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DOI:

[10.1063/1.5143504](https://doi.org/10.1063/1.5143504)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Kells, A., Koskin, V., Rosta, E., & Annibale, A. (2020). Correlation Functions, Mean First Passage Times and the Kemeny Constant. *Journal of Chemical Physics*, 152(10), 1-13. [104108]. <https://doi.org/10.1063/1.5143504>

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Correlation Functions, Mean First Passage Times and the Kemeny Constant

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(Dated: 18 February 2020)

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Markov processes are widely used models for investigating kinetic networks. Here we collate and present a variety of results pertaining to kinetic network models, in a unified framework. The aim is to lay out explicit links between several important quantities commonly studied in the field, including mean first passage times (MFPTs), correlation functions and the Kemeny constant. We provide new insights on (i) a simple physical interpretation of the Kemeny constant, (ii) a relationship to infer equilibrium distributions and rate matrices from measurements of MFPTs, and (iii) a protocol to reduce the dimensionality of kinetic networks, based on specific requirements that the MFPTs in the coarse-grained system should satisfy. We prove that this protocol coincides with the one proposed by Hummer and Szabo in¹ and it leads to a variational principle for the Kemeny constant. Finally, we introduce a modification of this protocol which preserves the Kemeny constant. Our work underpinning the theoretical aspects of kinetic networks will be useful in applications including milestone and path sampling algorithms in molecular simulations.

I. INTRODUCTION

Recently, kinetic networks have been important driving forces in molecular simulations of diverse applications^{2–13}. One of the simplest mathematical and physical descriptions of kinetic networks is provided by Markov State Models (MSM)^{14–21}. The broad applicability of MSM has seen them used in a wide variety of fields and has resulted in many aspects of the theory of Markov processes being derived on multiple occasions in diverse ways^{22–24}. In this study we aim to present a unified framework that links several results in the literature and provide some novel insights.

A quantity which has attracted a large interest, over the years, since its introduction in 1960 by Kemeny and Snell²⁵, is the so-called Kemeny constant, which represents the sum of relaxation timescales in a kinetic network or Markov chain. Remarkably, the Kemeny constant is also equivalent with the weighted sum of all mean first passage times (MFPTs) from a selected state i to all other states j , where the weights are the equilibrium populations of states j . Surprisingly, the Kemeny constant is independent on the starting state i . This intriguing constancy has been the subject of several studies^{26,27}. The Kemeny constant has also attracted considerable interest in the field of graph theory and networks science. In particular, it has been used to calculate the Kirchoff index of a graph²⁸ and it has been proposed as an objective function to optimize in graph clustering algorithms²⁹. In the context of graphs, a low Kemeny constant means, loosely speaking, that the time to travel between the nodes is on average small, so this is interpreted to mean that the graph is well-connected³⁰.

In this work, we derive relations for the Kemeny constant in terms of correlation functions, which lead to a simple interpretation of its physical meaning, in terms of decorrelation times. Furthermore, we derive relations for MFPTs in terms of rate matrices and correlation functions, and we derive a relation for the equilibrium dis-

tribution in terms of MFPTs and the Kemeny constant. Combined together, these relations allow to construct the rate matrix and the equilibrium distribution of a Markov processes, directly from the measurements of MFPTs.

Often, dynamical processes of interest occur on timescales that are very long compared to the shortest timescales in the system. This wide disparity of timescales can pose serious computational challenges. Over the last couple of decades, several computational methods have been introduced to sample rare events, in both equilibrium and nonequilibrium systems, most notably transition path sampling^{31–35}, milestone^{36–39} and adaptive sampling^{40–43}. Broadly, these techniques involve the estimation of the equilibrium populations and the full rate matrix of the process, from relatively short simulations along selected paths or in between selected states (milestones). Our formula to construct rate matrices and equilibrium distribution from MFPTs between pairs of states may be useful in enhancing these methods.

Finally, MSM of many biological and physical systems have typically a large dimensionality, which makes them prohibitively expensive to work with. Coarse graining methods have been introduced to reduce the dimensionality of these systems, capturing in particular their slowest kinetic processes^{1,6,20,21,44,45}. In this work we address the definition of computationally efficient coarse-graining protocols, based on enforcing specific relations between MFPTs in the original and in the coarse-grained system.

The manuscript is organised as follows. In Sec. (II) we review spectral properties of transition and rate matrices in Markovian dynamics and provide explicit expressions for MFPTs in terms of their eigenvalues and eigenvectors. In Sec. (III) we derive formulae for the MFPTs in terms of rate matrices and correlation functions and give a physical interpretation for the Kemeny constant, as well as a relationship to construct rate matrices from measurements of MFPTs. Taking advantage of these relations, we propose a protocol to reduce the dimensionality of kinetic networks, based on the requirement

that a certain relation between the MFPTs of the original and the coarse-grained system is satisfied. We show that this protocol coincides with the coarse-graining proposed recently by Hummer and Szabo in¹, and it leads to a variational principle for the Kemeny constant, which can be useful to optimise the dynamical coarse-graining of kinetic networks. Finally, we show that by suitably modifying this protocol, one can define a coarse-graining which ensures that the Kemeny constant is preserved.

II. THEORY

A. Markov Chains

A kinetic network consists of n discrete states labelled $i = \{1, \dots, n\}$. Each discrete state has a time dependent probability to be occupied $p_i(t)$. The evolution of these probabilities, in continuous time, is governed by the rate at which the system moves between different states. The rate k_{ji} of transition from state i to state j is given by

$$k_{ji} = \lim_{\tau \rightarrow 0} \frac{P(j, t + \tau | i, t)}{\tau}, \quad (1)$$

where $P(j, t + \tau | i, t)$ is the probability to make the transition in a small interval of time τ . The time-evolution of the probability of state occupation is given by the master equation

$$\frac{dp_i(t)}{dt} = \sum_{j \neq i} \left[k_{ij} p_j(t) - k_{ji} p_i(t) \right], \quad (2)$$

which can be written in matrix notation

$$\frac{d\mathbf{p}}{dt} = \mathbf{K}\mathbf{p} \quad (3)$$

using the fact that the diagonal elements of the rate matrix \mathbf{K} are necessarily given by $k_{ii} = -\sum_j k_{ji}$ for conservation of probability. If \mathbf{K} has a complete set of eigenvectors, equation (3) is solved by

$$\mathbf{p}(t) = e^{\mathbf{K}t} \mathbf{p}(0), \quad (4)$$

where the so-called propagator $e^{\mathbf{K}t}$ is a matrix which evolves the probability distribution at one time to a new distribution at a time t later.

In discrete time $t = \ell\tau$, where moves between states happen at multiples $\ell = 1, 2, \dots$ of a given time interval τ , one defines the transition matrix $\mathbf{Q}(\tau) = e^{\mathbf{K}\tau}$, whose elements give the transition probability over a single time step, for any pair of states. The probability vector at the ℓ -th time step can then be found as

$$\mathbf{p}(\ell) = [\mathbf{Q}(\tau)]^\ell \mathbf{p}(0). \quad (5)$$

We will draw particular attention to the distinction between continuous and discrete time dynamics, when deriving MFPTs expressions.

B. Eigenvalues and Eigenvectors

The rate matrix can be spectrally decomposed and represented in terms of its eigenvalues $\{\lambda_\ell\}_{\ell=1}^n$ and left and right eigenvectors, $\{\phi^{(\ell)}\}_{\ell=1}^n$ and $\{\psi^{(\ell)}\}_{\ell=1}^n$, respectively

$$\mathbf{K} = \sum_{\ell=1}^n \lambda_\ell \psi^{(\ell)} \phi^{(\ell)}. \quad (6)$$

We will focus on systems satisfying detailed balance, where eigenvalues are real. The largest eigenvalue of \mathbf{K} is 0 and so all other eigenvalues are negative. They are usually indexed in descending order

$$0 = \lambda_1 \geq \lambda_2 \geq \dots \geq \lambda_N. \quad (7)$$

The corresponding eigenvectors are indexed in the same manner. The right eigenvector corresponding to the zero eigenvalue $\psi^{(1)}$ is known as the stationary probability (or, for reversible dynamics, equilibrium probability) \mathbf{p}^{eq} with elements p_i^{eq} . The corresponding left eigenvector $\phi^{(1)}$ is the n -dimensional row vector with all the components equal to 1, $\mathbf{1}_n^T$.

It can be shown that the elements of the left and right eigenvectors are related by the equilibrium probability

$$\psi_i^{(\ell)} = \phi_i^{(\ell)} p_i^{\text{eq}} \quad (8)$$

and $\sum_i \psi_i^{(\ell)} = 0$ for $\ell > 1$. Hence, left and right eigenvectors associated to non-zero eigenvalues will have positive and negative entries. These contain useful kinetic information, as they are related to relaxation processes.

This link can be seen by using the spectral decomposition (6) in equation (4) and singling out the contribution from $\ell = 1$

$$p_i(t) - p_i^{\text{eq}} = \sum_{\ell \geq 2}^n e^{-|\lambda_\ell|t} \psi_i^{(\ell)} \phi^{(\ell)} \cdot \mathbf{p}(0), \quad (9)$$

where we have used $\psi_i^{(1)} = p_i^{\text{eq}}$, $\phi_j^{(1)} = 1 \forall j$, $\sum_j p_j(0) = 1$ and $\lambda_\ell < 0 \forall \ell \geq 2$. For large time, the right hand side (RHS) of (9) is dominated by the first term in the sum, so the probability distribution will tend towards the equilibrium distribution with a timescale given by $\tau_2 = 1/|\lambda_2|$ (often called the relaxation time). The other timescales, are each given by the inverse of the magnitude of the corresponding eigenvalue

$$\tau_\ell = 1/|\lambda_\ell| \quad (10)$$

and can be interpreted as the time with which the rate matrix moves probability density between the oppositely signed regions of the corresponding eigenvector. This can be seen by considering the evolution of the scalar product between the time-dependent probability and the different eigenvectors

$$\phi^{(s)} \cdot \mathbf{p}(t) = e^{-|\lambda_s|t} \phi^{(s)} \cdot \mathbf{p}(0). \quad (11)$$

Each scalar product vanishes on a timescale set by the inverse eigenvalue, indicating that the probability mass becomes distributed evenly across positive and negative entries of the eigenvector $\phi^{(s)}$, on the timescale $1/|\lambda_s|$.

C. Correlation Functions

The correlation function between two observables θ_i and θ_j at a lagtime τ is given by

$$C_{ji}(\tau, t) = \langle \theta_j(t + \tau) \theta_i(t) \rangle - \langle \theta_j(t + \tau) \rangle \langle \theta_i(t) \rangle \quad (12)$$

Defining $\theta_i(t)$ as the indicator function which takes value 1 when the system is in state i at time t and 0 otherwise, the first term of (12) gives the joint probability that the system is in state i at time t and in state j at a time τ later

$$\begin{aligned} C_{ji}(\tau, t) &= P(j, t + \tau; i, t) - p_j(t + \tau)p_i(t) \\ &= [P(j, t + \tau|i, t) - p_j(t + \tau)]p_i(t) \end{aligned} \quad (13)$$

where the conditional probability $P(j, t + \tau|i, t)$ is given by the ji 'th entry of the propagator matrix, and depends only on the lagtime τ , i.e. $P(j, t + \tau|i, t) = [e^{\mathbf{K}\tau}]_{ji} = P(j, \tau|i, 0)$. If the system is in equilibrium, where one-time quantities are time-independent, the correlation function becomes a function of only the lagtime

$$C_{ji}^{\text{eq}}(\tau) = [e^{\mathbf{K}\tau}]_{ji} p_i^{\text{eq}} - p_j^{\text{eq}} p_i^{\text{eq}}. \quad (14)$$

In many practical situations, one averages (13) over the earlier time t , with the expectation that if the system is ergodic (i.e. a sufficiently long trajectory will sample all states with equilibrium probability) the resulting time average equates the equilibrium correlator

$$\overline{C_{ji}(\tau, t)} = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T dt C_{ji}(\tau, t) \equiv C_{ji}^{\text{eq}}(\tau). \quad (15)$$

Repeating the same steps that led to equation (9), the equilibrium correlator (14) can be written as a superposition of exponential functions

$$C_{ji}^{\text{eq}}(\tau) = \sum_{\ell \geq 2} e^{-|\lambda_\ell| \tau} \psi_j^{(\ell)} \phi_i^{(\ell)} p_i^{\text{eq}} \quad (16)$$

decaying to zero at large lagtime. The area underneath the correlator, then serves as a measure of how quickly an initial probability distribution will tend to the equilibrium probability, and it can be expressed as a weighted sum of the timescales in the system

$$\int_0^\infty C_{ji}^{\text{eq}}(\tau) d\tau = \sum_{\ell \geq 2} \frac{1}{|\lambda_\ell|} \psi_j^{(\ell)} \phi_i^{(\ell)} p_i^{\text{eq}} = \sum_{\ell \geq 2} \tau_\ell \psi_j^{(\ell)} \psi_i^{(\ell)} \quad (17)$$

where we have also used (8). One final observation that will be useful in this study is that the above quantities can be rewritten as

$$\int_0^\infty C_{ji}^{\text{eq}}(\tau) d\tau = (\mathbf{p}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})_{ji}^{-1} p_i^{\text{eq}} - p_j^{\text{eq}} p_i^{\text{eq}}, \quad (18)$$

where we have used $\mathbf{p}^{\text{eq}} = \boldsymbol{\psi}^{(1)}$, $\mathbf{1}_n^T = \boldsymbol{\phi}^{(1)}$ and $(\boldsymbol{\psi}^{(1)} \boldsymbol{\phi}^{(1)} - \mathbf{K})^{-1} = \boldsymbol{\psi}^{(1)} \boldsymbol{\phi}^{(1)} - \sum_{\ell \geq 2} \lambda_\ell^{-1} \boldsymbol{\psi}^{(\ell)} \boldsymbol{\phi}^{(\ell)}$.

D. Mean First Passage Time

Next, we derive an expression for MFPTs, i.e. the expected time it takes to the system to first reach a state j given its current state is i , t_{ji} , within the fundamental theory of Markov processes. We will consider the discrete and continuous time cases separately to highlight the subtle theoretical difference between the two cases.

1. Discrete Time

First we consider the case where the system can make transitions at discrete intervals, without loss of generality we define our units of time such that this time interval is 1. This system is defined by a transition matrix \mathbf{Q} , such that $\sum_j Q_{ji} = 1 \forall i$, which has eigenvalues $1 = \lambda'_1 \geq \lambda'_2 \geq \dots \geq \lambda'_N$ and eigenvectors as for the rate matrix \mathbf{K} .

We will use a prime index to denote quantities in discrete time dynamics that differ from their analogues in continuous time dynamics, for which we will use the same symbols without the prime. Accordingly, we will denote with t'_{ji} the mean number of *time steps* that it takes to the system to first reach j from i , in discrete time dynamics, whereas the corresponding quantity in continuous time dynamics will be denoted with t_{ji} , and will measure the mean *time* for the first visit to j , from i , to occur.

When the system starts in state i , it can either move to j directly (i.e. in one time step), with probability Q_{ji} , or transition to some other state k with probability Q_{ki} (in one time step) and then move to j in a time of t'_{jk} , ($t'_{jk} + 1$ in total), leading to the recursion

$$t'_{ji} = Q_{ji} + \sum_{k \neq j} (t'_{jk} + 1) Q_{ki} = 1 + \sum_{k \neq j} t'_{jk} Q_{ki}. \quad (19)$$

We can rewrite (19) as

$$\sum_k t'_{jk} (\delta_{ki} - Q_{ki}) = 1 - Q_{ji} t'_{jj} \quad (20)$$

where δ_{ki} is the Kronecker delta, that leads to the more convenient matrix form

$$\mathbf{t}'_j{}^T (\mathbf{I} - \mathbf{Q}) = (1 - Q_{j1} t'_{jj}, \dots, 1 - Q_{jN} t'_{jj}) \quad (21)$$

where we have defined $\mathbf{t}'_j{}^T = (t'_{j1}, \dots, t'_{jN})$ as the row vector with the MFPTs to j as components.

If \mathbf{Q} has a complete set of orthonormal eigenvectors (which is guaranteed if detailed balance is satisfied), one can express $\mathbf{t}'_j{}^T$ as a linear combination of the (left) eigenvectors of \mathbf{Q} , for certain coefficients a_{nm} to be determined a posteriori

$$\mathbf{t}'_j{}^T = \sum_\ell a_{j\ell} \boldsymbol{\phi}^{(\ell)}. \quad (22)$$

Inserting in equation (21) gives the vector equation

$$\sum_\ell a_{j\ell} (1 - \lambda'_\ell) \boldsymbol{\phi}^{(\ell)} = (1 - Q_{j1} t'_{jj}, \dots, 1 - Q_{jN} t'_{jj}). \quad (23)$$

Next we consider the equation for the component r

$$\sum_{\ell} a_{j\ell}(1 - \lambda'_{\ell})\phi_r^{(\ell)} = 1 - Q_{jr}t'_{jj}. \quad (24)$$

Multiplying left and right hand sides times $\psi_r^{(s)}$ and summing over r gives

$$\sum_{\ell>1} a_{j\ell}(1 - \lambda'_{\ell})\delta_{\ell s} = \delta_{s1} - \lambda_s\psi_j^{(s)}t'_{jj} \quad (25)$$

where we have used that $\psi^{(s)}$ is the right eigenvector of \mathbf{Q} associated to eigenvalue λ'_s , and the properties of the eigenvectors of the matrix \mathbf{Q} , $\sum_r \psi_r^{(s)} = \delta_{s1}$, and $\sum_r \phi_r^{(\ell)} \psi_r^{(\ell)} = \delta_{\ell s}$. Equation (25) yields for $s = 1$

$$t'_{jj} = \frac{1}{p_j} \quad (26)$$

This quantity is greater than or equal to one, with equality holding for $p_j^{\text{eq}} = 1$, and it can be interpreted as the expected number of time steps it takes to the system to first visit state j , *after* its release from state j itself, also known as the "recurrence time" or Kac's lemma⁴⁶. Equation (26) can also be derived from (19) without assuming the existence of a complete set of eigenvectors of \mathbf{Q} . Multiplying (32) times p_i^{eq} , summing over i

$$\sum_i t'_{ji}p_i^{\text{eq}} = 1 + \sum_{ki} t'_{jk}Q_{ki}p_i^{\text{eq}} - \sum_i t'_{jj}Q_{ji}p_i^{\text{eq}} \quad (27)$$

and using $\sum_i Q_{ji}p_i^{\text{eq}} = p_j^{\text{eq}}$ one obtains $1 = t'_{jj}p_j^{\text{eq}}$ which gives (26). At this point it should be noted that some studies in the literature set this quantity to zero as a 'convention'. The analysis above shows that, in the discrete time formulation of MFPTs, convention (26) should be used. For $s > 1$, using (26) one gets from equation (25)

$$a_{js} = -\frac{1}{p_j^{\text{eq}}} \frac{\lambda'_s}{1 - \lambda'_s} \psi_j^{(s)}. \quad (28)$$

Singling out the contribution from a_{j1} in (22)

$$\mathbf{t}'_j = a_{j1}\phi^{(1)} + \sum_{\ell>1} a_{j\ell}\phi^{(\ell)} \quad (29)$$

using $\phi_k^{(1)} = 1 \forall k$ and (28), we get

$$t'_{jk} = a_{j1} - \frac{1}{p_j^{\text{eq}}} \sum_{\ell>1} \frac{\lambda'_{\ell}}{1 - \lambda'_{\ell}} \psi_j^{(\ell)} \phi_k^{(\ell)} \quad (30)$$

where a_{j1} can be determined by setting $j = k$ in the above and using (26)

$$a_{j1} = \frac{1}{p_j^{\text{eq}}} \left(1 + \sum_{\ell>1} \frac{\lambda'_{\ell}}{1 - \lambda'_{\ell}} \phi_j^{(\ell)} \psi_j^{(\ell)} \right). \quad (31)$$

Substituting in (30), we finally obtain an explicit relation for the MFPTs in terms of the eigenvalues and eigenvectors of the transition matrix

$$t'_{jk} = \frac{1}{p_j^{\text{eq}}} \left[1 + \sum_{\ell>1} \frac{\lambda'_{\ell}}{1 - \lambda'_{\ell}} \psi_j^{(\ell)} (\phi_j^{(\ell)} - \phi_k^{(\ell)}) \right]. \quad (32)$$

This formula, also derived in^{47,48}, will serve as a starting point to derive a number of useful relations in the following sections.

2. Continuous Time

Next we consider how these results differ when our system is described by a continuous time rate matrix \mathbf{K} instead of a discrete time transition probability matrix. Results for continuous time dynamics can be derived by setting the time step to τ in the discrete time dynamics, and taking the limit $\tau \rightarrow 0$ at the end. For small but finite τ , the transition matrix \mathbf{Q} can be written as $e^{\mathbf{K}\tau}$, and its eigenvalues are given by $\lambda'_{\ell} = e^{\lambda_{\ell}\tau}$. Defining $t_{ji} = t'_{ji}\tau$ as the mean first time from i to j , and using the same logic as in (19), we can write a similar recursion

$$t_{ji} = [e^{\mathbf{K}\tau}]_{ji}\tau + \sum_{k \neq j} [e^{\mathbf{K}\tau}]_{ki}(t_{jk} + \tau) = \tau + \sum_{k \neq j} [e^{\mathbf{K}\tau}]_{ki}t_{jk}, \quad (33)$$

that can be rearranged as in equation (34),

$$\sum_k (\delta_{ki} - [e^{\mathbf{K}\tau}]_{ki})t'_{jk} = 1 - [e^{\mathbf{K}\tau}]_{ji}t'_{jj}. \quad (34)$$

Following the same steps that led to (32) we can arrive at

$$t'_{ji} = \frac{1}{p_j^{\text{eq}}} \left[1 + \sum_{\ell>1} \frac{e^{\lambda_{\ell}\tau}}{1 - e^{\lambda_{\ell}\tau}} \psi_j^{(\ell)} (\phi_j^{(\ell)} - \phi_i^{(\ell)}) \right] \quad (35)$$

Finally, using $t_{ji} = t'_{ji}\tau$ and taking the limit $\tau \rightarrow 0$, gives a formula for the MFPTs in continuous time dynamics, in terms of eigenvalues and eigenvectors of the rate matrix

$$t_{ji} = \frac{1}{p_j^{\text{eq}}} \sum_{\ell>1} \frac{1}{|\lambda_{\ell}|} \psi_j^{(\ell)} (\phi_j^{(\ell)} - \phi_i^{(\ell)}). \quad (36)$$

Note that in contrast to the discrete time result (26), in continuous time dynamics, equation (36) implies

$$t_{jj} = 0, \quad (37)$$

which is intuitively understood, as here there is no time step to wait to return to the state.

As an aside, we observe that expanding (34) for small τ as in equation (38)

$$-\tau \sum_k t'_{jk} K_{ki} = 1 - (\delta_{ji} + \tau K_{ji})t'_{jj} \quad (38)$$

using (26), $t_{ji} = \tau t'_{ji}$ and *then* letting $\tau \rightarrow 0$, gives

$$\mathbf{t}\mathbf{K} = -\mathbf{1}_n \mathbf{1}_n^T + \mathbf{D}_n^{-1}, \quad (39)$$

where \mathbf{D}_n is an $n \times n$ diagonal matrix with \mathbf{p}^{eq} on the diagonal. Note that the order in which these operations are executed matters, as t'_{jj} and t_{jk} (with $j \neq k$) should remain finite as τ is sent to zero. Taking the limit naively, leads to the expression given in (40), with $\mathbf{t}_j^T = (t_{j1}, \dots, t_{jN})$

$$\mathbf{t}_j^T \mathbf{K} = -\mathbf{1}_n^T, \quad (40)$$

which is sometimes reported in the literature. This is equivalent to $\mathbf{t}\mathbf{K} = -\mathbf{1}_n \mathbf{1}_n^T$, thus it differs from (39) for the diagonal terms. It is easy to show that (39) is correct,

while (40) is not, e.g. by multiplying both expressions times \mathbf{p}^{eq} from right and using $\mathbf{K}\mathbf{p}^{\text{eq}} = 0$, $\mathbf{1}_n^T \mathbf{p}^{\text{eq}} = 1$ and $\mathbf{D}_n^{-1} \mathbf{p}^{\text{eq}} = \mathbf{1}_n$.

Finally we note that, although (39) provides a correct expression for the MFPTs, \mathbf{K} is not directly invertible due the presence of zero eigenvalues, hence MFPTs are more easily computed from relations that we will derive in the next sections, which directly follow from (36).

E. Kemeny Constant

Starting with equation (36) we can examine the quantity $\sum_j p_j^{\text{eq}} t_{ji}$ and make use of $\sum_j \psi_j^{(\ell)} = \delta_{\ell,1}$ and $\sum_j \phi_j^{(\ell)} \psi_j^{(\ell)} = 1$ for all ℓ , to get

$$\begin{aligned} \sum_j p_j^{\text{eq}} t_{ji} &= \sum_j \sum_{\ell>1} \frac{1}{|\lambda_\ell|} \psi_j^{(\ell)} (\phi_j^{(\ell)} - \phi_i^{(\ell)}) = \sum_{\ell>1} \frac{1}{|\lambda_\ell|} \\ &= \sum_{\ell>1} \tau_\ell \equiv \zeta. \end{aligned} \quad (41)$$

This result is known as the Kemeny constant^{25,26,49} and is remarkable as it relates a weighted sum of MFPTs starting from some state i to a sum over relaxation timescales (which is independent of the particular choice of i).

The corresponding quantity in discrete time dynamics is obtained summing (32) over j

$$\sum_j p_j^{\text{eq}} t'_{ji} - N = \sum_{\ell>1} \frac{\lambda'_\ell}{1 - \lambda'_\ell} (1 - \delta_{\ell,1}) = \sum_{\ell>1} \left(\frac{1}{1 - \lambda'_\ell} - 1 \right)$$

which, simplifies to

$$\sum_j p_j^{\text{eq}} t'_{ji} = 1 + \sum_{\ell>1} \frac{1}{1 - \lambda'_\ell} \quad (42)$$

or, using (26), to

$$\sum_{j(\neq i)} p_j^{\text{eq}} t'_{ji} = \sum_{\ell>1} \frac{1}{1 - \lambda'_\ell} \equiv \zeta'. \quad (43)$$

F. A simple proof of Kemeny Constant's constancy

A simple proof for the independence of the quantity $\sum_j p_j^{\text{eq}} t'_{ji}$, on the state i , which does not require the eigenvectors of \mathbf{Q} to form a complete set, and hence it holds for systems that violate detailed balance, can be derived as follows. Multiplying (19) times π_j and summing over j we get

$$\sum_j p_j^{\text{eq}} t'_{ji} = 1 + \sum_{jk} p_j^{\text{eq}} t'_{jk} Q_{ki} - \sum_j p_j^{\text{eq}} t'_{jj} Q_{ji} \quad (44)$$

Using (26) and $\sum_j Q_{ji} = 1$ one has

$$\mathbf{p}^{\text{eq}} \mathbf{t}' = \mathbf{p}^{\text{eq}} \mathbf{t}' \mathbf{Q} \quad (45)$$

showing that $\mathbf{p}^{\text{eq}} \mathbf{t}'$ is a left eigenvector of \mathbf{Q} associated to eigenvalue 1, hence it has to be proportional to $\mathbf{1}_n^T$ and all its entries must be identical.

For the continuous time dynamics, one can similarly prove the constancy of Kemeny constant starting from equation (39), that reads, in scalar form

$$\sum_j t_{ij} K_{j\ell} = -1 + \frac{1}{p_i^{\text{eq}}} \delta_{i\ell}. \quad (46)$$

Multiplying times p_i^{eq} and summing over i we get $\sum_{ij} p_i^{\text{eq}} t_{ij} K_{j\ell} = 0$ hence

$$\mathbf{p}^{\text{eq}} \mathbf{t} \mathbf{K} = 0. \quad (47)$$

This shows that $\mathbf{p}^{\text{eq}} \mathbf{t}$ is a left eigenvector of the rate matrix associated to eigenvalue zero, hence proportional to $\mathbf{1}_n^T$, and must have all its components must be equal.

III. RESULTS

With the theory laid out, we are now equipped to make some observations about how these quantities relate. In particular we will show two main results:

- A description of how MFPTs and Kemeny constant are related to rate matrices and correlation functions. This will lead to a simple interpretation of the Kemeny constant and to a recipe for reconstructing rate matrices from MFPTs measurements, which may be helpful in milestone^{19,36-39} and transition path sampling^{31-34,50}.
- An example of how this unified framework can be applied to derive a coarse grained rate matrix which ensures that the MFPTs of the high dimensional and low dimensional systems are the same.

From now on, we will focus on continuous time dynamics, as much of the focus on MFPTs in the literature is for discrete time dynamics.

A. Linking MFPTs and Kemeny Constants To Correlation Functions

In this section, we provide expressions for MFPTs in terms of rate matrices and correlation functions and provide a physical interpretation for Kemeny constants. We start by adding and subtracting $\psi_j^{(1)}$ from equation (36), using $\phi_i^{(1)} = 1 \forall i$ and $|\lambda_\ell| = -\lambda_\ell \forall \ell > 1$

$$\begin{aligned} t_{ji} &= \frac{1}{p_j^{\text{eq}}} \left[\psi_j^{(1)} \phi_j^{(1)} - \sum_{\ell>1} \frac{1}{\lambda_\ell} \psi_j^{(\ell)} \phi_j^{(\ell)} - \psi_j^{(1)} \phi_i^{(1)} \right. \\ &\quad \left. + \sum_{\ell>1} \frac{1}{\lambda_\ell} \psi_j^{(\ell)} \phi_i^{(\ell)} \right] \end{aligned} \quad (48)$$

to reformulate the expression for the MFPTs in terms of matrix elements

$$t_{ji} = \frac{1}{p_j^{\text{eq}}} \left[(\mathbf{p}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})_{jj}^{-1} - (\mathbf{p}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})_{ji}^{-1} \right] \quad (49)$$

where we have used $\mathbf{p}^{\text{eq}} = \boldsymbol{\psi}^{(1)}$ and $\mathbf{1}_n^T = \boldsymbol{\phi}^{(1)}$. This gives an explicit formula for MFPTs in continuous time dynamics, in terms of rate matrices, which complements similar results available in the literature for discrete time dynamics⁵¹, formulated in terms of the so-called 'fundamental matrix' $(\mathbf{p}\mathbf{1}_n^T + \mathbf{I} - \mathbf{Q})^{-1}$. Now using equation (18), one can provide yet another expression for MFPTs, in terms of time-integrated correlation functions

$$t_{ji} = \frac{1}{p_j^{\text{eq}}} \left[\frac{\int_0^\infty C_{jj}^{\text{eq}}(\tau) d\tau}{p_j^{\text{eq}}} - \frac{\int_0^\infty C_{ji}^{\text{eq}}(\tau) d\tau}{p_i^{\text{eq}}} \right] \quad (50)$$

which is appealing as it does not require the inversion of a high dimensional matrix, in the same way as (49) does. The Kemeny constant follows as

$$\zeta = \sum_j p_j^{\text{eq}} t_{ji} = \sum_j \left[\frac{\int_0^\infty C_{jj}^{\text{eq}}(\tau) d\tau}{p_j^{\text{eq}}} - \frac{\int_0^\infty C_{ji}^{\text{eq}}(\tau) d\tau}{p_i^{\text{eq}}} \right]. \quad (51)$$

Since $C_{ji}^{\text{eq}}(\tau)/p_i^{\text{eq}} = P(j, \tau|i, 0) - p_j^{\text{eq}}$ and $\sum_j P(j, \tau|i, 0) = 1 \forall \tau$, swapping sums with integrals in (51), which is valid for finite state space, it becomes clear that the second term on the RHS vanishes, giving

$$\zeta = \sum_j \frac{\int_0^\infty C_{jj}^{\text{eq}}(\tau) d\tau}{p_j^{\text{eq}}} \equiv \sum_j D_{jj} \quad (52)$$

$$= \sum_j \int_0^\infty [P(j, \tau|j, 0) - p_j] d\tau \quad (53)$$

The first term in the square brackets measures the fraction of trajectories that are in j at time τ , out of those that start in j at time 0. The second term measures the fraction of trajectories that are in j at a given time τ , out of all the trajectories. Equation (53) reveals that Kemeny constant can be regarded as the time-integrated difference between the conditional and the a priori probability to be in any given state, as similarly pointed out in²⁷. Furthermore, equation (52) shows that ζ can be written as the trace of a matrix, that is known as the 'deviation matrix' \mathbf{D} ^{27,52}.

A more convenient writing of (53), which avoids its formulation in terms of the (finite) difference between two divergent integrals, can be obtained by introducing the decorrelation time of a state i

$$T_i = \int_0^\infty \frac{C_{ii}^{\text{eq}}(\tau)}{C_{ii}^{\text{eq}}(0)} d\tau, \quad (54)$$

as the area underneath the normalised autocorrelation functions $\hat{C}_{ii}^{\text{eq}}(\tau) = C_{ii}^{\text{eq}}(\tau)/C_{ii}^{\text{eq}}(0)$. The latter takes values 1 for $\tau = 0$ and zero for $\tau \rightarrow \infty$, and it decays as a multi-exponential, thus yielding a convergent integral. Using $C_{ii}^{\text{eq}}(0) = p_i^{\text{eq}}(1 - p_i^{\text{eq}})$, one can express the Kemeny constant as in (55)

$$\zeta = \sum_i T_i (1 - p_i^{\text{eq}}). \quad (55)$$

This leads to a simple interpretation of the Kemeny constant, as a weighted sum of the decorrelation times of the individual states. Here, $1 - p_i^{\text{eq}}$ can be thought of

as the difference between the maximum value, 1, and the minimum value, p_i^{eq} , of the conditional probability $P(i, \tau|i, 0)$, (attained at $\tau = 0$ and $\tau = \infty$ respectively), while T_i measures how fast $P(i, \tau|i, 0)$ decays from the former to the latter value.

Note that for systems with a large number of states n and broad equilibrium distribution, one is normally interested in, individual state probabilities are small, i.e. $p_i^{\text{eq}} \ll 1 \forall j$, hence

$$\zeta \simeq \sum_{i=1}^n T_i, \quad n \gg 1 \quad (56)$$

To check the validity of the approximation in (56), we consider dynamics in a potential energy function $v(x)$, along the continuous reaction coordinate x between finite boundaries, x_{min} and x_{max} . Upon discretizing the continuous problem, we obtain a discrete state Markov processes, where the number of states n is given by the number of discretization bins and the transition rates between adjacent states are given by the Arrhenius law

$$k_{ji} = Ae^{-\frac{v(j)-v(i)}{k_B T}}. \quad (57)$$

In Figure (1) we plot the diagonal elements of the deviation matrix $D_{ii} = T_i(1 - \pi_i)$ and the decorrelation times T_i , for different numbers of bins, namely $n = 50$ and $n = 200$. We see that D_{ii} is almost indistinguishable from T_i for $n = 200$, while they show little deviation when the number of states is decreased to $n = 50$, the states with highest probabilities (i.e. with minimum potential energy) exhibiting the largest deviation. This confirms our intuition that, if the number of states is sufficiently high, the Kemeny constant converges to the sum of the decorrelation times of the individual states.

In conclusion, combining (55) and (41) provides an interesting chain of relations for MFPTs, relaxation times and decorrelation times

$$\sum_{j=1}^n p_j^{\text{eq}} t_{ji} = \sum_{\ell=2}^n \tau_\ell = \sum_{j=1}^n T_j (1 - p_j^{\text{eq}}) \approx \sum_{j=1}^n T_j \quad (58)$$

where the last approximation holds for large n and broad \mathbf{p}^{eq} .

B. Constructing Rate Matrices from MFPTs

With an explicit expression for MFPTs in terms of rate matrices, we can now invert this expression, to obtain a recipe for constructing rate matrices with given MFPTs. Upon defining \mathbf{z} as the vector with components $z_j = [(\mathbf{p}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})^{-1}]_{jj}$, we can write (49) in matrix form

$$\mathbf{D}_n \mathbf{t} = \mathbf{z} \mathbf{1}_n^T - (\mathbf{p}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})^{-1} \quad (59)$$

Rearranging, we obtain

$$\mathbf{K} = \mathbf{p}^{\text{eq}} \mathbf{1}_n^T - (\mathbf{z} \mathbf{1}_n^T - \mathbf{D}_n \mathbf{t})^{-1}, \quad (60)$$

where \mathbf{z} can be expressed in terms of \mathbf{t} by demanding $\mathbf{K} \mathbf{p}^{\text{eq}} = 0$

$$\mathbf{z} = \mathbf{p}^{\text{eq}} + \mathbf{D}_n \mathbf{t} \mathbf{p}^{\text{eq}}. \quad (61)$$

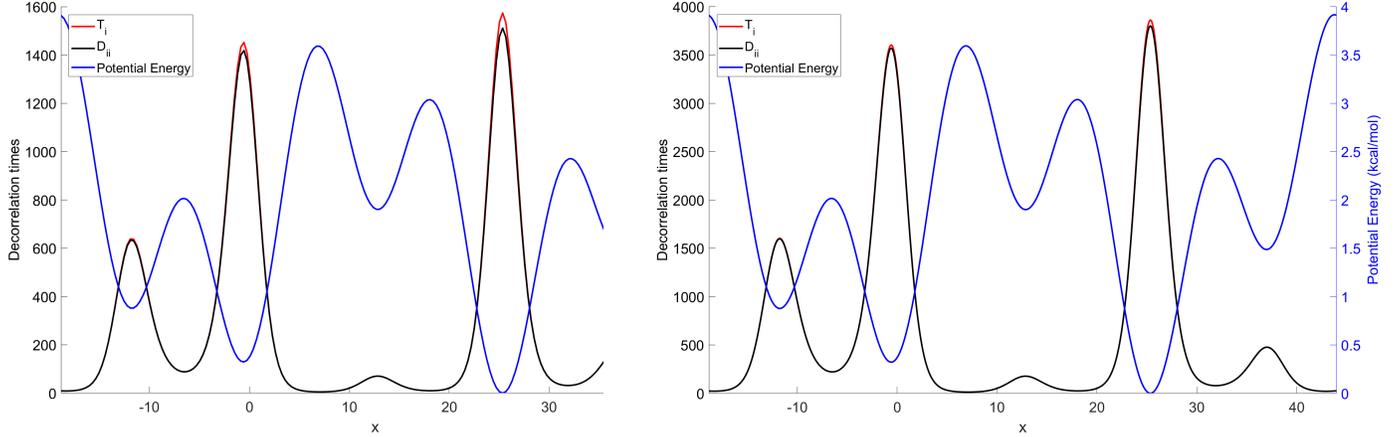


FIG. 1. Decorrelation times T_i (red line) and diagonal entries of the deviation matrix D_i (black line), as a function of the state i , with $i = 1, \dots, n$, for a system diffusing in the one-dimensional potential energy function $v(x) = \sin((x - \pi)/2) + \sin((x - \pi)/5)$ (blu line). Transition rates are given by (57) with $K_B T = 0.596$. In the left panel, the number of states is $n = 200$ and small deviations can be observed between D_i and T_i for the states with highest equilibrium populations. In the right panel, where the number of states is 500, spatial resolution is higher and the two quantities are almost indistinguishable. Note the different scaling of the y -axis for the potential energy.

Substituting into (60) then gives

$$\mathbf{K} = \mathbf{p}^{\text{eq}} \mathbf{1}_n^T - [\mathbf{p}^{\text{eq}} \mathbf{1}_n^T - \mathbf{D}_n \mathbf{t} (\mathbf{I} - \mathbf{p}^{\text{eq}} \mathbf{1}_n^T)]^{-1}. \quad (62)$$

It is easy to show that (62) also satisfies $\mathbf{1}_n^T \mathbf{K} = 0$, by noting that $\mathbf{1}_n^T \mathbf{D}_n = [\mathbf{p}^{\text{eq}}]^T$ and

$$[\mathbf{p}^{\text{eq}}]^T \mathbf{t} = \zeta \mathbf{1}_n^T, \quad (63)$$

which is implied by the definition of Kemeny constant (41). Equation (63) also shows that the equilibrium distribution can be fully determined from the matrix of MFPTs, as $[\mathbf{p}^{\text{eq}}]^T = \zeta \mathbf{1}_n^T \mathbf{t}^{-1}$ where ζ follows from the normalization of \mathbf{p}^{eq} , as $\zeta = 1/(\mathbf{1}_n^T \mathbf{t}^{-1} \cdot \mathbf{1}_n)$, so

$$[\mathbf{p}^{\text{eq}}]^T = \frac{\mathbf{1}_n^T \mathbf{t}^{-1}}{\mathbf{1}_n^T \mathbf{t}^{-1} \cdot \mathbf{1}_n}. \quad (64)$$

By using (63) and the Sherman-Morrison formula, as shown in Appendix (A), equation (62) can be simplified to obtain

$$\mathbf{K} = \mathbf{t}^{-1} (\mathbf{D}_n^{-1} - \mathbf{1}_n \mathbf{1}_n^T), \quad (65)$$

which could have also been derived from (39). Since \mathbf{D}_n follows directly from \mathbf{p}^{eq} , equations (64) and (65) show that \mathbf{p}^{eq} and \mathbf{K} can be both computed by inverting a single matrix (i.e. \mathbf{t}).

These equations then give a recipe to infer the equilibrium probability and the rate matrix of a system with n states, from the *sole* observation of MFPTs between pairs of states. This may be useful in practical situations where information about MFPTs is readily available, whereas information about the rate matrix and the equilibrium distribution is not.

We note that in Markov processes with ordered states, reflecting boundary conditions, and transitions only occurring between adjacent states, one has, for any pair of

states $i < j$, $t_{ij} = \sum_{k=i}^{j-1} t_{k,k+1}$. Hence, the full matrix \mathbf{t} can be determined from the knowledge of only MFPTs between adjacent states, $t_{k,k+1}, \forall k$. Equations (64) and (65) can then be used to reconstruct the full equilibrium distribution and rate matrix, from the observation of MFPTs between adjacent states, which can be computed efficiently, e.g. via the trajectory coloring procedure introduced in^{53,54}. This can be useful in milestoneing procedures, aimed at inferring the full kinetics of a system from the observation of many short trajectories, between adjacent states (milestones).

We note that for milestoneing on one-dimensional potentials, recipes to construct rate matrices have been given in terms of MFPTs *and* committor probabilities for adjacent milestones^{19,37}. Equation (65), equipped with (64), provides an alternative route which does not require to estimate committor probabilities. The above framework provides an intuitive explanation for the observed accuracy of milestoneing techniques, when applied to one-dimensional Smolochowski processes, in predicting the full distribution of MFPTs, by using rate matrices constructed from MFPTs between adjacent milestones^{19,37}: for these processes, MFPTs between adjacent states are sufficient to construct the whole MFPTs matrix, which univocally determines the rate matrix and the equilibrium distribution, as shown by (64) and (65).

An interesting pathway for future research would be to find optimal recipes to infer the rate matrix \mathbf{K} and the equilibrium distribution \mathbf{p}^{eq} from *partial* observations of the entries of matrix \mathbf{t} , for more general kinetic networks, where MFPTs between adjacent states do not encode the full distribution of MFPTs.

C. Constructing Transition Matrices from MFPTs

For completeness, in this section we provide an expression for MFPTs in terms of transition matrices in discrete time dynamics, and, conversely, we show how to construct transition matrices and equilibrium distributions from MFPTs. Starting with equation (32), rewriting $\lambda'_\ell/(1-\lambda'_\ell) = 1/(1-\lambda'_\ell) - 1$, using the spectral representation of the identity matrix element $I_{jk} = \sum_\ell \psi_j^{(\ell)} \phi_k^{(\ell)}$ and repeating the same reasoning that led to equation (49), we obtain

$$t'_{jk} = \frac{1}{p_j^{\text{eq}}} \left[I_{jk} + (\mathbf{p}^{\text{eq}} \mathbf{1}_n^T + \mathbf{I} - \mathbf{Q})_{jj}^{-1} - (\mathbf{p}^{\text{eq}} \mathbf{1}_n^T + \mathbf{I} - \mathbf{Q})_{jk}^{-1} \right] \quad (66)$$

Similarly to equation (59), this can be cast in vector notation

$$\mathbf{D}_n \mathbf{t} = \mathbf{I} + \mathbf{z}' \mathbf{1}_n^T - (\mathbf{p}^{\text{eq}} \mathbf{1}_n^T + \mathbf{I} - \mathbf{Q})^{-1} \quad (67)$$

where $\mathbf{z}' = [(\mathbf{p}^{\text{eq}} \mathbf{1}_n^T + \mathbf{I} - \mathbf{Q})^{-1}]_{jj}$. Rearranging for \mathbf{Q} and requiring $\mathbf{Q} \mathbf{p}^{\text{eq}} = \mathbf{p}^{\text{eq}}$ gives $\mathbf{z}' = \mathbf{D}_n \mathbf{t} \mathbf{p}^{\text{eq}}$ and

$$\mathbf{Q} = \mathbf{I} + \mathbf{p}^{\text{eq}} \mathbf{1}_n^T - (\mathbf{I} - \mathbf{D}_n \mathbf{t}' + \mathbf{D}_n \mathbf{t}' \mathbf{p}^{\text{eq}} \mathbf{1}_n^T)^{-1}. \quad (68)$$

Equation ((64)) remains true for \mathbf{t}' , as from ((63)) one has $[\mathbf{p}^{\text{eq}}]^T \mathbf{t}' = (1 + \zeta') \mathbf{1}_n^T$, with $1/(1 + \zeta') = \mathbf{1}_n^T \mathbf{t}'^{-1}$ following from normalization of \mathbf{p}^{eq} , so

$$[\mathbf{p}^{\text{eq}}]^T = \frac{\mathbf{1}_n^T \mathbf{t}'^{-1}}{\mathbf{1}_n^T \mathbf{t}'^{-1} \cdot \mathbf{1}_n}. \quad (69)$$

However, in discrete time dynamics, the equilibrium distribution can also be directly read off from the diagonal elements of \mathbf{t}' , as shown in (26).

An alternative expression for the transition matrix \mathbf{Q} , can be obtained by setting $\mathbf{Q} = e^{\mathbf{K}\tau}$ in equation (34). Rewriting this in vector notation

$$\mathbf{t}'(\mathbf{I} - \mathbf{Q}) = \mathbf{1}_n \mathbf{1}_n^T - \mathbf{D}_n^{-1} \mathbf{Q} \quad (70)$$

and rearranging for \mathbf{Q} gives

$$\mathbf{Q} = (\mathbf{I} - \mathbf{D}_n \mathbf{t}')^{-1} (\mathbf{p}^{\text{eq}} \mathbf{1}_n^T - \mathbf{D}_n \mathbf{t}'). \quad (71)$$

It can be easily shown that (68) and (71) coincide, by multiplying (68) times $(\mathbf{I} - \mathbf{D}_n \mathbf{t}' + \mathbf{D}_n \mathbf{t}' \mathbf{p}^{\text{eq}} \mathbf{1}_n^T)$ from left, expanding the products and using $\mathbf{1}_n^T \mathbf{Q} = \mathbf{1}_n^T$. In conclusion, like rate matrices, transition matrices can be computed by inverting a single matrix, involving MFPTs, e.g. $\mathbf{I} - \mathbf{D}_n \mathbf{t}'$.

D. Coarse Graining of Rate Matrices based on MFPTs

The unified framework set up above is deeply useful for investigating new relations and interpreting the results physically. As an example we use this framework to derive a coarse graining protocol which preserves the MFPTs of the system. Coarse graining involves projecting a high dimensional dynamics on to some coarse lower dimensional space. This involves grouping together microstates (labeled by lower case indices i, j)

in to macrostates (labeled by upper case indices I, J). In what follows, we will denote with $\hat{p}_I(t)$ the occupation probability of the macrostates $I = 1, \dots, N$, with $N < n$. Clearly, this must be equal to the sum of the probabilities of all microstates i in the macrostate I , i.e. $\hat{p}_I(t) = \sum_{i \in I} p_i(t)$. The sum can be encoded in to an $n \times N$ aggregation matrix \mathbf{A} , with elements $A_{iI} = 1$ if $i \in I$ and zero otherwise, which defines the clustering. Hence, $\hat{\mathbf{p}}(t) = \mathbf{A}^T \mathbf{p}(t)$.

There has been much recent research in to how best to perform a kinetic coarse graining^{1,18,20}, in particular on how to optimally define a coarse-grained rate matrix, for a given choice of the clustering \mathbf{A} , and how to optimally choose the latter. In^{18,20} it has been shown that meaningful grouping of states can be achieved by matching the relaxation time of the original rate matrix and the coarse-grained rate matrix proposed in¹, for which the second largest eigenvalue satisfies a variational principle. Here, we focus on the question of how to optimally choose a coarse-grained rate matrix for a given clustering \mathbf{A} of states. We propose that the link between MFPTs and rate matrices is used to define a coarse grained rate matrix which enforces a particular condition on the MFPTs.

In the previous sections we have shown that MFPTs fully determine the equilibrium and kinetic properties of a system. Hence, given the $N \times N$ matrix $\hat{\mathbf{t}}$ of MFPTs between the macrostates, the coarse-grained $N \times N$ rate matrix $\hat{\mathbf{K}}$ follows from (65) as

$$\hat{\mathbf{K}} = \hat{\mathbf{t}}^{-1} (\mathbf{D}_N^{-1} - \mathbf{1}_N \mathbf{1}_N^T), \quad (72)$$

where \mathbf{D}_N is the $N \times N$ diagonal matrix with $\hat{\mathbf{p}}^{\text{eq}}$ along its diagonal and $\mathbf{1}_N$ is the N -dimensional vector with all the entries equal to 1. A question that immediately arises, however, is: how should the MFPTs in the coarse grained system be defined or measured?

A minimal condition is that the coarse grained dynamics converges to the equilibrium distribution $\hat{\mathbf{p}}^{\text{eq}} = \mathbf{A}^T \mathbf{p}^{\text{eq}}$. Using (64), this results in the condition

$$\hat{\mathbf{p}}^{\text{eq}} = \frac{\mathbf{1}_N^T \hat{\mathbf{t}}^{-1}}{\mathbf{1}_N^T \hat{\mathbf{t}}^{-1} \mathbf{1}_N} \quad (73)$$

A second condition is that $\hat{t}_{II} = 0 \forall I$. In Appendix (B), we show that there is a whole family of vectors $\hat{\mathbf{t}}$ which satisfies these requirements, so further conditions have to be imposed.

One possibility is to require that if we choose two (different) macrostates with equilibrium probability, then the MFPT between them is the same as if we choose two microstates from within the macrostates with equilibrium probability, i.e.

$$\hat{t}_{JI} = \frac{1}{\hat{p}_I^{\text{eq}} \hat{p}_J^{\text{eq}}} \sum_{i \in I, j \in J} p_j^{\text{eq}} p_i^{\text{eq}} t_{ji} - \frac{1}{(\hat{p}_J^{\text{eq}})^2} \sum_{i, j \in J} p_j^{\text{eq}} p_i^{\text{eq}} t_{ji}, \quad (74)$$

where the second term on the r.h.s. removes the contribution from microstates belonging to the same macrostate and ensures that $\hat{t}_{II} = 0 \forall I$. Obviously, we could have subtracted the contribution from $I = J$ in a number of

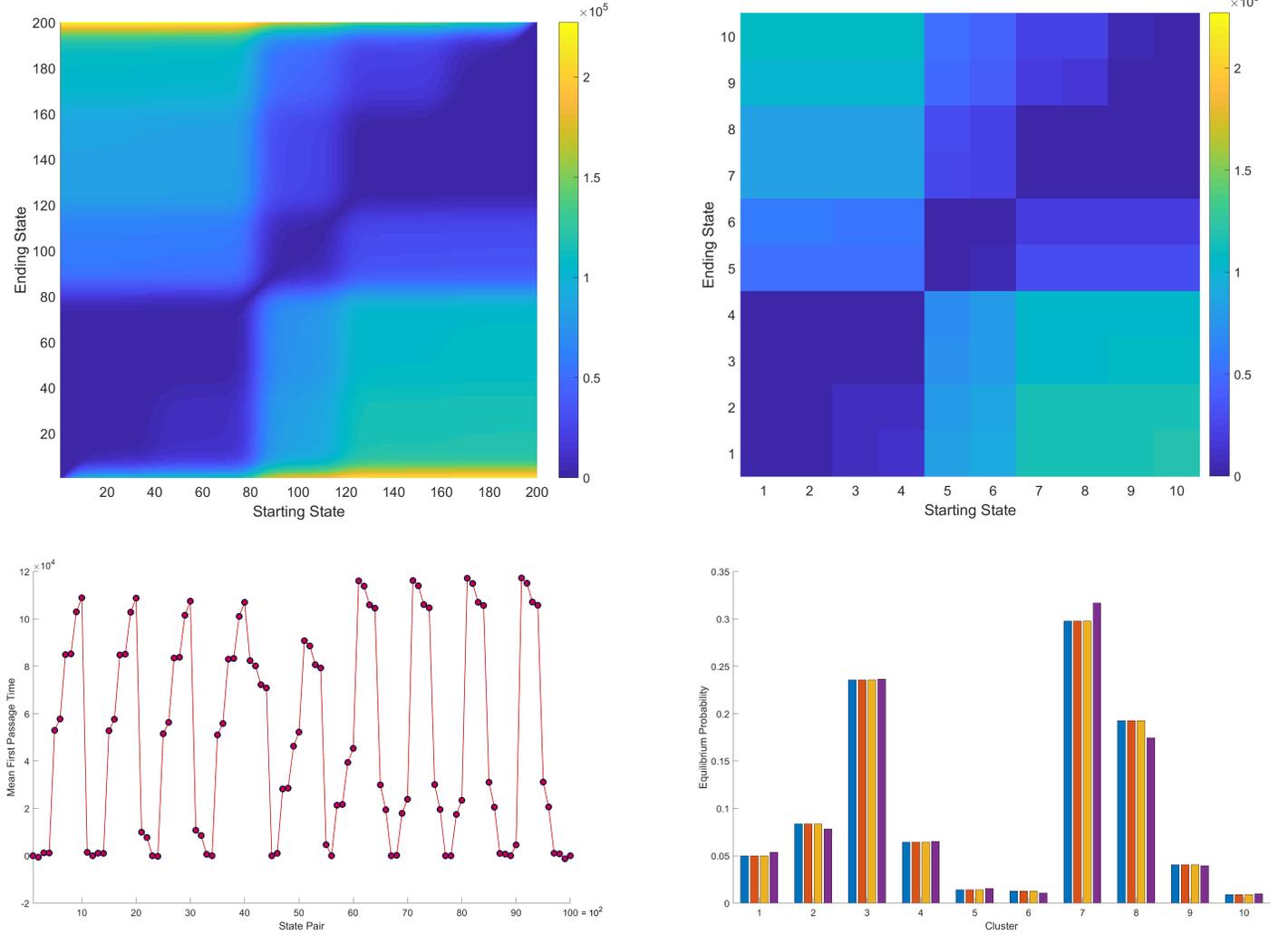


FIG. 2. MFPTs and equilibrium distribution of the system diffusing on the potential $v(x) = \sin((x - \pi)/2) + \sin((x - \pi)/5)$, coarse-grained from initially 200 into 10 bins, equally sized, in the interval $[-6\pi, 14\pi]$. Top left: MFPTs t_{ij} of the original system, as a function of $i, j \in \{1, \dots, 200\}$. Top right: coarse-grained MFPTs \hat{t}_{IJ} , as given in (74), as a function of the macrostates $I, J \in \{1, \dots, N\}$. Bottom left: comparison between the coarse-grained MFPTs \hat{t} , computed via formula (74) from the MFPTs \mathbf{t} of the original system (green line), and those computed via formula (49), from the coarse-grained rate matrices, given by the two equivalent expressions (78) (blue line) and (79) (pink line). For simplicity, \hat{t}_{IJ} is plotted here as a single index quantity $\hat{t}_{(J-1)N+I}$, versus its index. Bottom right: targeted equilibrium distribution $\mathbf{A}^T \hat{\mathbf{p}}^{\text{eq}}$ (blue), and equilibrium distribution $\hat{\mathbf{p}}^{\text{eq}}$ resulting from (73) with $\hat{\mathbf{t}}$ defined in (74) (orange) and (75) (purple), respectively. The former leads to the targeted distribution, while the latter does not. The yellow columns show results for a new protocol, defined by equation (80).

different ways, e.g.

$$\hat{t}_{JI} \hat{p}_I^{\text{eq}} \hat{p}_J^{\text{eq}} = (1 - \delta_{IJ}) \sum_{i \in I} \sum_{j \in J} p_i^{\text{eq}} p_j^{\text{eq}} t_{ji}, \quad (75)$$

however, one can show that this latter choice does not lead to the right equilibrium distribution (see Fig. (2)).

Below we derive analytically the rate matrix $\hat{\mathbf{K}}$ resulting from the MFPTs choice (74), and show that it leads to the steady state $\hat{\mathbf{p}}^{\text{eq}}$. Rewriting the summation on the r.h.s. of (74) in terms of \mathbf{A} , we have

$$\hat{t}_{JI} = (\mathbf{D}_N^{-1} \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1})_{JI} - z_J \quad (76)$$

where we have defined $z_J = (\mathbf{D}_N^{-1} \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1})_{JJ}$.

This translates to the matrix relation

$$\hat{\mathbf{t}} = \mathbf{D}_N^{-1} \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} - \mathbf{z} \mathbf{1}_N^T. \quad (77)$$

Multiplying times $\hat{\mathbf{K}}$ from right, using $\mathbf{1}_N^T \hat{\mathbf{K}} = 0$ and (72), we obtain

$$\hat{\mathbf{K}} = (\mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1})^{-1} (\mathbf{I} - \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T) \quad (78)$$

which clearly satisfies $\hat{\mathbf{K}} \hat{\mathbf{p}}^{\text{eq}} = 0$. An alternative expression, which is useful for later,

$$\hat{\mathbf{K}} = \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - [\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T + \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{p}^{\text{eq}} \mathbf{1}_N^T - \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}]^{-1}, \quad (79)$$

is derived in appendix (C).

In Appendix (D) we show that this coarse-graining protocol coincides with the one proposed by Hummer and Szabo in¹. An advantage of using (78) to calculate the rate matrix of the coarse-grained system, when compared to its formulation in¹, is that it only requires the inversion of a matrix with low dimensionality $N < n$, and is thus computationally highly efficient, provided the MFPTs and the equilibrium distribution of the original system are known.

In Section (III E), we show that a variational principle on the Kemeny constant exists for this coarse-graining protocol, namely the Kemeny constant of the coarse-grained system is bounded from above by the Kemeny constant of the original system.

As we have discussed above, there are other valid choices one could make for the coarse-grained MFPTs, which lead to alternative definitions of the coarse-grained rate matrices. In Appendix (B), we derive an alternative choice, which ensures that the Kemeny constant of the original and the clustered systems are identical, in contrast to (78) and¹:

$$\hat{\mathbf{t}} = \frac{1}{1 - \frac{1}{\zeta}[\mathbf{p}^{\text{eq}}]^T \mathbf{z}} [\mathbf{D}_N^{-1} \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} - \mathbf{z} \mathbf{1}_N^T], \quad (80)$$

where ζ is the Kemeny constant of the original system.

We test the above relations on the system defined in (57), diffusing on the one-dimensional potential plotted in Fig. (1). In the top panels of Figure (2) MFPTs are shown as heat maps for the original and the clustered system. In the bottom left panel, we plot the MFPTs computed via formula (49), for the rate matrices (78) and (79). As expected, these are identical, and coincide with the MFPTs calculated via formula (74). In the bottom right panel, we plot the equilibrium distribution resulting from (73) with $\hat{\mathbf{t}}$ defined in (74). As expected, this is identical to the targeted distribution $\mathbf{A}^T \mathbf{p}^{\text{eq}}$. For comparison, we also plot the distribution that would have resulted from the choice (75), which deviates from the targeted distribution $\mathbf{A}^T \mathbf{p}^{\text{eq}}$, as anticipated. Finally, we show the equilibrium distribution for the alternative clustering protocol given in (80), which preserves the Kemeny constant. This is seen to match the targeted distribution, in addition, it is verified numerically that it leads to the same Kemeny constant as the original system.

E. Variational principle for Kemeny Constant in Hummer-Szabo Coarse Graining

In²⁰ we have shown that a variational principle holds for the second largest eigenvalue of the rate matrix in the system coarse-grained according to the Hummer-Szabo prescription, namely its inverse (corresponding to the relaxation time in the coarse-grained system) is smaller than or equal to the inverse second largest eigenvalue of the rate matrix of the original system (giving the relaxation time of the original system). This variational principle has been used in¹⁸ to identify optimal clustering protocols. In this section we show that a similar variational principle holds for the Kemeny constant itself, for the coarse-graining protocol based on (74), that we prove

to be equivalent to the one proposed by Hummer-Szabo, in appendix (D). Summing (74) over J and rewriting $\sum_J \sum_{j \in J} = \sum_j$

$$\sum_j \sum_{i \in I} p_j^{\text{eq}} p_i^{\text{eq}} t_{ji} - \sum_J \frac{\hat{p}_I^{\text{eq}}}{\hat{p}_J^{\text{eq}}} \sum_{i,j \in J} p_j^{\text{eq}} p_i^{\text{eq}} t_{ji} = \sum_J \hat{p}_J^{\text{eq}} \hat{p}_I^{\text{eq}} \hat{t}_{JI} \quad (81)$$

and finally using (36) we obtain

$$\zeta = \sum_J \frac{1}{\hat{p}_J^{\text{eq}}} \sum_{i,j \in J} p_j^{\text{eq}} p_i^{\text{eq}} t_{ji} + \zeta^{\text{CG}} \quad (82)$$

where ζ^{CG} is the Kemeny constant in the coarse-grained system. Since the first term on the RHS of the equation above is non-negative, we have

$$\zeta^{\text{CG}} \leq \zeta. \quad (83)$$

This extends the variational principle previously found for the relaxation time, to the sum of all the timescales in the system. We intend to explore in future work variational clusterings based on Kemeny constants.

F. Coarse Graining of Transition Matrices based on MFPTs

Similarly, a relation for the coarse-grained transition matrix $\hat{\mathbf{Q}}$, in discrete time dynamics, would follow from (71) as

$$\hat{\mathbf{Q}} = (\mathbf{I} - \mathbf{D}_N \hat{\mathbf{t}}')^{-1} (\mathbf{p}^{\text{eq}} \mathbf{1}_N^T - \mathbf{D}_N \hat{\mathbf{t}}'), \quad (84)$$

where $\hat{\mathbf{t}}'$ is the matrix of discrete-time MFPTs in the coarse-grained system. A definition of the latter that would seem physically meaningful would be

$$\hat{t}'_{JI} \hat{p}_I^{\text{eq}} = \sum_{i \in I} p_i^{\text{eq}} \bar{t}'_{Ji} \quad (85)$$

where \bar{t}'_{Ji} denotes the MFPT from a microstate i to a macrostate J , which can be calculated via a recursive equation, analogous to (19),

$$\bar{t}'_{Ji} = \sum_{j \in J} Q_{ji} + \sum_{k \notin J} (\bar{t}'_{Jk} + 1) Q_{ki} = 1 + \sum_{k \notin J} \bar{t}'_{Jk} Q_{ki}. \quad (86)$$

This is rewritten more conveniently by defining $M_{ki}^{(J)} = Q_{ki}$ for $k \notin J$ and $M_{ki}^{(J)} = 0$ for $k \in J$,

$$\sum_k \bar{t}'_{Jk} (\delta_{ki} - M_{ki}^{(J)}) = 1 \quad (87)$$

which allows to compute each row of the rectangular $N \times n$ matrix $\bar{\mathbf{t}}'$, $[\bar{\mathbf{t}}']^T = (\bar{t}'_{J1}, \dots, \bar{t}'_{Jn})$, simply by inverting matrix $\mathbf{B}^{(J)}$, with elements $B_{ki}^{(J)} = \delta_{ki} - M_{ki}^{(J)}$

$$[\bar{\mathbf{t}}']^T = \mathbf{1}_n^T [\mathbf{B}^{(J)}]^{-1} \quad (88)$$

and to finally compute $\hat{\mathbf{t}}'$ using (85).

Intriguingly, however, the equilibrium distribution computed from (69) for this natural choice of MFPTs, does not lead to the right equilibrium distribution

$\mathbf{A}^T \mathbf{p}^{\text{eq}}$, for arbitrary choices of \mathbf{A} . Note that, nevertheless, the diagonal terms of the MFPTs matrix so defined, trivially retrieve the equilibrium probabilities: upon multiplying equation (86) times p_i^{eq} , summing over i and using $\sum_i Q_{ki} p_i^{\text{eq}} = p_k^{\text{eq}}$, we obtain the relation

$$\sum_{k \in J} \bar{t}_{Jk}^I p_k^{\text{eq}} = 1, \quad (89)$$

which combined with (85), leads to $\hat{t}_{II}^I = 1/\hat{p}_I^{\text{eq}} \forall I$. Given this surprising outcome, the definition of physically meaningful coarse-grained MFPTs in discrete-time dynamics remains an interesting pathway for future work.

IV. CONCLUSIONS AND OUTLOOK

In this study we have presented and linked together several results existing in the literature for mean first passage times and the Kemeny constant and have provided new relations in terms of correlation functions. These relations lead to a new writing of the Kemeny constant, and a simple interpretation in terms of decorrelation times.

In addition, we have provided a recipe to infer the equilibrium distribution and the rate matrix of a process, from measurements of MFPTs. This does not require the estimation of committor probabilities and it only requires the inversion of a single matrix (with MFPTs between pairs of states as entries). For systems whose transitions are well approximated by memoryless jumps between adjacent states, as the one dimensional Smoluchowski process, MFPTs between any pair of states can be expressed in terms of MFPTs between adjacent states, hence the rate matrix can be constructed from the sole measurements of MFPTs between adjacent states, using this recipe.

This observation provides an intuitive explanation for the accuracy of milestone techniques in inferring the whole MFPTs distribution, from short trajectories between adjacent milestones, which has been pointed out in^{19,37}. An interesting pathway for future work would be to define optimal recipes to infer rate matrices, from partial observations of MFPTs, in more complex kinetic networks, where MFPTs between adjacent states are not sufficient to reconstruct the full MFPTs matrix.

The derived relation between rate matrices and MFPTs, given in equation (65), may find application in several domains. For example, in transport networks, the mean travelling times of passengers between two stations (a proxy for MFPTs), may be readily available from smart cards, and can be used to infer the rates at which passengers move along the links of the network, which might be more difficult to measure in practice. Often, a simple diffusive process (controlled by the degrees of the nodes) is assumed, but due to the varying importance of different nodes, this assumption may be invalid⁵⁵. Equation (65) may thus be used to model such processes more accurately.

Another application we can mention, is the inference of gene regulatory networks from the time series generated in gene knock-out experiments⁵⁶, which provide information on the first time at which the expression of a gene

j is modified, as a result of knocking out a gene i . This can be regarded as the MFPT to reach node j from node i on the relevant gene regulatory network. Using this information, an effective rate matrix can be computed via (65), which may give information on the rate at which a perturbation of gene i propagates to gene j , thus providing insights on the interactions between genes.

Finally, we have shown how the relations between MFPTs and rate matrices can be used to introduce clustering protocols that preserve MFPTs. One such protocol leads to an expression for the coarse-grained rate matrix which coincides with the one derived by Hummer-Szabo, and can be computed at low computational cost when information about MFPTs and equilibrium distribution in the original system is available. We have shown that such coarse-graining leads to a variational principle for the Kemeny constant, which may be used to optimise the coarse-graining protocol. Finally, we have shown that an alternative definition of the coarse-graining protocol exists, which preserves the Kemeny constant. The identification of optimal ways to cluster states, based on this latter definition of the coarse-grained rate matrix, constitutes another interesting pathway for future work. Additionally, it remains to be tested if our formalism using mean first passage times might help overcome statistical uncertainties⁵⁷ often arising in coarse-graining of MSMs using spectral decomposition methods.

Appendix A: Equivalence between (39) and (62)

We start with equation (62) and multiply left and right hand sides times \mathbf{t} , from left, and times \mathbf{D}_n from right

$$\mathbf{tKD}_n = \mathbf{t} \mathbf{p}^{\text{eq}} \mathbf{1}_n^T \mathbf{D}_n - [\mathbf{D}_n^{-1} \mathbf{p}^{\text{eq}} \mathbf{1}_n^T \mathbf{t}^{-1} - \mathbf{t} (\mathbf{I} - \mathbf{p}^{\text{eq}} \mathbf{1}_n^T) \mathbf{t}^{-1}]^{-1} \quad (\text{A1})$$

Using (63) and $\mathbf{D}_n^{-1} \mathbf{p}^{\text{eq}} = \mathbf{1}_n$, we get

$$\begin{aligned} \mathbf{tKD}_n &= \mathbf{t} \mathbf{p}^{\text{eq}} [\mathbf{p}^{\text{eq}}]^T - \left[\frac{1}{\zeta} \mathbf{1}_n [\mathbf{p}^{\text{eq}}]^T - \left(\mathbf{I} - \frac{1}{\zeta} \mathbf{t} \mathbf{p}^{\text{eq}} [\mathbf{p}^{\text{eq}}]^T \right) \right]^{-1} \\ &= \mathbf{t} \mathbf{p}^{\text{eq}} [\mathbf{p}^{\text{eq}}]^T + \left[\mathbf{I} - \frac{1}{\zeta} (\mathbf{1}_n + \mathbf{t} \mathbf{p}^{\text{eq}}) [\mathbf{p}^{\text{eq}}]^T \right]^{-1} \end{aligned} \quad (\text{A2})$$

Upon using the Sherman-Morrison formula

$$(\mathbf{I} + \mathbf{u} \mathbf{v}^T)^{-1} = \mathbf{I} - \frac{\mathbf{u} \mathbf{v}^T}{1 + \mathbf{u}^T \mathbf{v}} \quad (\text{A3})$$

(63) and $\mathbf{p}^T \mathbf{1}_n = 1$, we find

$$\mathbf{tKD}_n = -\mathbf{1}_n \mathbf{p}^T + \mathbf{I} \quad (\text{A4})$$

from which (65) follows.

Appendix B: Condition on the Coarse Grained MFPTs.

Consider a matrix $\boldsymbol{\tau}$ satisfying

$$[\hat{\mathbf{p}}^{\text{eq}}]^T \boldsymbol{\tau} = \phi \mathbf{1}_N^T \quad (\text{B1})$$

where ϕ is an arbitrary parameter. First we prove that any vector $\hat{\boldsymbol{\tau}} = \boldsymbol{\tau} - \mathbf{w} \mathbf{1}_N^T$, where \mathbf{w} is an arbitrary vector,

will satisfy

$$[\hat{\mathbf{p}}^{\text{eq}}]^T = \frac{\mathbf{1}_N^T \hat{\boldsymbol{\tau}}^{-1}}{\mathbf{1}_N^T \hat{\boldsymbol{\tau}}^{-1} \mathbf{1}_N} \quad (\text{B2})$$

By using the Sherman-Morrison formula (A3)

$$\hat{\boldsymbol{\tau}}^{-1} = \boldsymbol{\tau}^{-1} + \frac{1}{\phi} \frac{\boldsymbol{\tau}^{-1} \mathbf{w} \mathbf{p}^{\hat{\text{eq}} T}}{\mathbf{1} - \frac{1}{\phi} \mathbf{p}^{\hat{\text{eq}} T} \mathbf{w}} \quad (\text{B3})$$

This gives

$$\mathbf{1}_N^T \hat{\boldsymbol{\tau}}^{-1} = \frac{1}{\phi - \mathbf{p}^{\hat{\text{eq}} T} \mathbf{w}} [\mathbf{p}^{\hat{\text{eq}}}]^T \quad (\text{B4})$$

and $\mathbf{1}_N^T \hat{\boldsymbol{\tau}}^{-1} \mathbf{1}_N = (\phi - [\mathbf{p}^{\hat{\text{eq}}}]^T \mathbf{w})^{-1}$. Secondly, one can show that

$$\hat{\boldsymbol{\tau}}^{-1} (\mathbf{D}_N^{-1} - \mathbf{1}_N \mathbf{1}_N^T) = \boldsymbol{\tau}^{-1} (\mathbf{D}_N^{-1} - \mathbf{1}_N \mathbf{1}_N^T) \quad (\text{B5})$$

A choice of $\boldsymbol{\tau}$ that satisfies (B1) for $\hat{\mathbf{p}}^{\text{eq}} = \mathbf{A}^T \mathbf{p}^{\text{eq}}$ is

$$\boldsymbol{\tau} = \frac{\phi}{\zeta} \mathbf{D}_N^{-1} \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}. \quad (\text{B6})$$

Since subtraction of any matrix $\mathbf{w} \mathbf{1}_N^T$ will lead to the same equilibrium distribution and rate matrix, one can define the MFPTs $\hat{\mathbf{t}}$ in the coarse grained system as

$$\hat{\mathbf{t}} = \boldsymbol{\tau} - \frac{\phi}{\zeta} \mathbf{z} \mathbf{1}_N^T$$

with $z_J = (\mathbf{D}_N^{-1} \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1})_{JJ}$. This definition is guaranteed to satisfy $\hat{t}_{JJ} = 0 \forall J$, in addition to $\mathbf{p}^{\hat{\text{eq}}} = \mathbf{1}_N^T \hat{\mathbf{t}}^{-1} / \mathbf{1}_N^T \hat{\mathbf{t}}^{-1} \mathbf{1}_N$. Setting $\phi = \zeta$ corresponds to the choice (74). For this choice, the resulting Kemeny constant in the coarse grained system is $\hat{\zeta} \equiv 1 / \mathbf{1}_N^T \hat{\mathbf{t}}^{-1} \mathbf{1}_N = \zeta - [\mathbf{p}^{\hat{\text{eq}}}]^T \hat{\mathbf{w}}$, and the variational principle $\hat{\zeta} \leq \zeta$ holds. We show in (D) that this choice corresponds to the coarse graining protocol defined by Hummer and Szabo in¹.

However, other choices are possible. In particular, it is possible to choose ϕ in such a way that the sum of relaxation times in the clustered and in the original system are the same $\hat{\zeta} = \zeta$, by requiring

$$\hat{\zeta} \equiv \phi - [\mathbf{p}^{\hat{\text{eq}}}]^T \mathbf{w} = \zeta \quad (\text{B7})$$

with $\mathbf{w} = \mathbf{z} \phi / \zeta$. This leads to

$$\phi = \frac{\zeta}{1 - \frac{1}{\zeta} [\mathbf{p}^{\hat{\text{eq}}}]^T \mathbf{z}} \quad (\text{B8})$$

and results in the choice, for the MFPTs in the clustered system, given in (80).

Appendix C: Derivation of (79)

Multiplying (74) times \hat{p}_J^{eq} , we can make use of (49) to express the MFPT in the coarse-grained system, in terms of the coarse grained rate matrix, to get

$$\begin{aligned} & (\mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1})_{JI} - (\mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1})_{JJ} \\ &= (\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - \hat{\mathbf{K}})_{JJ}^{-1} - (\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - \hat{\mathbf{K}})_{JI}^{-1} \end{aligned} \quad (\text{C1})$$

Defining $u_J = (\mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1})_{JJ}$ and $v_J = (\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - \mathbf{R})_{JJ}^{-1}$, equation (C1) can be written in matrix form and rearranged to yield an expression for the reduced rate matrix

$$\hat{\mathbf{K}} = \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - [(\mathbf{v} + \mathbf{u}) \mathbf{1}_N^T - \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}]^{-1}. \quad (\text{C2})$$

The vector \mathbf{v} can be determined by demanding that $\hat{\mathbf{p}}^{\text{eq}}$ is the steady state of the dynamics described by $\hat{\mathbf{K}}$, i.e. $\hat{\mathbf{K}} \hat{\mathbf{p}}^{\text{eq}} = 0$. Using $\mathbf{1}_N^T \hat{\mathbf{p}}^{\text{eq}} = 1$, $\mathbf{D}_N^{-1} \hat{\mathbf{p}}^{\text{eq}} = \mathbf{1}_N$, $\mathbf{A} \mathbf{1}_N = \mathbf{1}_n$ and $\mathbf{D}_n \mathbf{1}_n = \mathbf{p}_n^{\text{eq}}$, as well as that an invertible matrix has the same eigenvectors as its inverse (with inverse eigenvalues), we get

$$\mathbf{v} = \hat{\mathbf{p}}^{\text{eq}} - \mathbf{u} + \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{p}^{\text{eq}}. \quad (\text{C3})$$

Substituting (C3) in (C2) this finally gives (79). We check below that (79) automatically satisfies also the condition $\mathbf{1}_N^T \hat{\mathbf{K}} = 0$. By multiplying the above equation times $\mathbf{1}_N^T$ from left and equating to zero, we get

$$\zeta \mathbf{1}_N^T = \mathbf{1}_n^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \quad (\text{C4})$$

where we have used $\mathbf{1}_N^T \mathbf{A}^T = \mathbf{1}_n^T$, $\mathbf{1}_n^T \mathbf{D}_n = [\mathbf{p}^{\text{eq}}]^T$ and (63). Substituting (59) into the above equation

$$\begin{aligned} \zeta \mathbf{1}_N^T &= \mathbf{1}_n^T \mathbf{z} \mathbf{1}_n^T \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \\ &\quad - \mathbf{1}_n^T (\mathbf{p} \mathbf{1}_n^T - \mathbf{K})^{-1} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}, \end{aligned} \quad (\text{C5})$$

and using $\mathbf{1}_n^T \mathbf{z} = (1 + \zeta) \mathbf{1}_n^T$, $\mathbf{1}_n^T (\mathbf{p} \mathbf{1}_n^T - \mathbf{K})^{-1} = \mathbf{1}_n^T$, $\mathbf{1}_n^T \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} = \mathbf{1}_N^T$, and $\mathbf{1}_n^T \mathbf{p} = 1$, shows that (C5) is identically satisfied.

Finally, it is straightforward to show that (79) coincides with (78). Upon multiplying (79), from left, times $[\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T + \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{p}^{\text{eq}} \mathbf{1}_N^T - \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}]$, and using $\mathbf{1}_N^T \hat{\mathbf{K}} = 0$, we get

$$\begin{aligned} -\mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \hat{\mathbf{K}} &= [\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T + \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{p}^{\text{eq}} \mathbf{1}_N^T \\ &\quad - \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}] \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - \mathbf{I}. \end{aligned} \quad (\text{C6})$$

Expanding the product on the r.h.s.,

$$\begin{aligned} -\mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \hat{\mathbf{K}} &= \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T + \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{p}^{\text{eq}} \mathbf{1}_N^T \\ &\quad - \mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - \mathbf{I}. \end{aligned} \quad (\text{C7})$$

and using $\mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T = \mathbf{D}_n \mathbf{A} \mathbf{1}_N \mathbf{1}_N^T = \mathbf{D}_n \mathbf{1}_n \mathbf{1}_n^T = \mathbf{p}^{\text{eq}} \mathbf{1}_N^T$, the second and third term on the r.h.s. cancel, leading to

$$\mathbf{A}^T \mathbf{D}_n \mathbf{t} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} \hat{\mathbf{K}} = \mathbf{I} - \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T \quad (\text{C8})$$

and thus to (78).

Appendix D: Retrieval of Hummer-Szabo Coarse Graining

In this section we show that the proposed coarse graining, based on equation (74), coincides with the one proposed by Hummer and Szabo in¹, which equates the areas underneath the correlation functions

$$\sum_{i \in I, j \in J} \int_0^\infty dt C_{ij}(t) = \int_0^\infty dt C_{IJ}(t) \quad (\text{D1})$$

By inserting (59) in (79), we have

$$\hat{\mathbf{K}} = \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - [\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T + \mathbf{A}^T \mathbf{z} \mathbf{1}_n^T \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - \mathbf{A}^T (\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})^{-1} \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - \mathbf{A}^T \mathbf{z} \mathbf{1}_n^T \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} + \mathbf{A}^T (\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})^{-1} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}]^{-1} \quad (\text{D2})$$

Using $(\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})^{-1} \hat{\mathbf{p}}^{\text{eq}} = \hat{\mathbf{p}}^{\text{eq}}$, $\mathbf{A}^T \hat{\mathbf{p}}^{\text{eq}} = \hat{\mathbf{p}}^{\text{eq}}$ and $\mathbf{1}_n^T \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1} = \mathbf{1}_N^T$ this simplifies to

$$\hat{\mathbf{K}} = \hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_N^T - [\mathbf{A}^T (\hat{\mathbf{p}}^{\text{eq}} \mathbf{1}_n^T - \mathbf{K})^{-1} \mathbf{D}_n \mathbf{A} \mathbf{D}_N^{-1}]^{-1} \quad (\text{D3})$$

which coincides with the expression derived by Hummer-Szabo by imposing (D1). In contrast to (79), this formulation requires the inversion of a large dimensional matrix, hence (79) may be computationally more efficient when MFPTs and equilibrium distribution are known.

ACKNOWLEDGEMENTS

All the authors gratefully thank Attila Szabo (NIDDK, NIH), for numerous discussions and suggestions. A.K. is supported by the EPSRC Centre for Doctoral Training in Cross-Disciplinary Approaches to Non-Equilibrium Systems (CANES, EP/L015854/1). E.R. acknowledges support from EPSRC (EP/R013012/1) and ERC (project 757850 BioNet).

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