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ABSTRACT

Several types of dynamics at stationarity can be described in terms of a Markov jump process among a finite number N of representative sites. Before dealing with the dynamical aspects, one basic problem consists in expressing the *a priori* steady-state occupation probabilities of the sites. In particular, one wishes to go beyond the mere black-box computational tools and find expressions in which the jump rate constants appear explicitly, therefore allowing for a potential design/control of the network. For strongly connected networks admitting a unique stationary state with all sites populated, here we express the occupation probabilities in terms of a formula that involves powers of the transition rate matrix up to order $N-1$. We also provide an expression of the derivatives with respect to the jump rate constants, possibly useful in sensitivity analysis frameworks. Although we refer to dynamics in (bio)chemical networks at thermal equilibrium or under nonequilibrium steady-state conditions, the results are valid for any Markov jump process under the same assumptions.

I. INTRODUCTION

In recent years, there has been a renewal of interest for the theory of Markov jump processes, especially in connection with stochastic thermodynamics. Several dynamics, in fact, do conform to such a kind of process, at least as a good approximation. For instance, we might think of conformational transitions in flexible molecules (jumps among energy wells), or to the stochastic evolution of a small reactive system (jumps in the space of the copy numbers of the molecules), or to the dynamics of tagged molecules/moieties in a macroscopic reactive mixture (jumps among hosting molecules when elementary reactions take place),[1–4] and so on. These examples are depicted in Fig. 1. In the nonequilibrium steady-state scenario, the Markov jump process proved to be the best conceptual platform to discover the so-called thermodynamic uncertainty relations,[5,6] to describe hopping processes[7] and provide a minimalistic description of molecular motors,[8,9] and to investigate biochemical mechanisms such as complex catalytic schemes[10,11] and the kinetic proofreading.[12,13] Apart from chemistry, the Markov jump process can be a valuable model also in other contexts in which the system is truly discrete or a coarse-graining allows for a good level of description, and if the Markov assumption ("memoryless process") is applicable.

A key aspect to be considered, even before exploring the full dynamical features of such a kind of processes, is the characterization of the stationary occupation probabilities of the discrete states in which the system can be found. Henceforth, such states will be called "sites." The *a priori* steady-state occupation probabilities will be denoted by p_α^{ss}, where $\alpha = 1, \ldots, N$ with N being the finite number of sites. From now on, we assume that the network is "strongly connected"; hence, the stationary state is unique and $p_\alpha^{ss} > 0$ for all the sites.[14] The p_α^{ss} are determined by the topology (connectivities) of the network and by the set of site-to-site jump rate constants $k_{i\to j}$ between connected sites. In the case of multi-path transition between sites, such rate constants are meant to be the cumulative ones $k_{i\to j} = \sum_\mu k_{i \xrightarrow{\mu} j}$, where μ labels the single physical transition channels.

Let us briefly indicate some of the reasons why the steady-state probabilities are relevant. First, the p_α^{ss} enter the expression of some basic kinetic properties. In particular, the key quantity is $F_{\alpha\beta}^{(\mu)} = p_\alpha^{ss} k_{\alpha \xrightarrow{\mu} \beta}$, the average steady-state probability flux over the channel μ of the $\alpha \to \beta$ transition; it gives the average number of jumps from

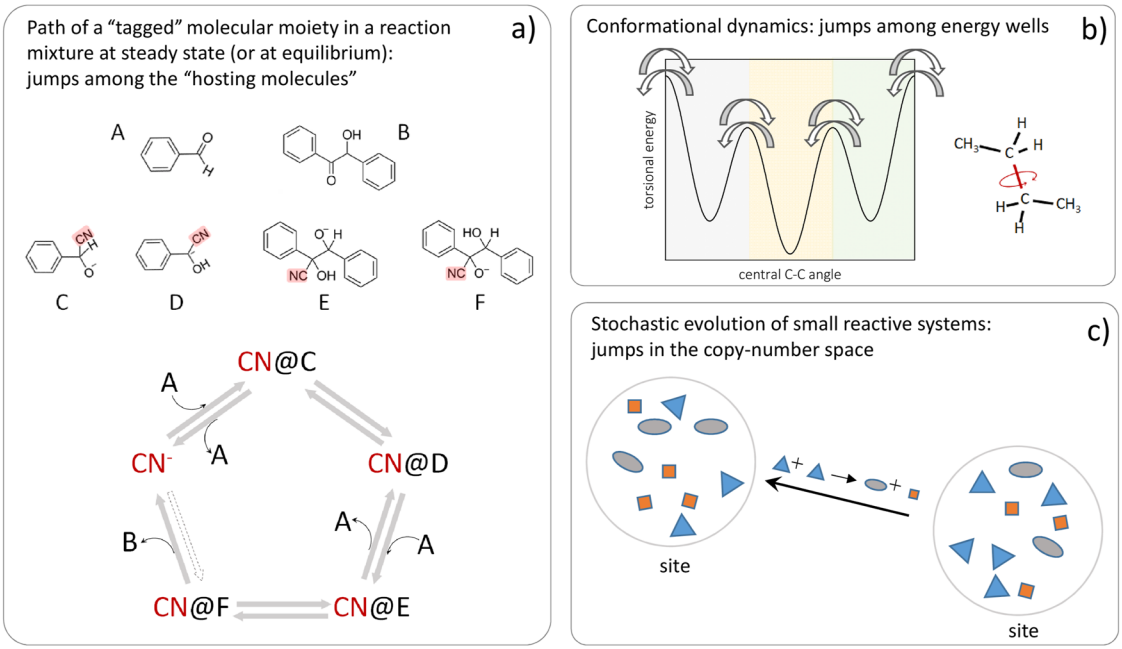

FIG. 1. Some examples of Markov jump processes in the (bio)chemical context. (a) Jump dynamics of a tagged molecular moiety in a macroscopic reaction mixture. This panel shows a simplified mechanism of benzoin condensation catalyzed by the cyanide anion. A tagged cyanide moiety undergoes jump dynamics among the states in which it can be found (free anion and hosted by the various intermediate molecules). (b) Conformational transitions in flexible molecules. This panel shows the case of torsional dynamics of *n*-butane in the liquid phase. The sites correspond to the conformations that pertain to the three energy wells. (c) Stochastic evolution of a small reactive system. A site corresponds to the array of the copy numbers of the species; a jump from site to site occurs when a reaction takes place.

site α to site β via the channel μ per unit of time, and its inverse corresponds to the average recurrence time of such jumps.[1] These fluxes are the building blocks to construct other dynamical quantities, such as the steady-state average probability currents over each oriented connection, the "mean dynamical activity" of the network,[15] and the average rate of entropy production (if all transition channels are reversible).[16] Even more importantly, the explicit link between p_α^{ss} on one side, and the network's topology and kinetic parameters on the other side, would enable a sensitivity analysis to understand how p_α^{ss} could be selectively controlled. This would allow us to establish useful cause–effect relations, especially when the jump dynamics takes place in a nonequilibrium steady state and an external tuning of some of the jump rate constants is feasible. For these reasons, the exact determination of the p_α^{ss}, or at least the discovery of general thermodynamic bounds on them,[17–22] is of crucial importance.

To determine p_α^{ss}, let us consider that the system's evolution is ruled by the master equation $d\mathbf{p}(t)/dt = -\mathbf{R}\mathbf{p}(t)$, where $\mathbf{p}(t)$ is the column array whose components are the occupation probabilities at the generic time t starting from a given initial condition $\mathbf{p}(0)$, and $\mathbf{R}$ is the $N \times N$ transition rate matrix whose elements are

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

with δ being Kronecker's delta. The property $\sum_i R_{ij} = 0$ for all j ensures the system's conservation (absence of irreversible sink processes). The stationary solution in the limit $t \to \infty$ is the array $\mathbf{p}^{ss}$ that satisfies

$$\mathbf{R}\mathbf{p}^{ss} = \mathbf{0}. \tag{2}$$

In spite of the simplicity of the formulation, the *analytical* solution of the problem in Eq. (2) employing linear algebra methods is feasible only for small dimensions N. As N increases, in fact, one has to resort to black-box numerical tools. Typically, $\mathbf{p}^{ss}$ is, indeed, obtained as the right-eigenvector of $\mathbf{R}$ (fixing the sum of its components to 1) associated with the unique null eigenvalue; many numerical routines are available to diagonalize real-non-symmetric matrices like $\mathbf{R}$. In this way, however, the *explicit* relationship between p_α^{ss} and the rate constants is rapidly lost and the level of understanding degrades. To circumvent this issue, alternative routes have been devised to translate the mathematical–numerical problem into more transparent and manageable formulations.

A powerful approach consists is making use of the so-called matrix-tree theorem (MTT). An early formulation of the MTT comes from Kirchhoff in the context of electrical circuits,[23] but the modern version framed in graph theory was proposed one century later by Tutte[24] to solve a combinatorial problem of partitions. The MTT was later reprised and applied to the statistical physics of reaction networks[25] and to the handling of the master equation dynamics.[16] In recent years, there has been a renewed interest for the MTT, especially after Gunawardena's work on the statistics of the first-order processes underlying the chemical reaction networks.[26]

For instance, the MTT has been employed to derive general thermodynamic bounds on the steady-state probabilities and on their ratios,[17,20] useful to inspect the response of networks of biochemical relevance to various types of perturbation. The basic MTT idea consists in viewing the network of sites as a graph and individuating all subgraphs, called "spanning trees," which contribute to the steady-state probabilities (see Ref. 26 for a comprehensive review). The crucial problem is that the number of spanning trees to be considered grows exponentially with N, and, therefore, in practice, the benefits offered by the MTT are rapidly lost. Thus, although the MTT is quite powerful to make general inferences and discover useful mutual bounds about static and dynamic properties of systems whose evolution is akin to Markov jump processes,[22,27–35] alternative approaches to evaluate $p^{\rm ss}_\alpha$ are welcome. For instance, Aslyamov and Esposito[22] have recently shown that $p^{\rm ss}_\alpha$ can be computed by means of an expression that contains the inverse of a modified rate matrix; an expression for sensitivity parameters is then derived.

Here, we present an explicit expression of the steady-state probabilities in terms of powers of the matrix $\mathbf{R}$ up to order $N-1$. In particular, the traces of the matrix powers enter as arguments of the multivariate "complete Bell polynomials,"[36] whose essential properties are summarized in Appendix A. The main result is Eq. (3), which is proved in Appendix B 2 as a special case of a more general theorem regarding the eigenvectors of singular matrices (the theorem is stated and proved in Appendix B 1). The strength of this explicit expression for $p^{\rm ss}_\alpha$ lies in the simplicity of the matrix-power operation and on the ease of generating the required terms thanks to the recursive properties of the Bell polynomials. This places our result between the explicit graph approach of the MTT and the brute-force calculus. In addition, Eq. (3) could be a useful starting point for further elaborations. In this regard, we provide the explicit expression of the partial derivative of $p^{\rm ss}_\alpha$ with respect to a generic rate constant of the network. For illustrative purposes, we will consider a simple 3-site network in enzyme catalysis with substrate inhibition, where the sites are the possible states in which a tagged molecule of enzyme can be found.

II. STEADY-STATE PROBABILITIES

A. Expression in terms of complete Bell polynomials

Let us go straight to the result of the elaboration,

$$p^{\rm ss}_\alpha = \delta_{\alpha,\beta} + \sum_{i=1}^{N-1} w_i\, (\mathbf{R}^i)_{\alpha\beta}, \quad \text{any } \beta, \tag{3}$$

where the factors w_i, for $0 \le i \le N-1$, are given by

$$w_i = \frac{(N-1)!}{(N-1-i)!}\,\frac{\mathcal{B}_{N-1-i}(a_1, a_2, \ldots, a_{N-1-i})}{\mathcal{B}_{N-1}(a_1, a_2, \ldots, a_{N-1})} \tag{4}$$

with $\mathcal{B}_n(\cdot)$ being the "complete Bell polynomial" of order n (see below) and

$$a_l = -(l-1)!\ \mathrm{Tr}\,(\mathbf{R}^l) \tag{5}$$

with "Tr" standing for the trace of the matrix.[37] The complete Bell polynomials[36,38] are multivariate polynomials,[39] whose definition and basic properties are given in Appendix A. In particular, they can be recursively generated [see Eq. (A2)] and the first ones are

$$\begin{aligned}
\mathcal{B}_0 &= 1,\\
\mathcal{B}_1(a_1) &= a_1,\\
\mathcal{B}_2(a_1, a_2) &= a_1^2 + a_2,\\
\mathcal{B}_3(a_1, a_2, a_3) &= a_1^3 + 3a_1a_2 + a_3,\\
\mathcal{B}_4(a_1, a_2, a_3, a_4) &= a_1^4 + 6a_1^2a_2 + 4a_1a_3 + 3a_2^2 + a_4,\\
\mathcal{B}_5(a_1, a_2, a_3, a_4.a_5) &= a_1^5 + 10a_1^3a_2 + 15a_1a_2^2 + 10a_1^2a_3\\
&\quad +10a_2a_3 + 5a_1a_4 + a_5.
\end{aligned} \tag{6}$$

Concerning the factors w_i, we have that $w_0 = 1$, while for $i \ge 1$, there is evidence of sign alternation $(-1)^i w_i > 0$. This claim derives from numerical inspections on randomly generated networks and has to be taken with caution until a formal proof is provided.[40]

Equation (3) is proved in Appendix B 2 as a special case of a more general theorem concerning the eigenvector corresponding to the null eigenvalue for generic real-valued singular matrices. The theorem is stated and proved in Appendix B 1. To the best of our knowledge, this is an original result. However, due to the relevance of the topic and to the huge mathematical literature on matrix theory, we cannot exclude that the result is already known in somehow equivalent forms. The correctness of Eq. (3) has been verified numerically for networks randomly generated, either with sites fully connected or with missing connections, and checking the fulfillment for any chosen site β (coincident with α, directly connected to α, or even not connected to α).[41]

At the computational level, depending on the magnitude and spread of the rate constants, Eq. (3) might become problematic as N is larger and larger. Accuracy issues could arise from the exponential growth/suppression of the single factors (this can be, however, mitigated by means of a suitable scaling of the rate constants) and from the ever larger number of algebraic operations that are required to compute the factors w_i and $(\mathbf{R}^i)_{\alpha\beta}$. However, if the purpose is the mere numerical evaluation of $p^{\rm ss}_\alpha$, other methods are more efficient and convenient. The value of Eq. (3) lies, instead, in the fact that it connects $p^{\rm ss}_\alpha$ to the kinetic parameters in an (almost) explicit way. Although such connection is not really fully explicit, the matrix-power operation is conceptually simple and the recursive relation Eq. (A2) is easily implementable to generate all required Bell polynomials up to order $N-1$. Thus, we may say that Eqs. (3)–(5) fit between the brute-force calculus and the MTT graphical representation.

B. Derivatives for sensitivity analysis

In the sensitivity analysis framework, one deals with partial derivatives of a given property with respect to a certain parameter. In our context, key derivatives are $\partial p^{\rm ss}_\alpha / \partial k_{q \xrightarrow{\mu} q'}$, where $k_{q \xrightarrow{\mu} q'}$ is the rate constant of a transition channel $q \to q' \ne q$ between connected sites. The sign and the absolute magnitude of these derivatives tell us how $p^{\rm ss}_\alpha$ responds to selective perturbations of the rate constants. This could be relevant for the optimal design and control of a network, supposing being able to intervene on some of the rate constants.

Let us first consider the derivative with respect to a cumulative rate constant $k_{q\to q'}$, which, we recall, is the sum of the rate constants

for the single transition channels (possibly only one). The following expression can be obtained from Eq. (3) by means of a few algebraic steps (the derivation is provided in the supplementary material):

$$\frac{\partial p_\alpha^{ss}}{\partial k_{q\to q'}} = \sum_{i=1}^{N-1}\sum_{m=1}^{N-1} w_i\, w_m\, G_{im}(\alpha,q,q') - \sum_{i=1}^{N-1}\sum_{m=1}^{N-1-i} w_{m+i}\, G_{im}(\alpha,q,q') + \sum_{i=1}^{N-1} w_i\, H_i(\alpha,q,q'), \tag{7}$$

where

$$G_{im}(\alpha,q,q') = (\mathbf{R}^i)_{\alpha\alpha}\left[(\mathbf{R}^{m-1})_{qq} - (\mathbf{R}^{m-1})_{qq'}\right] \tag{8}$$

with $G_{i1}(\alpha,q,q') = (\mathbf{R}^i)_{\alpha\alpha}(1-\delta_{q,q'})$, and

$$H_1(\alpha,q,q') = \delta_{\alpha,q},$$

$$H_{i\geq 2}(\alpha,q,q') = (\delta_{\alpha,q}-\delta_{\alpha,q'})(\mathbf{R}^{i-1})_{q\alpha} + \left[(\mathbf{R}^{i-1})_{\alpha q} - (\mathbf{R}^{i-1})_{\alpha q'}\right]\delta_{q,\alpha} + \sum_{m=1}^{i-2}\left[(\mathbf{R}^m)_{\alpha q} - (\mathbf{R}^m)_{\alpha q'}\right](\mathbf{R}^{i-m-1})_{q\alpha}. \tag{9}$$

The correctness of the above expression has been verified numerically for randomly generated networks of various dimensions, checking that the derivatives directly obtained from incremental ratios were coincident with the values calculated with Eq. (7).

Then, if the transition $q \to q'$ can take place via various channels and if we were interested in the derivative with respect to $k_{q\overset{\mu}{\to}q'}$, we simply have that $\partial p_\alpha^{ss}/\partial k_{q\overset{\mu}{\to}q'} \equiv \partial p_\alpha^{ss}/\partial k_{q\to q'}$ because $k_{q\overset{\mu}{\to}q'}$ is one of the additive contributions to $k_{q\to q'}$. Thus, the right-hand side of Eq. (7) also gives such specific sensitivity parameters.

Derivatives of higher order, such as the second order ones needed to build the Hessian, can be obtained making use of the recurring derivatives given in Appendix C.

C. Example

As an example, let us consider the simple catalytic scheme with substrate inhibition[3,42] shown in panel (a) of Fig. 2. Let us assume to be in steady-state conditions maintained by fixing the concentration of the substrate. Let us adopt the viewpoint of a tagged molecule of enzyme that can jump among three sites: free enzyme (site 1), enzyme bound to one molecule of the substrate (site 2), and enzyme bound to two molecules of the substrate (site 3); the 3-site network and the jump rate constants are shown in panel (b) of Fig. 2. Let us express p_α^{ss} taking site 1 as site β. The transition rate matrix reads

$$\mathbf{R} = \begin{bmatrix} k_{1\to2} & -k_{2\to1} & 0 \\ -k_{1\to2} & k_{2\to1}+k_{2\to3} & -k_{3\to2} \\ 0 & -k_{2\to3} & k_{3\to2} \end{bmatrix}. \tag{10}$$

By evaluating also $\mathbf{R}^2$ and then applying Eq. (5), we get

$$a_1 = -(k_{1\to2}+k_{2\to1}+k_{2\to3}+k_{3\to2}),$$

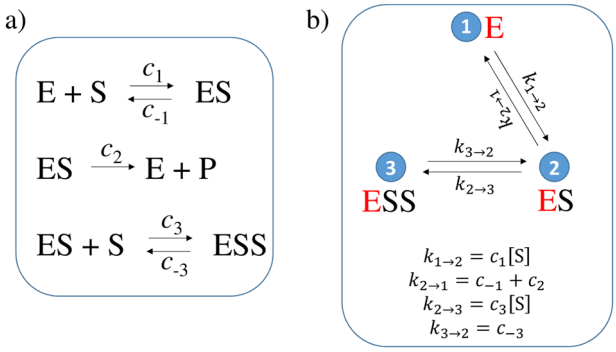

FIG. 2. Catalytic scheme with substrate inhibition. (a) The reaction scheme. (b) The 3-site network from the viewpoint of a tagged molecule of enzyme, and relations between the jump rate constants and the kinetic constants of the reactions given in panel (a); here, [S] stands for the fixed volumetric concentration of the substrate.

$$a_2 = -\left(k_{1\to2}^2+k_{2\to1}^2+k_{2\to3}^2+k_{3\to2}^2\right) - 2(k_{2\to1}k_{2\to3}+k_{3\to2}k_{2\to3}+k_{1\to2}k_{2\to1}). \tag{11}$$

From Eq. (4), we then obtain the factors w_1 and w_2 taking into account Eq. (6) for the explicit expression of the Bell polynomials up to the second order,

$$w_1 = \frac{2a_1}{a_1^2+a_2}, \quad w_2 = \frac{2}{a_1^2+a_2}. \tag{12}$$

By applying Eq. (3) with $(\mathbf{R}^2)_{11} = k_{1\to2}^2 + k_{1\to2}k_{2\to1}$, $(\mathbf{R}^2)_{21} = -k_{1\to2} - k_{1\to2}k_{2\to1} - k_{1\to2}k_{2\to3}$, and $(\mathbf{R}^2)_{31} = k_{1\to2}k_{2\to3}$, we finally get

$$p_1^{ss} = 1 + w_1 k_{1\to2} + w_2\left(k_{1\to2}^2 + k_{1\to2}k_{2\to1}\right), \quad p_2^{ss} = 1 - p_1^{ss} - p_3^{ss}, \quad p_3^{ss} = w_2\, k_{1\to2}k_{2\to3}. \tag{13}$$

It can be checked that the final results are the same if we take β to be site 2 or site 3.

We might be interested in assessing the sensitivity of p_1^{ss} (for the free enzyme) with respect to a selective small perturbation of the rate constant $k_{2\to3}$ (formation of the ESS species). Although in this simple case $\partial p_1^{ss}/\partial k_{2\to3}$ can be obtained directly by deriving p_1^{ss} given in Eq. (13), here we make use of the general formula Eq. (7). By employing Eq. (8), we readily get the factors that enter the first two summations in Eq. (7): $G_{11} = R_{11}$, $G_{12} = R_{11}(R_{22}-R_{23})$, $G_{21} = (\mathbf{R}^2)_{11}$, and $G_{22} = (\mathbf{R}^2)_{11}(R_{22}-R_{23})$ (only G_{11} enters the second summation). Explicitly,

$$G_{11} = k_{1\to2}, \quad G_{12} = k_{1\to2}(k_{2\to1}+k_{2\to3}+k_{3\to2}), \quad G_{21} = k_{1\to2}^2 + k_{1\to2}k_{2\to1}, \quad G_{22} = (k_{1\to2}^2 + k_{1\to2}k_{2\to1})(k_{2\to1}+k_{2\to3}+k_{3\to2}). \tag{14}$$

The factors H_1 and H_2 required in the third summation of Eq. (7) are both zero because $\alpha \neq q$, $\alpha \neq q'$, and $i-2$ is at most 0 [see Eq. (9)].

Then, taking into account that $w_1 = a_1 w_2$, and using the expression of a_1 given in Eq. (11), with a few algebraic steps, we arrive at

$$\frac{\partial p_1^{ss}}{\partial k_{2\to 3}} = -k_{1\to 2} w_2 + k_{1\to 2}^2 (k_{2\to 3} + k_{3\to 2}) w_2^2. \tag{15}$$

Similarly, we might be interested in expressing the derivative $\partial p_1^{ss}/\partial k_{1\to 2}$. In this case, $\alpha = q = 1$ and $q' = 2$. The factors entering the first two summations of Eq. (7) are now $G_{11} = R_{11}$, $G_{12} = R_{11}(R_{11} - R_{12})$, $G_{21} = (\mathbf{R}^2)_{11}$, and $G_{22} = (\mathbf{R}^2)_{11}(R_{11} - R_{12})$, and the factors required in the third summation are $H_1 = 1$ and $H_2 = 2R_{11} - R_{12}$. Recalling again that $w_1 = a_1 w_2$, with a few steps, we get

$$\frac{\partial p_1^{ss}}{\partial k_{1\to 2}} = w_2 \left(a_1 + k_{1\to 2} + k_{2\to 1}\right) + w_2^2 \, k_{1\to 2} \left(a_1 + k_{1\to 2} + k_{2\to 1}\right)^2. \tag{16}$$

Obviously, this simple 3-site case would be treatable much easily solving the system of two linear equations obtained from Eq. (2) with the enforcement of the normalization condition. Then, any derivative could be obtained by direct differentiation of p_α^{ss}. However, we should think that such an approach becomes rapidly unfeasible as N increases, while Eqs. (3) and (7) remain potentially useful and can be implemented in computer codes with symbolic calculus.

III. FINAL REMARKS AND CONCLUSIONS

For Markov jump processes on N sites, we have faced the problem of expressing the steady-state site occupation probabilities p_α^{ss} in terms of closed analytical forms easily implementable in computer codes. The main result is Eq. (3), which requires the powers of the transition rate matrix $\mathbf{R}$ up to order $N - 1$. In a sense, our result lies between the most explicit matrix-tree theorem graph approach and the brute-force numerical computation.

The algebraic handling of Eq. (3) is rather tedious, but the procedure is straightforward and could be automatized in the computational practice to get, in principle, the explicit expression of p_α^{ss} for a generic N. Furthermore, the inspection of the mathematical structure of Eqs. (3)–(5) might unveil interesting features to obtain approximations of p_α^{ss}, to work out bounds on it, or to perform useful operations with/on the steady-state probabilities. For instance, we have provided the expression of the first-order partial derivatives $\partial p_\alpha^{ss}/\partial k_{q\xrightarrow{\mu} q'}$, which quantify the sensitivity with respect to selective perturbations of the network. We might also use Eqs. (3)–(5) to get ensemble averages $\langle f \rangle = \sum_\alpha f_\alpha p_\alpha^{ss}$ for some property whose values f_α are site-dependent. If such property does not depend by itself on the jump rate constants, from Eq. (7) , we immediately get also the derivatives $\partial \langle f \rangle / \partial k_{q\xrightarrow{\mu} q'}$.

Let us also recall that p_α^{ss} are directly connected to some basic *dynamic* quantities built on the basis of the steady-state average probability fluxes $F_{\alpha\beta}^{(\mu)} = p_\alpha^{ss} k_{\alpha\xrightarrow{\mu}\beta}$. Equation (7) can then be used to express the derivatives

$$\frac{\partial F_{\alpha\beta}^{(\mu)}}{\partial k_{q\xrightarrow{\mu'} q'}} = F_{\alpha\beta}^{(\mu)} \frac{\partial \ln p_\alpha^{ss}}{\partial k_{q\xrightarrow{\mu'} q'}} + p_\alpha^{ss} \delta_{q,\alpha} \delta_{q',\beta} \delta_{\mu',\mu} \tag{17}$$

and hence to quantify the *dynamic* sensitivity of the network to selective perturbations. It is worth noting that interesting relations have been recently obtained for the fluxes and for their sensitivity parameters in the case of specific perturbations. For instance, in Ref. 3, some inequalities have been obtained for the sensitivity parameters when $q = \alpha$, $q' = \beta$, or $q = \alpha$, $q' \neq \beta$, or $q \neq \alpha$, $q' = \alpha$. In Ref. 43, a scaling law has been derived for $F_{\alpha\beta}^{(\mu)}$ in chemical networks when the perturbation regards only the energy of the sites. The explicit relations here obtained for $F_{\alpha\beta}^{(\mu)}$ and their derivatives could open the way to mathematically discover new useful and general relations to be then interpreted at the microscopic physical level.

Finally, let us bear in mind that although here we are mainly interested in (bio)chemical applications, the results are applicable to any Markov jump process with steady state on a strongly connected network of sites.

SUPPLEMENTARY MATERIAL

The supplementary material contains the derivation of Eqs. (7) and (C1)–(C4).

AUTHOR DECLARATIONS

Conflict of Interest

The author has no conflicts to disclose.

Author Contributions

Diego Frezzato: Conceptualization (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

APPENDIX A: COMPLETE BELL POLYNOMIALS

For a comprehensive presentation of the complete Bell polynomials, we address the reader to the original work of Bell[36] and to Ref. 38. Here, we report only the definition and a few useful relations.

The polynomials are generated by

$$\mathcal{B}_n(x_1, \ldots, x_n) = \frac{\partial^n}{\partial s^n} \left(e^{\sum_{j=1}^{n} x_j s^j / j!} \right) \Bigg|_{s=0} \tag{A1}$$

or, more conveniently, by the following recursive relation:

$$\mathcal{B}_{n+1}(x_1, \ldots, x_n, x_{n+1}) = \sum_{i=0}^{n} \binom{n}{i} \mathcal{B}_{n-i}(x_1, \ldots, x_{n-i}) \, x_{i+1}, \qquad \mathcal{B}_0 = 1. \tag{A2}$$

They fulfill the binomial-like relation

$$\mathcal{B}_n(x_1+y_1,\ldots,x_n+y_n)=\sum_{i=0}^{n}\binom{n}{i}\mathcal{B}_{n-i}(x_1,\ldots,x_{n-i})\;\mathcal{B}_i(y_1,\ldots,y_i) \tag{A3}$$

and the following partial-derivative formula:

$$\frac{\partial\mathcal{B}_n(x_1,\ldots,x_n)}{\partial x_i}=\binom{n}{i}\mathcal{B}_{n-i}(x_1,\ldots,x_{n-i}). \tag{A4}$$

APPENDIX B: MATHEMATICS

1. A general theorem for singular matrices

In this appendix, we prove a theorem valid for generic real-valued singular matrices with a unique null eigenvalue.[44] The theorem is then specified for the case of transition rate matrices **R**, which, indeed, have a unique null eigenvalue because of the assumption of strongly connected network.

Theorem. *Let* **M** *be a* $N\times N$ *real-valued singular matrix with a unique null eigenvalue, and let* **x** *be the corresponding eigenvector* ($\mathbf{Mx}=\mathbf{0}$). *In what follows, let* $\mathcal{B}_n(\cdot)$ *be the "complete Bell polynomial" of order n, and*

$$a_l=-(l-1)!\;\mathrm{Tr}\,(\mathbf{M}^l). \tag{a}$$

The following statements hold:

(i) *If the* n^**th component of* **x** *is non-null, we can set* $x_{n^*}=1$ *and express the other components as*

$$x_\alpha=u_0\,\delta_{\alpha,\beta}+\sum_{i=1}^{N-1}u_i\,(\mathbf{M}^i)_{\alpha\beta},\quad\text{any }\beta \tag{b}$$

with the factors u_i, *for* $0\le i\le N-1$, *given by*

$$u_i=\frac{z_i}{z_0\,\delta_{n^*,\beta}+\sum_{s=1}^{N-1}z_s\,(\mathbf{M}^s)_{n^*\beta}}, \tag{c}$$

where

$$z_i=\frac{1}{(N-1-i)!}\,\mathcal{B}_{N-1-i}(a_1,a_2,\ldots,a_{N-1-i}). \tag{d}$$

(ii) *If the sum of the components of* **x** *is non-null, then the* x_α, *with sum fixed to* $\sum_{\alpha=1}^{N}x_\alpha=1$, *can be expressed as*

$$x_\alpha=w_0\,\delta_{\alpha,\beta}+\sum_{i=1}^{N-1}w_i\,(\mathbf{M}^i)_{\alpha\beta},\quad\text{any }\beta \tag{e}$$

with the factors w_i, *for* $0\le i\le N-1$, *given by*

$$w_i=\frac{z_i}{z_0+\sum_n\sum_{s=1}^{N-1}z_s\,(\mathbf{M}^s)_{n\beta}} \tag{f}$$

and z_i *already defined in Eq. (d). If, in addition,* **M** *is such that* $\sum_i M_{ij}=0$ *for all j, then Eq. (f) simplifies to*

$$w_i=\frac{(N-1)!}{(N-1-i)!}\,\frac{\mathcal{B}_{N-1-i}(a_1,a_2,\ldots,a_{N-1-i})}{\mathcal{B}_{N-1}(a_1,a_2,\ldots,a_{N-1})} \tag{g}$$

with $w_0=1$.

Remark. The theorem also allows for the determination of the real-valued eigenvector $\mathbf{x}^{(\lambda)}$ for any other real-valued eigenvalue λ of **M**. In fact, it suffices to consider the singular matrix $\mathbf{M}'=\mathbf{M}-\lambda\mathbf{I}$ (with **I** being the identity matrix) in place of **M**.

Proof of the theorem. Let us prove statement (*i*) for the generic component x_α of **x**. We first prove the statement for $x_\alpha\neq 0$ and then generalize to the case of a component possibly equal to zero.

Let us choose a generic β and introduce the matrix

$$\mathbf{K}(\epsilon)=\mathbf{M}+\epsilon\mathbf{\Delta}, \tag{B1}$$

where $\epsilon\neq 0$ is a fixed real-valued parameter and $\mathbf{\Delta}$ is the matrix with a single non-null entry specified by the pair α and β,

$$\Delta_{ij}=\delta_{i,\beta}\,\delta_{j,\alpha}. \tag{B2}$$

Let us multiply both members of Eq. (B1) by the eigenvector **x** taking into account that $\mathbf{Mx}=\mathbf{0}$. We get $\mathbf{K}(\epsilon)\mathbf{x}=\epsilon\mathbf{\Delta x}$, where the column vector $\epsilon\mathbf{\Delta x}$ has all components equal to zero except the one at the position β, which is equal to $\epsilon\,x_\alpha$. This implies that if $x_\alpha\neq 0$, the matrix $\mathbf{K}(\epsilon)$ is invertible for any $\epsilon\neq 0$ (possibly vanishingly small). Thus, it is licit to write $\mathbf{x}=\epsilon\mathbf{K}(\epsilon)^{-1}\mathbf{\Delta x}$ from which

$$x_n=\epsilon\,(\mathbf{K}(\epsilon)^{-1})_{n\beta}\,x_\alpha. \tag{B3}$$

By assumption, $x_{n^*}\neq 0$ for a certain n^*. Fixing $x_{n^*}=1$, we thus have

$$x_\alpha=\left(\epsilon(\mathbf{K}(\epsilon)^{-1})_{n^*\beta}\right)^{-1},\quad x_{n^*}=1. \tag{B4}$$

In order to get rid of ϵ, in what follows we shall take $\epsilon\to 0$ and, in the end, we will see that Eq. (B4) remains meaningful also in such a limit.

Thanks to the Cayley–Hamilton theorem,[45] the inverse matrix of a non-singular $N\times N$ matrix **A** can be expressed in terms of powers of **A**. It has been shown[46] (see also related contents in Ref. 38 and in Appendix B of Ref. 47) that the Cayley–Hamilton expression can be given in terms of complete Bell polynomials,

$$\mathbf{A}^{-1}=\frac{1}{\det(\mathbf{A})}\sum_{s=1}^{N}\mathbf{A}^{s-1}\,\frac{(-1)^{N-1}}{(N-s)!}\,\mathcal{B}_{N-s}(t_1,\ldots,t_{N-s}) \tag{B5}$$

with the determinant expressed as

$$\det(\mathbf{A})=\frac{(-1)^N}{N!}\,\mathcal{B}_N(t_1,\ldots,t_N) \tag{B6}$$

and where $t_l=-(l-1)!\,\mathrm{Tr}(\mathbf{A}^l)$. In our specific case, from Eq. (B4), we have

$$x_\alpha=-\lim_{\epsilon\to 0}\frac{\mathcal{B}_N(t_1,\ldots,t_N)}{\epsilon\sum_{s=1}^{N}\phi_s\frac{N!}{(N-s)!}\,\mathcal{B}_{N-s}(t_1,\ldots,t_{N-s})}, \tag{B7}$$

where t_l and ϕ_s, both dependent on ϵ, are

$$t_l=-(l-1)!\;\mathrm{Tr}\,(\mathbf{K}^l),\quad l\ge 1, \tag{B8}$$

and

$$\phi_s=(\mathbf{K}^{s-1})_{n^*\beta},\quad s\ge 1. \tag{B9}$$

Let us now elaborate the expressions for t_l and ϕ_s to be inserted in Eq. (B7). By considering Eq. (B1), the powers of $\mathbf{K}$ are given by

$$\begin{aligned}
\mathbf{K} &= \mathbf{M} + \epsilon\mathbf{\Delta},\\
\mathbf{K}^2 &= \mathbf{M}^2 + \epsilon(\mathbf{M\Delta} + \mathbf{\Delta M}) + \epsilon^2\mathbf{\Delta}^2,\\
\mathbf{K}^3 &= \mathbf{M}^3 + \epsilon(\mathbf{M}^2\mathbf{\Delta} + \mathbf{M\Delta M} + \mathbf{\Delta M}^2)\\
&\quad + \epsilon^2(\mathbf{M\Delta}^2 + \mathbf{\Delta M\Delta} + \mathbf{\Delta}^2\mathbf{M}) + \epsilon^3\mathbf{\Delta}^3,\\
\mathbf{K}^4 &= \mathbf{M}^4 + \epsilon(\mathbf{M}^3\mathbf{\Delta} + \mathbf{M}^2\mathbf{\Delta M} + \mathbf{M\Delta M}^2 + \mathbf{\Delta M}^3)\\
&\quad + \epsilon^2\big(\mathbf{M}^2\mathbf{\Delta}^2 + \mathbf{M\Delta M\Delta} + \mathbf{M\Delta}^2\mathbf{M} + \mathbf{\Delta M}^2\mathbf{\Delta}\\
&\quad + \mathbf{\Delta M\Delta M} + \mathbf{\Delta}^2\mathbf{M}^2\big)\\
&\quad + \epsilon^3(\mathbf{M\Delta}^3 + \mathbf{\Delta M\Delta}^2 + \mathbf{\Delta}^2\mathbf{M\Delta} + \mathbf{\Delta}^3\mathbf{M}) + \epsilon^4\mathbf{\Delta}^4\\
&\quad \cdots
\end{aligned} \tag{B10}$$

and their traces result to be

$$\begin{aligned}
\mathrm{Tr}\,(\mathbf{K}) &= \mathrm{Tr}\,(\mathbf{M}) + \epsilon\delta_{\alpha,\beta},\\
\mathrm{Tr}\,(\mathbf{K}^2) &= \mathrm{Tr}\,(\mathbf{M}^2) + 2\epsilon M_{\alpha\beta} + \epsilon^2\delta_{\alpha,\beta},\\
\mathrm{Tr}\,(\mathbf{K}^3) &= \mathrm{Tr}\,(\mathbf{M}^3) + 3\epsilon(\mathbf{M}^2)_{\alpha\beta} + \big(3\epsilon^2 M_{\alpha\beta} + \epsilon^3\big)\delta_{\alpha,\beta},\\
\mathrm{Tr}\,(\mathbf{K}^4) &= \mathrm{Tr}\,(\mathbf{M}^4) + 4\epsilon(\mathbf{M}^3)_{\alpha\beta} + \epsilon^2\big[4(\mathbf{M}^2)_{\alpha\beta}\delta_{\alpha,\beta} + 2M^2_{\alpha\beta}\big]\\
&\quad + 4\epsilon^3 M_{\alpha\beta}\delta_{\alpha,\beta} + \epsilon^4\delta_{\alpha,\beta}\\
&\quad \cdots.
\end{aligned} \tag{B11}$$

The use of Eq. (B11) in Eq. (B8) yields t_l, which, taking the leading terms in the small-ϵ limit, is expressed as

$$t_l = a_l + b_l \tag{B12}$$

with

$$a_l = -(l-1)!\,\mathrm{Tr}\,(\mathbf{M}^l), \quad l \geq 1, \tag{B13}$$

and

$$\begin{aligned}
b_1 &= -\epsilon\,\delta_{\alpha,\beta},\\
b_{l\geq 2} &= -l!\,\epsilon\,(\mathbf{M}^{l-1})_{\alpha\beta} + 0(\epsilon^2).
\end{aligned} \tag{B14}$$

Let us now focus on ϕ_s. By considering Eq. (B10) and taking the specific matrix element indicated in Eq. (B9), we get that the leading terms for $\epsilon \to 0$ are

$$\begin{aligned}
\phi_1 &= \delta_{n^*,\beta},\\
\phi_s &= (\mathbf{M}^{s-1})_{n^*\beta} + 0(\epsilon), \quad s \geq 2.
\end{aligned} \tag{B15}$$

For instance, $\phi_2 = M_{n^*\beta} + \epsilon\delta_{n^*,\beta}\delta_{\alpha,\beta}$, $\phi_3 = (\mathbf{M}^2)_{n^*\beta} + \epsilon\big[\delta_{n^*,\beta}M_{\alpha\beta} + \delta_{\alpha,\beta}M_{n^*\beta}\big] + \epsilon^2\delta_{\alpha,\beta}\delta_{n^*,\beta}$, and so on.

Let us now go back to Eq. (B7). By exploiting the decomposition of t_l given in Eq. (B12), and making use of the binomial-like relation Eq. (A3), the quantity at the numerator of Eq. (B7) becomes

$$\mathcal{B}_N(t_1,\ldots,t_N) = \sum_{i=0}^{N}\binom{N}{i}\mathcal{B}_{N-i}(a_1,\ldots,a_{N-i})\;\mathcal{B}_i(b_1,\ldots,b_i). \tag{B16}$$

Explicitly,

$$\begin{aligned}
\mathcal{B}_N(t_1,\ldots,t_N) &= \mathcal{B}_N(a_1,\ldots,a_N)\;\mathcal{B}_0\\
&\quad + N\,\mathcal{B}_{N-1}(a_1,\ldots,a_{N-1})\;\mathcal{B}_1(b_1)\\
&\quad + \binom{N}{2}\mathcal{B}_{N-2}(a_1,\ldots,a_{N-2})\;\mathcal{B}_2(b_1,b_2)\\
&\quad + \binom{N}{3}\mathcal{B}_{N-3}(a_1,\ldots,a_{N-3})\;\mathcal{B}_3(b_1,b_2,b_3) + \cdots.
\end{aligned} \tag{B17}$$

The first term is zero because $\mathcal{B}_N(a_1,\ldots,a_N) = (-1)^N N!\,\det(\mathbf{M}) = 0$ since $\det(\mathbf{M}) = 0$ with $\mathbf{M}$ being singular. Then, let us consider the explicit expressions of the complete Bell polynomials: $\mathcal{B}_0 = 1$, $\mathcal{B}_1(b_1) = b_1$, $\mathcal{B}_2(b_1,b_2) = b_1^2 + b_2$, $\mathcal{B}_3(b_1,b_2,b_3) = b_1^3 + 3b_1b_2 + b_3$, and so on. By using b_l given in Eq. (B14), the following expression is finally obtained keeping only the linear terms in the small-ϵ limit:

$$\mathcal{B}_N(t_1,\ldots,t_N) = -\epsilon\sum_{i=1}^{N}\binom{N}{i}\mathcal{B}_{N-i}(a_1,\ldots,a_{N-i})\;i!\,(\mathbf{M}^{i-1})_{\alpha\beta} + 0(\epsilon^2). \tag{B18}$$

Let us now focus on the summation at the denominator of Eq. (B7) and write it directly in the small-ϵ limit,

$$\begin{aligned}
&\sum_{s=1}^{N}\phi_s\frac{N!}{(N-s)!}\mathcal{B}_{N-s}(t_1,\ldots,t_{N-s})\\
&\qquad = \sum_{s=1}^{N}\frac{N!}{(N-s)!}\mathcal{B}_{N-s}(a_1,\ldots,a_{N-s})(\mathbf{M}^{s-1})_{n^*\beta} + 0(\epsilon),
\end{aligned} \tag{B19}$$

where for ϕ_s we have used the approximations in Eq. (B15), and the t_l at the argument of the Bell polynomials have been directly replaced by a_l.

Let us plug Eqs. (B18) and (B19) into Eq. (B7) and take the limit $\epsilon \to 0$. The factor ϵ at the denominator cancels with ϵ in the expression at the numerator [see Eq. (B18)]. By expanding the binomials and simplifying the factorials, we obtain

$$x_\alpha = \frac{\sum_{i=1}^{N}\frac{1}{(N-i)!}\mathcal{B}_{N-i}(a_1,\ldots,a_{N-i})\,(\mathbf{M}^{i-1})_{\alpha\beta}}{\sum_{s=1}^{N}\frac{1}{(N-s)!}\mathcal{B}_{N-s}(a_1,\ldots,a_{N-s})\,(\mathbf{M}^{s-1})_{n^*\beta}}. \tag{B20}$$

Equation (b) with the factors given in Eq. (c) is finally obtained by rewriting Eq. (B20) as $x_\alpha = \sum_{i=1}^{N} u_{i-1}(\mathbf{M}^{i-1})_{\alpha\beta}$, where $u_{i-1} = z_{i-1}/\big\{\sum_{s=1}^{N} z_{s-1}(\mathbf{M}^{s-1})_{n^*\beta}\big\}$ in which $z_{i-1} = \mathcal{B}_{N-i}(a_1,\ldots,a_{N-i})/(N-i)!$, and then shifting back the summation indexes by one unit.

The above derivation has been carried out under the assumption $x_\alpha \neq 0$ because, only in this case, the matrix $\mathbf{K}(\epsilon)$ is invertible and the mathematical steps are licit. However, we may see that the final result also holds when $x_\alpha = 0$. Indeed, if $x_\alpha = 0$, the corresponding matrix $\mathbf{K}$ is singular, which means that $\mathcal{B}_N(t_1,\ldots,t_N) = 0$ in Eq. (B7), and, hence, the summation over i in Eq. (B18) is equal to zero. Ultimately, this leads to see that the numerator in Eq. (B20) is zero, so obtaining the correct result.

Statement (*ii*) of the theorem follows immediately restarting from Eq. (B3) and taking the summation over n at both members.

If the eigenvector's components have non-null sum, we can fix the summation to 1 and hence

$$x_\alpha = \left(\epsilon \sum_n \left(\mathbf{K}(\epsilon)^{-1}\right)_{n\beta}\right)^{-1}, \quad \sum_\alpha x_\alpha = 1. \tag{B21}$$

The derivation made for statement (*i*) remains the same, except for the fact that the factors ϕ_s are now defined as $\phi_s = \sum_n \left(\mathbf{K}(\epsilon)^{s-1}\right)_{n\beta}$. Equation (B15) is thus replaced by $\phi_1 = 1$ and $\phi_{s\geq 2} = \sum_n \left(\mathbf{M}^{s-1}\right)_{n\beta} + 0(\epsilon)$. Ultimately, what changes is that the element $\left(\mathbf{M}^{s-1}\right)_{n^*\beta}$ at the denominator of Eq. (B20) is replaced by the summation $\sum_n \left(\mathbf{M}^{s-1}\right)_{n\beta}$. This leads to the factors w_i (in place of u_i) given in Eq. (f). Finally, in the special case in which $\sum_n M_{n\beta} = 0$ (for any β), all $\phi_{s\geq 2}$ go to zero in the limit $\epsilon \to 0$ and the only ϕ_s to be taken into account at the denominator of Eq. (B7) is $\phi_1 = 1$; eventually, this leads to w_i given in Eq. (g). More directly, from Eq. (f) , we get $w_i = z_i/z_0$. As above, Eq. (e) remains valid when $x_\alpha = 0$.

The correctness of Eqs. (b)–(g) has been verified numerically for matrices $\mathbf{M}$ randomly generated under the fulfillment of the requisites of the statements.

2. The special case of Eq. (3)

In the special case in which $\mathbf{M}$ is a transition rate matrix $\mathbf{R}$, we can adopt Eq. (g) of the theorem. Indeed, $\mathbf{p}^{\rm ss}$ with $\sum_\alpha p_\alpha^{\rm ss} = 1$ is the eigenvector corresponding to the null eigenvalue, and $\sum_i R_{ij} = 0$ for all j. This leads directly to Eq. (3). It is worth noting that the theorem allows us to express also the eigenvectors $\mathbf{x}^{(\lambda)}$ of $\mathbf{R}$ corresponding to the real-valued eigenvalues $\lambda > 0$ (if there are any). It suffices to set $\mathbf{M} = \mathbf{R} - \lambda\mathbf{I}$ and apply Eq. (c) because $\sum_n x_n^{(\lambda)} = 0$ for $\lambda > 0$.

It is interesting to note that when $\mathbf{M}$ is a transition rate matrix $\mathbf{R}$, Eq. (B21) acquires a physical meaning in connection with the statistics of the recurrence times of the jump processes. This is discussed in what follows.

Let us first consider the transition from a site α of interest to a directly connected site β. Such a transition could take place via several channels, so let us consider the μth one. The average recurrence time of the $\alpha \xrightarrow{\mu} \beta$ transition can be expressed (see for instance Appendix A of Ref. 3) as $\langle \tau_{\alpha\beta}^{(\mu)} \rangle = \sum_n \left(\mathbf{K}^{-1}\right)_{n\beta}$, where the $N \times N$ matrix $\mathbf{K}$ has elements $K_{ij} = R_{ij} + k_{\alpha \xrightarrow{\mu} \beta}\delta_{i,\beta}\delta_{j,\alpha}$. In short, the derivation consists in solving a modified master equation, in which $\mathbf{R}$ is replaced by the matrix $\mathbf{K}$ specific of the $\alpha \xrightarrow{\mu} \beta$ transition, and assuming, as an initial condition, that such a transition has just occurred. The solution of the modified master equation yields the occupation probability of being in site α under the condition that the transition did not take place yet; the multiplication by $k_{\alpha \xrightarrow{\mu} \beta}$ then gives the distribution of the first occurrence (recurrence) time of the jump, and the above expression for the average $\langle \tau_{\alpha\beta}^{(\mu)} \rangle$ is finally obtained with a few algebraic steps. Note that $\mathbf{K}$, differently from $\mathbf{R}$, is invertible. It was also shown that $\langle \tau_{\alpha\beta}^{(\mu)} \rangle = \left(p_\alpha^{\rm ss} k_{\alpha \xrightarrow{\mu} \beta}\right)^{-1}$. This implies that $p_\alpha^{\rm ss}$ can be obtained from $\left(k_{\alpha \xrightarrow{\mu} \beta} \langle \tau_{\alpha\beta}^{(\mu)} \rangle\right)^{-1}$, independently of the choice of site β directly reachable from α, and also of the specific channel μ taken into account.

Going through the derivation in Ref. 3, one realizes that the expression of the average recurrence time remains valid also when considering a *virtual* jump process, with rate constant ϵ, from α to *any* other site β of the network. Site β could coincide with α itself. In this case, the process $\alpha \to \alpha$ would be a virtual neutral process that does not affect the time evolution of the site occupation probabilities. Then, β could be a site truly directly reachable jumping out from α with a rate constant $k_{\alpha \xrightarrow{\mu} \beta}$. In this case, we may think of splitting the true $\alpha \xrightarrow{\mu} \beta$ into two channels and assign the rate constant $\epsilon \leq k_{\alpha \xrightarrow{\mu} \beta}$ to one of them; such a split does not alter the time evolution of the occupation probabilities. Finally, site β can even be a site not directly reachable from α if the $\alpha \to \beta$ connection is missing. In this case, in the master equation dynamics, we would need to include the $\alpha \to \beta$ transition and assign to it the rate constant ϵ, which, ultimately, will be taken vanishingly small.

The elaboration made in Ref. 3 remains valid also for the average recurrence time of such virtual jump processes, leading to establishing that

$$p_\alpha^{\rm ss} = \lim_{\epsilon \to 0} \left(\epsilon \sum_n \left(\mathbf{K}(\epsilon)^{-1}\right)_{n\beta}\right)^{-1} \tag{B22}$$

with the ϵ-dependent matrix $\mathbf{K}(\epsilon)$ having elements

$$K_{ij}(\epsilon) = R_{ij} + \epsilon\, \delta_{i,\beta}\delta_{j,\alpha}. \tag{B23}$$

The limit $\epsilon \to 0$ in Eq. (B22) is taken to comprise all situations (including the non-physical case in which site β is not directly reachable from α). We can see that Eq. (B22) corresponds to Eq. (B21).

APPENDIX C: USEFUL DERIVATIVES

Let us consider a generic pair of connected sites q and $q' \neq q$, with $k_{q\to q'}$ being the (cumulative) rate constant of the transition from q to q'. The following expressions are derived in the supplementary material:

$$\frac{\partial R_{\alpha\beta}}{\partial k_{q\to q'}} = (\delta_{\alpha,q} - \delta_{\alpha,q'})\delta_{\beta,q}, \tag{C1}$$

$$\begin{aligned} n \geq 2: \quad \frac{\partial (\mathbf{R}^n)_{\alpha\beta}}{\partial k_{q\to q'}} &= (\delta_{\alpha,q} - \delta_{\alpha,q'})(\mathbf{R}^{n-1})_{q\beta} \\ &+ \left[(\mathbf{R}^{n-1})_{\alpha q} - (\mathbf{R}^{n-1})_{\alpha q'}\right]\delta_{q,\beta} \\ &+ \sum_{m=1}^{n-2} \left[(\mathbf{R}^m)_{\alpha q} - (\mathbf{R}^m)_{\alpha q'}\right](\mathbf{R}^{n-m-1})_{q\beta}, \end{aligned} \tag{C2}$$

$$n \geq 1: \quad \frac{\partial \,\mathrm{Tr}\,(\mathbf{R}^n)}{\partial k_{q\to q'}} = n\left[(\mathbf{R}^{n-1})_{qq} - (\mathbf{R}^{n-1})_{qq'}\right], \tag{C3}$$

$$\begin{aligned} \frac{\partial w_i}{\partial k_{q\to q'}} &= w_i \sum_{m=1}^{N-1} w_m \left[(\mathbf{R}^{m-1})_{qq} - (\mathbf{R}^{m-1})_{qq'}\right] \\ &- \sum_{m=1}^{N-1-i} w_{m+i}\left[(\mathbf{R}^{m-1})_{qq} - (\mathbf{R}^{m-1})_{qq'}\right]. \end{aligned} \tag{C4}$$

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[37] Interestingly, for $\beta = \alpha$, Eq. (3) resembles the solution of Derrida for the steady-state occupation probabilities in cyclical hopping processes [see Eq. (24) of Ref. 7 and the subsequent extension in Ref. 8]. However, it has been numerically checked that although the value of the steady-state probabilities is obviously the same, the single addends that enter the two expressions are different In other words, Eq. (3) and Derrida's special result are different and independent expansions. Moreover, Eq. (3) is valid for general irreducible networks.
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[40] The check of $(-1)^i w_i > 0$ for $i \geq 1$ has been done for randomly generated networks with N from 3 to 10. Given N, each instance of network was generated as follows. (i) The probability that a (cumulative) rate constant be zero is first fixed; such probability is randomly assigned between 0 and the value $(N-2)/(N-1)$ corresponding to the limit case of sites cyclically connected with one-way connections. (ii) The rate constants are generated by assigning the value 0 (with the prescribed probability) or a non-null value drawn between 10^{-2} and 1 with uniform distribution on the logarithmic scale. (iii) All rate constants are scaled to fix their highest value to 1 (this step is a mere scaling not strictly necessary). (iv) It is checked that the resulting network is strongly connected, otherwise a new generation is done. A total number of 10^6 generations was done for each N. For each N, a further set of 10^6 random generations was done for the specific case of sites connected forming a cycle. No violation of $(-1)^i w_i > 0$ was detected with this setup. Rare violations were instead detected for large N (9 and 10) when the rate constants were allowed to span a wider range of values (three orders of magnitude or larger). In such cases, however, the violations might be ascribed to numerical issues; further inspections are needed to clarify this point.
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