence time" of the system in a given site. We call "residence time" the time of permanence in the site, i.e., the time between the jump into the site and the instant when the system leaves that site. Our focus is on the statistical average of such time under steady-state conditions. Equivalently, the average residence time defined in this way corresponds to the "average exit time" from the site, and to the "average lifetime" of the site seen as a transient state. The assessment of the average lifetime of a certain transient state might be of particular relevance in (bio)chemical networks when the transient state of interest cannot be observed in practice.

From now on, let us indicate with β the site we are interested in, and let $\overline{\tau}_\beta^{res}$ be its average residence time. Note that $\overline{\tau}_\beta^{res}$ is related to the steady-state occupation probability of the site, but also to the specific dynamical features of the network

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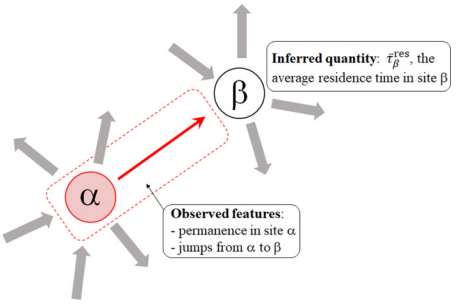

FIG. 1. Abstract representation of a network with several sites. The aim is to obtain an upper bound on the average residence time (average exit time) of the system in the unobserved site β from a long time record of the following observed features: the persistence in one linked site α and the detection of the transitions from α to β.

[21]. For instance, in the case of networks at the thermal equilibrium, $\overline{\tau}_\beta^{res}$ is determined not only by the energetic stability of the site (hence, by the Boltzmann occupation probability at equilibrium), but also by the rates of entry/exit into/from the site (hence, by features such as activation energies).

If the jump rate constants from the site β to the directly linked sites were known, we could determine the average residence time as

$$\overline{\tau}_\beta^{res} = \left(\sum_{j \neq \beta} k_{\beta \to j} \right)^{-1} . \tag{1}$$

Indeed, if we imagine employing Gillespie's algorithm [5,22] to simulate the jump dynamics, the distribution of the exit (residence) time is $\rho(\tau_\beta^{res}) = a_\beta \exp\{-a_\beta \tau_\beta^{res}\}$ where $a_\beta = \sum_{j \neq \beta} k_{\beta \to j}$ is the total propensity of leaving the site β. The average time over this distribution is exactly the $\overline{\tau}_\beta^{res}$ given in Eq. (1).

The crucial point is making an inference on $\overline{\tau}_\beta^{res}$ when the set of jump rate constants $k_{\beta \to j}$ is not known [hence, Eq. (1) is not useful] and only a limited knowledge about the network is available from a direct but partial observation of it. In our context, the wording "partial observation" refers to the situation in which one is able to experimentally monitor only part of the network's features, meaning that the rest remains invisible [23].

Here we focus on the drastic case in which we are only able to observe a single site α directly connected with β, and to detect when a jump $\alpha \to \beta$ takes place. The situation is depicted in Fig. 1. Suppose to be able to store the times of permanence in the site α and the instants at which a jump $\alpha \to \beta$ takes place (imagine "hearing a click" when such a jump occurs). Having only this type of information at disposal, can we make some inference on the average residence time of the unobserved site β?

We will see that what we can provide is an *upper* bound on $\overline{\tau}_\beta^{res}$. The result is Eq. (2) presented in the next section. The bound, which is proved and discussed in Appendix B, is tested by means of simulations made on small networks with randomly generated jump rate constants. The bound is then illustrated for a simulated multicyclic enzymatic reaction network.

Before proceeding, it is worth making a comment on the "observability" of a network. The observability might be concrete or hypothetical depending on the technology currently available. For instance, optical traps and single-molecule fluorescence techniques [10] allow the monitoring of conformational transitions in biomolecules under action, such as enzymes under turnover conditions or molecular motors. Such methodologies started to be available about thirty years ago [24], and nowadays they allow the tracking of single molecules even in living cells [25]. If the sites correspond instead to the chemical states of a tagged molecule (or of a tagged molecular moiety), and the site can change when that molecule (or the molecule currently carrying the tagged moiety) is involved in chemical reactions, then we should think of a hypothetical experimental technique that enables us to observe on the fly that specific molecule/moiety among all others of the same type. In the context of macroscopic and well-stirred reactive mixtures, the jump dynamics of such single tagged molecule (or molecular moiety) is a Markov process [6,7] and, under macroscopic stationary conditions, the jump rate constants are related to the kinetic rate constants of the elementary reactions and to the composition of the mixture [1,8,9]. For chemical reactions involving low numbers of reactant molecules, instead, the deterministic mass-action rate equations written in terms of volumetric concentrations are inadequate; rather, the system's state is captured by the ensemble of copy numbers of each species [5]. In this case, the technique should be able to detect (some of) such global configurations and the jumps between (some of) them. Note that similar dynamics are also encountered in minimal epidemic models [26] where, in place of molecules, one deals with individuals in various health states such as "susceptible," "infectious," "recovered," and possibly others. Under simplifying assumptions, the dynamics of the system (single individual or whole population) is again an autonomous Markov jump process whose monitoring could be facilitated by the fact that we deal with living beings rather than molecules.

In short, what we illustrate in the following applies to any situation that conforms to a Markov jump process at the steady state, provided that a technique enables us to observe at least one site (α) and the transition from such site to the one of interest (β).

II. RESULTS AND ILLUSTRATIVE CALCULATIONS

Let us introduce the *recurrence* time $\tau_{\alpha\beta}$ as the time between two consecutive $\alpha \to \beta$ transitions. Similarly, let $\tau_{\alpha\beta|\alpha}$ be the time of the first *occurrence* of the $\alpha \to \beta$ transition if the system starts from the site α. The statistics of the recurrence and occurrence times is summarized in Appendix A. Then, let us introduce $\mathrm{Prob}\{\tau_{\alpha\beta} \leqslant \tau\}$, the probability that $\tau_{\alpha\beta}$ falls below a value τ; similarly, $\mathrm{Prob}\{\tau_{\alpha\beta|\alpha} \leqslant \tau\}$ for the occurrence time $\tau_{\alpha\beta|\alpha}$. With these positions, in Appendix B we show that $\overline{\tau}_\beta^{res}$ is upperbounded as follows:

$$\overline{\tau}_\beta^{res} \leqslant \min_\tau \left\{ \frac{\mathrm{Prob}\{\tau_{\alpha\beta|\alpha} \leqslant \tau\} - \mathrm{Prob}\{\tau_{\alpha\beta} \leqslant \tau\}}{\rho_{\alpha\beta}(\tau)} \right\}, \tag{2}$$

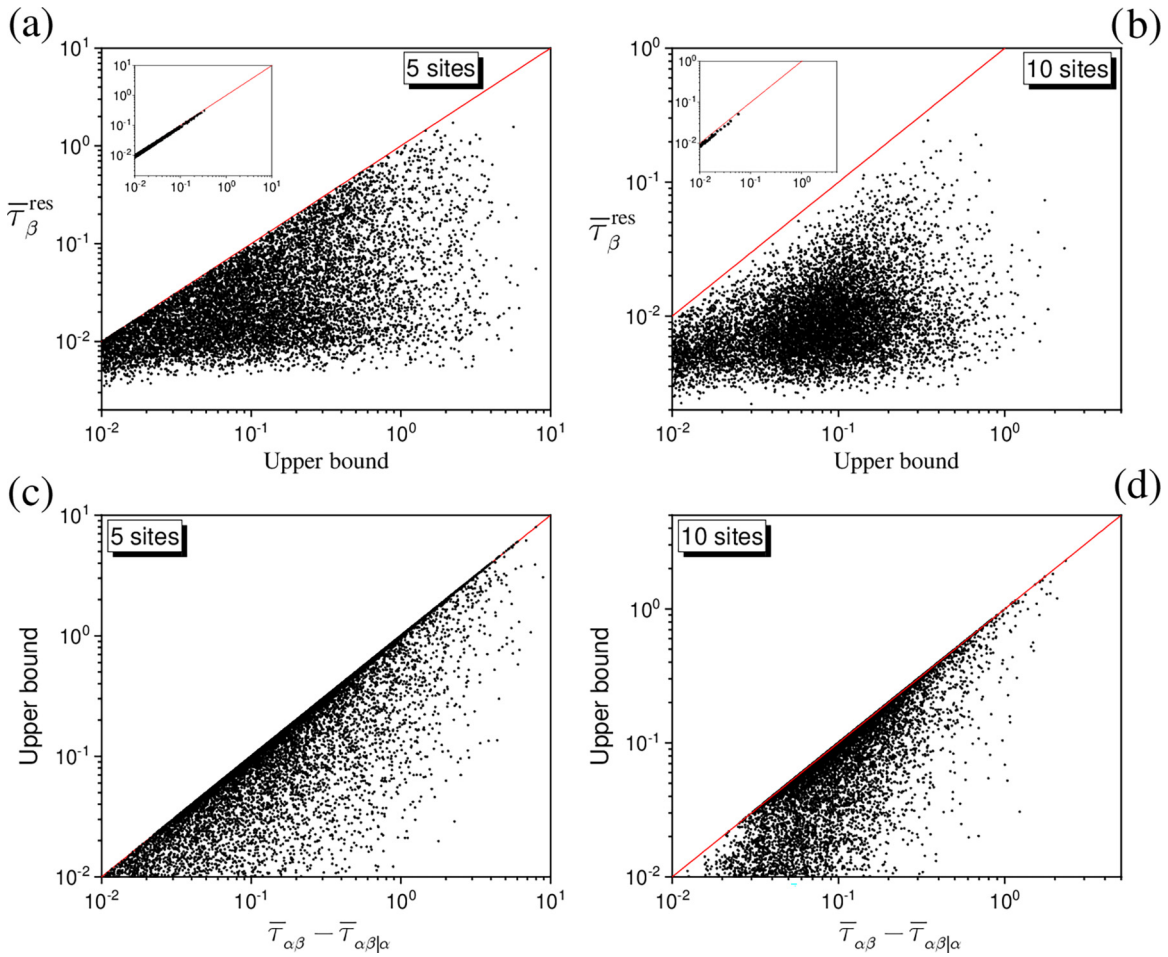

FIG. 2. Illustration of the bound Eq. (2) for randomly generated instances of networks with five sites [panel (a)] and 10 sites [panel (b)] all directly connected with each other with forward and backward transitions. The dots are 10^4 instances and the straight red lines have slope 1. The insets show only the points for which $k_{\beta\to\alpha}/a_\beta \geqslant 0.8$. Panels (c) and (d) show, for the same instances, that the upper bound is more stringent than the trivial bound $\overline{\tau}_{\alpha\beta} - \overline{\tau}_{\alpha\beta|\alpha}$ (all points fall below the diagonal). The time units here are immaterial.

where $\rho_{\alpha\beta}$ is the distribution function of the recurrence time. The proof of Eq. (2) makes use of Eq. (A8) derived in Appendix A (a set of differential equations that directly specify the mutual interrelations between the distribution functions of the occurrence times) and exploits the physical fact that the system, for undergoing the $\alpha \to \beta$ jump, first has to reach the site α. Let us note that a "trivial" upper bound can also be established [27]: $\overline{\tau}_\beta^{\rm res} \leqslant \overline{\tau}_{\alpha\beta} - \overline{\tau}_{\alpha\beta|\alpha}$. We will see, however, that Eq. (2) is a more stringent bound.

As pointed out in the second part of Appendix B, the inequality in Eq. (2) becomes an exact equality, even regardless of τ, only in the two-site case. In all other situations, the closeness of the bound to the true value depends on the features of the whole network (extension, topology, and kinetic parameters), hence the tightness cannot be assessed in the absence of any further information on the unobserved part of the system. A full characterization of the situations in which Eq. (2) becomes tight is hardly achievable. However, as shown in Appendix B, a qualitative picture emerges by considering the relevant sites directly reachable jumping from β. The term "relevant" comes from the comparison between the rate constants $k_{\beta\to j}$ (with $j \neq \beta$). The relevant sites are those for which the relative rates $k_{\beta\to j}/a_\beta$ have high values and are comparable to each other (if all exit processes have comparable rates, then all the reachable sites are relevant). The clearest situation in which the bound Eq. (2) likely becomes tight is when α is the only relevant site; that is, the $\beta \to \alpha$ transition (if allowed) is much faster than all other exit jumps from β taken as a whole (i.e., if $k_{\beta\to\alpha}/a_\beta$ is close to 1). If, instead, there are (also) other relevant sites different from α, it is required that the reaching of α from each of such sites via connecting pathways be on average much faster than the subsequent evolution up to the $\alpha \to \beta$ jump. Finally, it is important to stress that the bound *could* be loose against the expectation if the reaching of α from β is on average much faster than the subsequent evolution up to the $\alpha \to \beta$.

Figure 2 shows the effectiveness of Eq. (2) for randomly generated instances of small networks with 5 and 10 sites. In the simulations, all sites were taken to be directly connected with each other with forward and backward transitions. The jump rate constants were randomly generated by adopting $k_{i\to j} = 10^x$ with x drawn at random between -1 and $+2$ with uniform distribution. Given the set of rate constants, the statistical distributions of $\tau_{\alpha\beta}$ and $\tau_{\alpha\beta|\alpha}$ were computed by means of Eq. (A4) in Appendix A. The required probabilities at the numerator on the right-hand side of Eq. (2) were then obtained

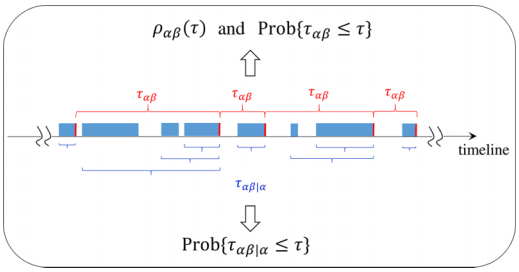

FIG. 3. Pictorial representation of the time record of the observed features of a network. The rectangles represent the permanence of the system in the site α and the vertical red lines are instants when the transition $\alpha \to \beta$ takes place.

by integration, and the point of minimum was numerically determined by means of a scan of τ in a wide range [28]. The exact value of $\overline{\tau}_\beta^{\rm res}$ was obtained from Eq. (1). The results are shown in panels (a) and (b) of Fig. 2. The dots represent 10^4 instances and the dashed line has slope 1. As can be seen, all points fall below the line, which corresponds to the fulfillment of Eq. (2). The insets show the points corresponding to the instances for which the only relevant exit process from β is the $\beta \to \alpha$ transition ($k_{\beta\to\alpha}/a_\beta \geqslant 0.8$ was adopted for such selection) and the bound is expected to be tight. Indeed, the points fall close to the diagonal. Let us recall that there are, however, other situations in which the bound can be tight. Panels (c) and (d) show that the quantity on the right-hand side of Eq. (2) falls below $\overline{\tau}_{\alpha\beta} - \overline{\tau}_{\alpha\beta|\alpha}$, hence Eq. (2) is a bound more stringent than the trivial one mentioned above. Further simulations were also performed for networks in which some of the site-to-site connections were missing [29] without finding any qualitative difference with respect to the outcomes in Fig. 2.

Let us now discuss the *practical* utility of Eq. (2). While in the above simulations all details of the network were known, in the practice one has little knowledge, or even no knowledge, about the number of sites directly connected with β, the site-to-site connectivities, and the value of the jump rate constants. As already stated, we suppose to only have access to the very limited portion depicted in Fig. 1: we can see when the system jumps into α (regardless of the origin site), when the system leaves α (regardless of the arrival site), and when the system leaves α jumping into β. Figure 3 depicts the time record of such a type of observation. The rectangles represent the permanence of the system in the site α. The system can leave α jumping into several arrival sites. The vertical red lines are collocated where we "hear a click" corresponding to a $\alpha \to \beta$ transition. Let us suppose to have a long time record of this type at disposal. From the separation between the vertical lines we get an ensemble of recurrence times $\tau_{\alpha\beta}$ and, therefore, the corresponding distribution function and the probability Prob$\{\tau_{\alpha\beta} \leqslant \tau\}$ for any chosen τ. Then, the separation between the starting time of a rectangle and the closest vertical line to the right corresponds to an occurrence time $\tau_{\alpha\beta|\alpha}$. From the ensemble of occurrence times we can get the probability Prob$\{\tau_{\alpha\beta|\alpha} \leqslant \tau\}$ for any τ. With such information, obtained from the analysis of the "experimental" time record, we can evaluate the right-hand side of Eq. (2).

For illustrative purposes, the type of analysis illustrated above was performed for one of the enzymatic networks used by Barato and Seifert in an early application of the thermodynamic uncertainty relation [30]. The network, which consists of six sites, is shown in panel (a) of Fig. 4. On chemical grounds, the system is a tagged enzyme molecule which can be found in six different states (the sites): free enzyme (E), enzyme bound to one molecule (ES) or two molecules (ESS) of substrate, bound to one molecule (EP) or two molecules (EPP) of product, and bound to substrate and product (ESP). Under chemostating conditions for both substrate and product, all transitions are first-order kinetic processes with time-independent jump rate constants. Such rates were generated at random in the same way as in the previous simulations. The state ES was chosen as site α, and ESS as site β. We imagine being able to observe the permanence of the enzyme in the state ES and the transition ES $\to$ ESS. The objective is getting an upper bound on the average residence time of the enzyme in the state ESS.

In order to mimic the experimental practice, a long stochastic path among the sites was generated by means of Gillespie's stochastic simulation algorithm [5]. The path was interrupted after 10^6 transitions ES(α) $\to$ ESS(β). With this record (of the type depicted in Fig. 3) at disposal, we could obtain all the statistical quantities that are required on the right-hand side of Eq. (2). The distribution function of the recurrence time of the transition ES $\to$ ESS is shown in panel (c) of Fig. 4. The circles (the "experimental outcome") correspond to the distribution obtained by means of a histogram construction from the simulated record, whereas the dashed line is the exact profile calculated by means of Eq. (A4) given in Appendix A. Panel (d) shows the two τ-dependent probabilities that enter Eq. (2). These probabilities were directly obtained from the simulated record by determining, for each given τ, the fractions of values $\tau_{\alpha\beta} \leqslant \tau$ and $\tau_{\alpha\beta|\alpha} \leqslant \tau$. With the information in panels (c) and (d), the quantity $\varphi_{\alpha\beta}(\tau) = [\text{Prob}\{\tau_{\alpha\beta|\alpha} \leqslant \tau\} - \text{Prob}\{\tau_{\alpha\beta} \leqslant \tau\}]/\rho_{\alpha\beta}(\tau)$ was computed. The profile is shown in panel (b). The circles correspond to the values from the simulated record whereas the dashed line is the exact profile. The horizontal thick red line is placed in correspondence of the exact value of $\overline{\tau}_\beta^{\rm res}$. As we see, the exact profile of $\varphi_{\alpha\beta}(\tau)$ versus τ starts flat, goes down to a minimum, and then increases and stabilizes on a plateau. The minimum is indeed higher (and in this case only slightly) than the true value of $\overline{\tau}_\beta^{\rm res}$. The profile of $\varphi_{\alpha\beta}(\tau)$ obtained from the simulated record closely follows the exact profile except for deviations due to numerical issues at low τ values where the statistics are poor, and at high τ values where both the probabilities at the numerator tend to one and the distribution at the denominator tends to zero.

Let us note that the upper bound is close to the true value $\overline{\tau}_\beta^{\rm res} = 0.037$, with a ratio of only 1.17. Further calculations were done with smaller values of both $k_{\text{ESS}(\beta)\to\text{ES}(\alpha)}$ and $k_{\text{ESP}\to\text{ES}(\alpha)}$. The reduction of both rates by a factor of 10 produced a ratio of 3.42 (with $\overline{\tau}_\beta^{\rm res} = 0.108$), and the reduction by a factor of 100 produced an even larger ratio of 19.05 (with $\overline{\tau}_\beta^{\rm res} = 0.134$). This behavior is in accord with the expectation that the bound becomes looser when the fastest exit process from the site β (ESS) becomes the jump into ESP [because we are reducing $k_{\text{ESS}(\beta)\to\text{ES}(\alpha)}$] and the way

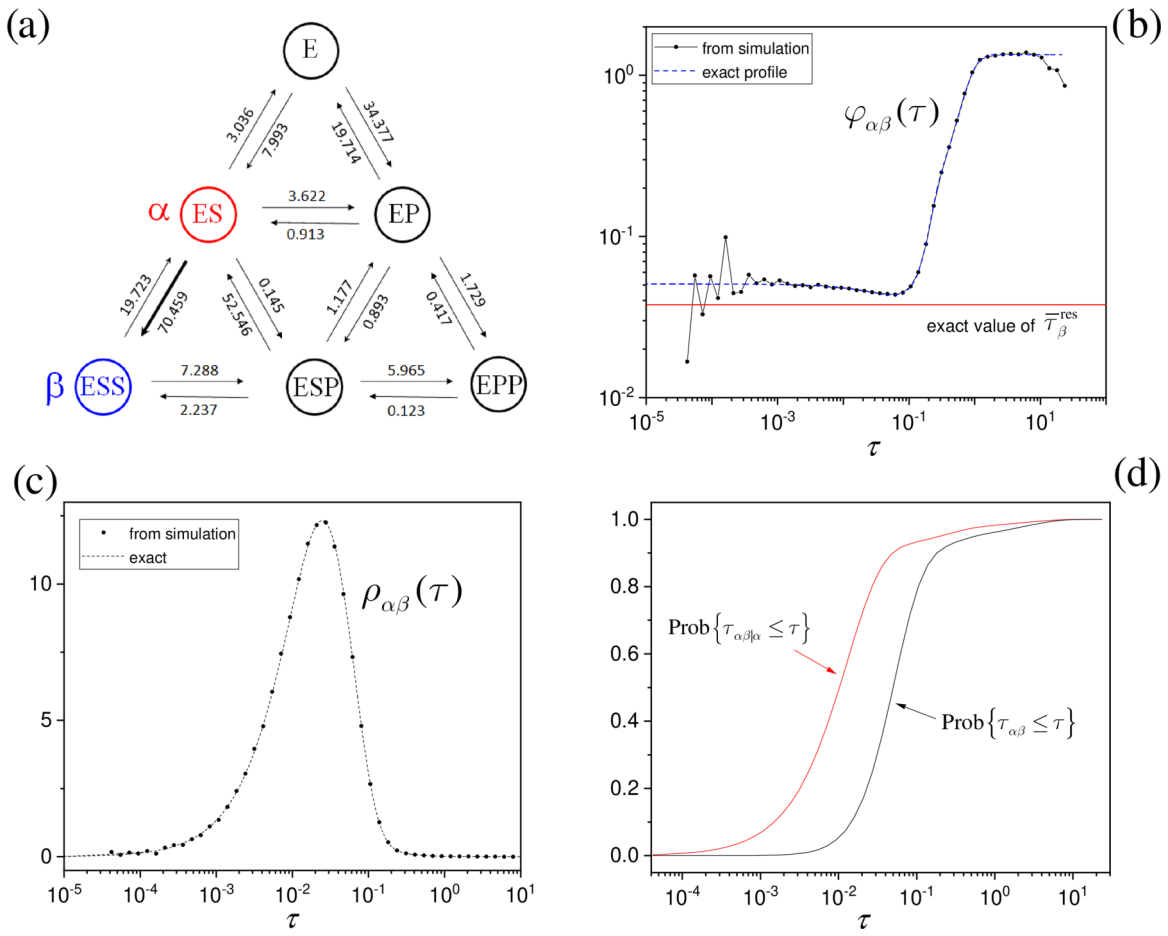

FIG. 4. Illustration of the practical utility of the bound Eq. (2). Panel (a) shows the six-site network under consideration. The arrows indicate the directed site-to-site connections, and the close numbers are the corresponding jump rate constants randomly generated. The time units here are immaterial. The sites α and β correspond, respectively, to the tagged enzyme molecule in the states ES and ESS. Panel (b) shows the exact value of $\overline{\tau}_\beta^{\rm res}$ (horizontal red line), the exact profile of $\varphi_{\alpha\beta}(\tau) = [\text{Prob}\{\tau_{\alpha\beta|\alpha} \leqslant \tau\} - \text{Prob}\{\tau_{\alpha\beta} \leqslant \tau\}]/\rho_{\alpha\beta}(\tau)$ versus τ (dashed blue line) and the profile of $\varphi_{\alpha\beta}(\tau)$ obtained from the simulation (full circles). Panel (c) shows the distribution of the recurrence time of the $\alpha \to \beta$ transition; the dashed line is the exact profile whereas the circles correspond to the histogram construction from the outcomes of the simulation. Panel (d) shows the τ dependence of the two probabilities that enter the expression of $\varphi_{\alpha\beta}(\tau)$; these profiles were obtained from the simulation.

back to the site α becomes slower [because $k_{\text{ESP}\to\text{ES}(\alpha)}$ is also reduced].

The take-home message is that if one is able to construct a profile like that in Fig. 4(b) from the direct observation of the network of interest, and if the problematic regions at low and high τ are detected and neglected, what remains is a regular central portion whose minimum can be safely taken as an upper bound on $\overline{\tau}_\beta^{\rm res}$. Unfortunately, the total lack of information about the unobserved part of the network implies that the tightness of the bound cannot be assessed. The deviation from the true value depends on the features of the whole system and, as we have seen in the above example, it can be very sensitive even to a few of them.

III. CONCLUSIONS AND PERSPECTIVES

In discrete Markov models with finite number of sites, the average residence time in a site (average lifetime of the site) quantifies the persistence of the system in that site at the steady state. Here we faced the practical problem of getting an upper bound on the average residence time $\overline{\tau}_\beta^{\rm res}$ of an unobserved site β from a very partial observation of the network: the observation of only one linked site α and the detection of the $\alpha \to \beta$ occurrence. The inequality Eq. (2) is the bound, which has been proved, numerically tested, and illustrated for a model of steady-state enzymatic catalysis.

It has been pointed out that the closeness of the bound to the true value depends on the features of the whole network, hence the tightness cannot be assessed if we have no information about the unobserved part. This is an inevitable limitation. Of course, the upper bound on $\overline{\tau}_\beta^{\rm res}$ can be improved if we imagine being able to monitor several transitions from different sites (say, α, α', $\cdots$) to β, perform independent experiments in which we collect time records like that in Fig. 3 for each of the monitored transitions, apply Eq. (2), and then take the lowest value [31]. In addition, the spread of the outcomes could indirectly provide us some qualitative information about the unobserved part of the network. This perspective requires further inspections.

The basis for obtaining the bound was Eq. (A8) derived in Appendix A. This is a system of differential equations governing the evolution of the whole set of statistical distributions

of the first-occurrence times of the $\alpha \to \beta$ transition starting from the various initial sites. Apart from simple mathematical elaborations, the crucial step to get the bound consisted in enforcing the *physical* fact that the system first needs to reach the site α for later jumping into β. Different elaborations of Eq. (A8), and the enforcement of other physical constraints, could lead to further nontrivial relations for steady-state Markov jump processes.

Finally, it is worth stressing that the statistics of occurrence/recurrence times presented in Appendix A can be generalized to events more complex than the single site-to-site transition. One should start again from the construction of the specific matrix $\mathbf{K}$ for the given event of interest, solve the corresponding master equation, and finally build the specific distribution function for the occurrence/recurrence time of that event. For instance, if we were able to observe several transitions $\alpha \to \beta$, $\alpha' \to \beta$, ... in the course of the *same* experiment, and if the detectable event is the jump into β regardless of the origin site $(\alpha, \alpha', \ldots)$, we might ask if a more stringent bound on $\overline{\tau}^{\rm res}_{\beta}$ can be obtained from such augmented information at disposal. This is a further aspect that deserves inspection.

APPENDIX A: STATISTICS OF OCCURRENCE/RECURRENCE TIMES

Let us consider a network with N sites. Let us introduce the N-dimensional column array $\mathbf{p}^{{\rm no}\,\mathcal{E}}(t)$ whose ith component is the probability that, starting from a given initial condition at the time-zero, at the time t the system is in the site i and the transition $\alpha \to \beta$ (the "event" $\mathcal{E}$ of interest) did not occur up to time t. The quantity $p^{{\rm no}\,\mathcal{E}}_{\alpha}(\tau) \times k_{\alpha\to\beta}\delta\tau$ corresponds to the probability that the first $\alpha \to \beta$ transition occurs between τ and $\tau + \delta\tau$. It has been shown that $\mathbf{p}^{{\rm no}\,\mathcal{E}}(t)$ evolves according to the following modified master equation [7,15]:

$$\frac{d\mathbf{p}^{{\rm no}\,\mathcal{E}}(t)}{dt} = -\mathbf{K}\,\mathbf{p}^{{\rm no}\,\mathcal{E}}(t), \tag{A1}$$

in which $\mathbf{K}$ is the $N \times N$ matrix with elements

$$K_{ij} = R_{ij} + k_{\alpha\to\beta}\,\delta_{i,\beta}\delta_{j,\alpha}, \tag{A2}$$

where δ is the Kronecker delta function, and where $\mathbf{R}$ is the transition matrix of the jump process [i.e., the matrix that governs the evolution of the occupation probabilities according to the master equation $d\mathbf{p}(t)/dt = -\mathbf{R}\mathbf{p}(t)$]:

$$R_{ij} = -k_{j\to i}\,(1-\delta_{i,j}) + \delta_{i,j}\sum_{n\neq j} k_{j\to n}. \tag{A3}$$

Let us now consider the distribution function of the occurrence time $\tau_{\alpha\beta|i}$ of the $\alpha \to \beta$ transition starting from the generic site i. Let us indicate such distribution with $\rho_{\alpha\beta|i}(\tau)$, where τ implicitly corresponds to the specific occurrence time of interest. [The recurrence case corresponds to $i = \beta$, hence $\rho_{\alpha\beta}(\tau) \equiv \rho_{\alpha\beta|\beta}(\tau)$]. If the system is initially in the site i, the quantity $p^{{\rm no}\,\mathcal{E}}_{\alpha}(\tau) \times k_{\alpha\to\beta}$ gives exactly $\rho_{\alpha\beta|i}(\tau)$. By using $p^{{\rm no}\,\mathcal{E}}_{j}(0) = \delta_{i,j}$ as the initial condition, the formal solution of Eq. (A1) is

$$\rho_{\alpha\beta|i}(\tau) = k_{\alpha\to\beta}[e^{-\tau\mathbf{K}}]_{\alpha i}. \tag{A4}$$

With this distribution at disposal, any average quantity can be computed. In particular, the moments of the distribution can be expressed as [7,15]

$$\overline{\tau^{n}_{\alpha\beta|i}} = n!\sum_{j}[\mathbf{K}^{-n}]_{ji}. \tag{A5}$$

For the purpose of this work, we go ahead a step further to work out a set of differential equations, of the type of Eq. (A1), in which the unknown quantities are directly the distribution functions $\rho_{\alpha\beta|i}(\tau)$. Let us take the derivative with respect to τ at both sides of Eq. (A4). This yields $\partial\rho_{\alpha\beta|i}(\tau)/\partial\tau = -k_{\alpha\to\beta}\sum_j[e^{-\tau\mathbf{K}}]_{\alpha j}\,K_{ji}$. By considering that $k_{\alpha\to\beta}[e^{-\tau\mathbf{K}}]_{\alpha j} = \rho_{\alpha\beta|j}(\tau)$, and recalling Eq. (A2), it follows that

$$\frac{\partial\rho_{\alpha\beta|i}(\tau)}{\partial\tau} = -\sum_{j} R_{ji}\,\rho_{\alpha\beta|j}(\tau) \; - k_{\alpha\to\beta}\,\delta_{i,\alpha}\,\rho_{\alpha\beta|\beta}(\tau). \tag{A6}$$

In compact form we have

$$\frac{d\boldsymbol{\rho}(\tau)}{d\tau} = -\mathbf{K}^{T}\,\boldsymbol{\rho}(\tau), \tag{A7}$$

where $\boldsymbol{\rho}(\tau)$ is the column array whose ith component is $\rho_{\alpha\beta|i}(\tau)$, and T stands for transposed array. Equation (A7) closely resembles Eq. (A1), but here the unknowns are the statistical distributions of the occurrence times and the variable is τ. Explicitly,

$$\frac{\partial\rho_{\alpha\beta|i}(\tau)}{\partial\tau} = \sum_{j\neq i} k_{i\to j}\,\rho_{\alpha\beta|j}(\tau) \; - \rho_{\alpha\beta|i}(\tau)\sum_{j\neq i} k_{i\to j} - k_{\alpha\to\beta}\,\delta_{i,\alpha}\,\rho_{\alpha\beta|\beta}(\tau). \tag{A8}$$

APPENDIX B: THE BOUND EQ. (2)

1. Proof

For the sake of notation, let us introduce

$$P_i(\tau) := {\rm Prob}\{\tau_{\alpha\beta|i} \geqslant \tau\}. \tag{B1}$$

With this position, by writing Eq. (A8) for τ' (in place of τ) and integrating at both members from 0 to τ, we get

$$\rho_{\alpha\beta|i}(\tau) = -\sum_{j\neq i} k_{i\to j}\,P_j(\tau) \; + a_i\,P_i(\tau) + k_{\alpha\to\beta}\,\delta_{i,\alpha}\,P_\beta(\tau), \tag{B2}$$

where we have introduced

$$a_i := \sum_{j\neq i} k_{i\to j}. \tag{B3}$$

To obtain Eq. (B2) it has been considered that $\rho_{\alpha\beta|i}(0) = k_{\alpha\to\beta}\,\delta_{i,\alpha}$ and that $\int_0^\tau d\tau'\,\rho_{\alpha\beta|i}(\tau') = {\rm Prob}\{\tau_{\alpha\beta|i} \leqslant \tau\} = 1 - P_i(\tau)$.

Now comes the crucial *physical* step, which consists in invoking the following inequality:

$${\rm Prob}\{\tau_{\alpha\beta|\alpha} \leqslant \tau\} \;\geqslant\; {\rm Prob}\{\tau_{\alpha\beta|i} \leqslant \tau\} \tag{B4}$$

for all i and all τ values. This inequality expresses the obvious fact that, for jumping from α to β, the system first has to reach the site α. This implies that, for any chosen time τ, the probability of observing the jump $\alpha \to \beta$ within the time

τ is for sure the largest when the system is initially already in the site α. The inequality (B4) is then converted into the corresponding relation:

$$P_\alpha(\tau) \leqslant P_i(\tau). \tag{B5}$$

By using $P_j(\tau) \geqslant P_\alpha(\tau)$ in the summation on the right-hand side of Eq. (B2), we obtain

$$\rho_{\alpha\beta|i}(\tau) \leqslant a_i\,[P_i(\tau) - P_\alpha(\tau)] + k_{\alpha\to\beta}\,\delta_{i,\alpha}\,P_\beta(\tau). \tag{B6}$$

Different choices of i lead to different inequalities. In particular, for i corresponding to the site β, Eq. (B6) yields $\rho_{\alpha\beta|\beta}(\tau) \leqslant a_\beta[P_\beta(\tau) - P_\alpha(\tau)]$. Recalling that $a_\beta = 1/\overline{\tau}_\beta^{\rm res}$ [from Eq. (B3) with Eq. (1)], we finally get

$$\overline{\tau}_\beta^{\rm res} \leqslant \frac{\text{Prob}\{\tau_{\alpha\beta|\alpha} \leqslant \tau\} - \text{Prob}\{\tau_{\alpha\beta} \leqslant \tau\}}{\rho_{\alpha\beta|\beta}(\tau)}. \tag{B7}$$

This inequality holds for all τ values. The most stringent bound is hence obtained by taking the minimum of the quantity on the right-hand side. This gives Eq. (2), in which $\rho_{\alpha\beta}(\tau)$ is written in place of $\rho_{\alpha\beta|\beta}(\tau)$.

2. On the tightness

Looking back at the derivation of Eq. (B7), and in particular writing Eq. (B2) directly for $i = \beta$, we readily see that, for any τ, the inequality in (B7) reduces to an exact equality only in the two-site case (α and β). For general networks, what we can say is that the final bound given in Eq. (2) tends to be tight when the quantity $\sum_{j\neq\beta} k_{\beta\to j}P_j(\tau^*)$ is close to $P_\alpha(\tau^*)\sum_{j\neq\beta} k_{\beta\to j}$, where τ^* is the time corresponding to the condition of minimum in Eq. (2). In fact, the inequality in Eq. (2) comes from the replacement of the former quantity with the latter.

For the sake of notation, let us denote with $\mathcal{C}_\beta$ the set of sites $j \neq \beta$ that are directly reachable by jumping from β. By introducing the relative rates $\gamma_j := k_{\beta\to j}/a_\beta$ for $j \in \mathcal{C}_\beta$, with $\sum_{j\in\mathcal{C}_\beta}\gamma_j = 1$, the requisite for the tightness becomes

$$\sum_{j\in\mathcal{C}_\beta} \gamma_j P_j(\tau^*) \simeq P_\alpha(\tau^*). \tag{B8}$$

Further elaborations of Eq. (B8) are hampered by the fact that the probabilities depend on the details of the whole network. Moreover, these probabilities have to be evaluated at the time τ^* which also depends on the network's features in a rather intricate manner. We can only identify some physical situations in which the bound is *expected* to be close to the true value of $\overline{\tau}_\beta^{\rm res}$.

Let us first note that the sites of $\mathcal{C}_\beta$ could be differentiated from each other on the basis of the associate γ_j value. We term "relevant" the sites for which the γ_j have high values and are comparable to each other. Let us denote with $\mathcal{R}_\beta \subseteq \mathcal{C}_\beta$ such a subset of sites. For the other sites linked to β we assume that $\sum_{j\notin\mathcal{R}_\beta}\gamma_j \ll 1$. Clearly, $\mathcal{R}_\beta$ coincides with the whole $\mathcal{C}_\beta$ if all $k_{\beta\to j}$ have comparable values. Let us now consider the situations in which the following conditions hold: (i) $P_{j\in\mathcal{R}_\beta}(\tau^*) \simeq P_\alpha(\tau^*)$ for all the relevant sites, (ii) $\Delta = \sum_{j\notin\mathcal{R}_\beta}\gamma_j P_j(\tau^*) \ll P_\alpha(\tau^*)$. The fulfillment of both conditions would imply the fulfillment of Eq. (B8). Condition (ii) is ignored when $\mathcal{R}_\beta$ coincides with $\mathcal{C}_\beta$ since $\Delta = 0$ in that case.

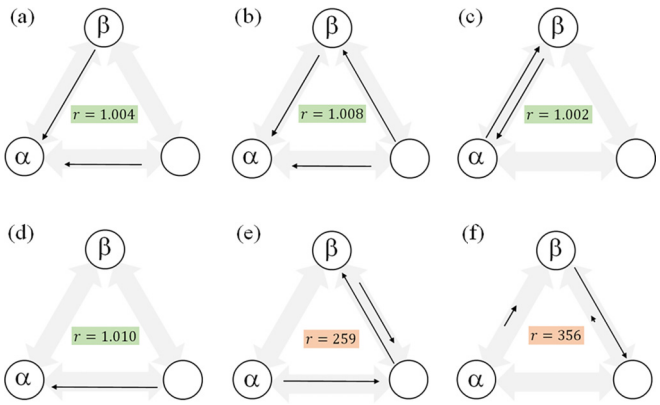

FIG. 5. Examples of three-site networks with randomly generated jump rate constants. The lengths of the arrows graphically correspond to the value of rate constants (the arrows are not displayed for rate constants too small). In the panels, r is the ratio between the upper bound from Eq. (2) and the true value of $\overline{\tau}_\beta^{\rm res}$. Panels (a)–(d) are situations in which the bound is tight, whereas panels (e) and (f) show instances with upper bound much higher than the true value.

Condition (i) is exactly fulfilled for the site α (if the jump $\beta \to \alpha$ is allowed and if α belongs to the relevant sites), whereas for all other sites of $\mathcal{R}_\beta$ it is required that the reaching of α from such sites via connecting pathways be on average a process much faster than the subsequent evolution up to the $\alpha \to \beta$ jump. Condition (ii) requires that the $P_{j\notin\mathcal{R}_\beta}(\tau^*)$ not be much larger than $P_\alpha(\tau^*)$, otherwise the condition could be violated even if $\gamma_j \ll 1$. This vaguely tells us that the reaching of α from the sites $j \notin \mathcal{R}_\beta$ should not be exceedingly slow compared to the subsequent evolution up to the $\alpha \to \beta$ jump. A precise quantitative statement, however, cannot be made. Finally, let us note that the bound *could* be loose against the expectation when $P_\beta(\tau^*)$ is close to $P_\alpha(\tau^*)$, which happens when the reaching of α starting from β is, on average, much faster than the subsequent evolution up to the $\alpha \to \beta$ jump. In such cases, $P_\beta(\tau^*) - P_\alpha(\tau^*)$ could be of the same order of magnitude of the difference between the two members in Eq. (B8), hence the approximations would become potentially critical. Note that the reaching of α from β could take place either via the direct $\beta \to \alpha$ (if allowed) or via connecting pathways.

The global qualitative picture is the following: the bound Eq. (2) *could* be tight when, among the relevant sites directly reachable from β, we find α and/or other sites from which the return to α is on average fast with respect to the subsequent evolution up to the $\alpha \to \beta$ transition [32]. If the reaching of α from β is on average much faster than the subsequent evolution up to the $\alpha \to \beta$, the bound could be loose against the expectation.

Figure 5 illustrates the above claims for a simple three-site network with all sites directly connected with each other with forward and backward transitions. The jump rate constants were generated at random in a range covering three orders of magnitude. The figure shows typical cases among those for which the ratio r between upper bound and $\overline{\tau}_\beta^{\rm res}$ was close to one [panels (a)–(d)] or very large [panels (e) and (f)]. The

lengths of the arrows correspond to the relative values of the jump rate constants (missing arrows correspond to rates very small). In (a), (b) and (c), the jump $\beta \to \alpha$ is the only relevant exit process from the site β. In panel (d), both the jumps from β to α and from β to the third site must be considered since they have comparable (and small) rates; then, from the third site there is a fast [32] and direct way back to α without passing through β. In all these situations, the bound is tight as expected. In panel (e), the only relevant exit process from β is the jump into the third site, but then from this site the main pathway back to α passes through β. Although the reaching of α from the third is found to be fast compared to the subsequent evolution up to the $\alpha \to \beta$ transition [32], the fact that β is visited on the pathway warns us that $P_\beta(\tau^*)$ could be sufficiently close to $P_\alpha(\tau^*)$ to make the bound loose, as indeed it is. In panel (f), the relevant exit process from β is again the jump into the third site, and from this site the return back to α is slow [32]. Also in this case, as expected, the bound is loose.

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[21] Indeed, we can write $\bar{\tau}_\beta^{\rm res} = p_\beta^{\rm ss}/r_\beta$, where $p_\beta^{\rm ss}$ is the steady-state occupation probability of the site β, and $r_\beta = \lim_{t_{\rm obs}\to\infty}[n_\beta(t_{\rm obs})/t_{\rm obs}]$ with $n_\beta(t_{\rm obs})$ the average number of times that the site is visited within a time-window of duration $t_{\rm obs}$. Explicitly, we also have $r_\beta = \sum_{j\neq\beta} p_j^{\rm ss} k_{j\to\beta}$. This readily follows from the stationarity condition applied to the site β [i.e., $\sum_j R_{\beta j} p_j^{\rm ss} = 0$ where $R_{\beta j}$ are elements of the transition matrix given in Eq. (A3)] together with Eq. (1).

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[23] Note that, in different contexts, "partial observation" could refer to the case in which, in the given observation timewindow, some site-to-site transitions are not seen because they are too rare. In such a case, the whole network is accessible but some features simply do not manifest themselves in the finite-time observation window. In a different situation, a global process could be "partially observable" because of the presence of inaccessible (hidden) variables that, however, affect the dynamics of the observed part. These situations differ from the one treated here.

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[27] To prove this, imagine starting from the site β and following a path up to the next $\alpha \to \beta$ transition. The total time is, by definition, the recurrence time $\tau_{\alpha\beta}$. At the beginning, the system spends a time $\tau_\beta^{\rm res}$ before leaving the site β (such site might be

visited other times later, but this is not important). At a certain time, the system reaches the site α and, from that instant, a time $\tau_{\alpha\beta|\alpha}$ is waited before making the $\alpha \to \beta$ transition (in between, the system might leave and re-enter the site α several times, but this is not important). Thus, with reference to this path, we can write $\tau_{\alpha\beta} \geqslant \tau_{\beta}^{\mathrm{res}} + \tau_{\alpha\beta|\alpha}$. By taking the average over the statistical ensemble of paths we get $\overline{\tau}_{\alpha\beta} \geqslant \overline{\tau}_{\beta}^{\mathrm{res}} + \overline{\tau}_{\alpha\beta|\alpha}$.

[28] By denoting with $\lambda_{\min}$ and $\lambda_{\max}$ the smallest and the largest eigenvalues of the matrix $\mathbf{K}$ defined in Eq. (A2), τ was varied between $(10\lambda_{\max})^{-1}$ and $10/\lambda_{\min}$ taking 10^3 points distributed on a logarithmic scale. The stability of the results with respect to the increase of the number of points was checked. The extension of the range was automatically prescribed in case the point of minimum was found coincident with one of the end points (this never occurred in the calculations done here).

[29] In those simulations, each single rate constant $k_{i\to j}$ (except $k_{\alpha\to\beta}$) was randomly set equal to zero with probability 0.2. Given the set of rate constants, it was then checked that the network was connected and irreducible, otherwise a new set of rate constants was generated.

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[31] For example, if in the scheme of Fig. 4 we choose ESP as site α (instead of ES) the bound results to be 0.137 (higher than 0.037).

[32] Provisionally (and subjectively) we may proceed as follows to establish if the reaching of α from a generic site j is on average much faster than the subsequent evolution up to the $\alpha \to \beta$ transition. We may check if $\overline{\tau}_{\alpha\beta|\alpha}$ is much longer than the average time $\overline{\tau}_{\to\alpha|j}$ required to reach α starting from j (of course, $\overline{\tau}_{\to\alpha|\alpha} = 0$). This is the criterion adopted in the inspection of the 3-site networks of Fig. 5. The average time $\overline{\tau}_{\to\alpha|j}$ is computed with an approach similar to the one illustrated in Appendix A, where a different matrix $\mathbf{K}$ accounts for all jumps into α from the adjacent sites, and the same processes are considered when building the distribution $\rho_{\to\alpha|j}(\tau)$ from which the average time is then obtained.