

AN ANALYSIS ON MARKOV STATIONARY PROPERTIES USING CIRCULATION THEORY

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ABSTRACT

This paper analyses the properties of the continuous Time Markov Chains using circulation theory. Applying the Hill's circulation theory on Markov chains, the Steady state probabilities of the Markov chains are calculated. The dynamics of ecological systems can be conveniently described as a Markovian stochastic process. Entropy production can successfully characterize ecological systems with cyclic competition. Ecological systems display a wide variety of nonlinear and non equilibrium behavior. Random interactions between individuals and the finiteness of the population lead to intrinsic stochasticity. Nonequilibrium results when interactions between individuals of different species include cyclic dependencies. This paper analyzes the Entropy production in terms of Markovian Steady State Probabilities.

Keywords: Entropy production, circulation rate, cycle Flux, trajectory, Markov chains, Free energy, Non equilibrium Steady state (NESS).

I. INTRODUCTION

The continuous-time discrete-state master equation with Q matrix is well established as a cogent model for reactions on the mesoscopic level [19]. A Q matrix has all nondiagonal elements $q_{ij} \geq 0$ [26] and summation of each row being 0. It can be classified either as reversible or irreversible [6] corresponding to the physical system being detail balanced or under pumping [20, 14]. The respective long time behaviors are equilibrium and Non Equilibrium Steady State (NESS) [20]. A reversible Q matrix has only non positive real eigenvalues [21]. Hence, the time-correlation functions of equilibrium fluctuations are multi exponential and monotonic. When a reaction is pumped, the eigenvalues of the irreversible Q can be complex (but never purely imaginary [22] known as power spectrum "peaking" [21]. It has also been shown that a sufficient and necessary condition for NESS is the existence of circulation (probabilistic flux) in a system [24, 14], and the stationarity is maintained via circular balance rather than detail balance [25]. Circulation leads to positive entropy production [23]. The cyclic population dynamics yields a non equilibrium steady state that is characterized by oscillations, large or small, around the internal fixed point.

A Markov chain is used to define the circulation rate in the sense of trajectories and the expression of circulation rate is calculated by deriving the remaining Markov chains. A Markov chain with net circulations

has positive entropy production rate and vice versa. The trajectories of an Ergodic recurrent Markov chain complete cycles incessantly. If the stationary Markov chain is taken as a model of Hill theory on cycle fluxes then each state of the Markov chain corresponds to a Mesoscopic state of polymers. The entropy production in these dissipative systems is the dissipation of free energy. Given a stationary Markov chain modeling the combination and transformation of bio chemical polymers, the stationary distribution is given by

$$\pi = \frac{e^{-F_i/K_B T}}{\sum_j e^{-F_j/K_B T}}$$

With i in the state space, then under the condition of detailed balance, F_i is just the free energy of the system. The transition from state i to j results in the dissipation of free energy $F_i - F_j$. But in the reversible case, this kind of transitions can result in the emission of energy which may correspond to the phenomenon of biological fluorescence.

Also the entropy production rate of the stationary Markov chain $\{\xi\}$ can be expressed in terms of the circulation distribution $\{w_e; e \in C_\infty\}$ as

$$e_p = \frac{1}{2} \sum_{e \in C_\infty} (w_e - w_{e^-}) \log \frac{w_e}{w_{e^-}}$$

where C_∞ is the collection of directed cycles occurring along almost all the sample paths and $C_.$ denotes the reversed cycle of c .

$$\text{i.e., } e_p = \frac{1}{2} \sum_{i,j \in S} (\pi_i P_{ij} - \pi_j P_{ji}) \log \frac{\pi_i P_{ij}}{\pi_j P_{ji}}$$

Also $\pi_i P_{ij} - \pi_j P_{ji} = \sum_{C \in C_\infty} (w_e - e_{e^-} J_e(i, j))$ is called the

circulation decomposition of the Markov chain and is in general not unique. Hence a Markov chain ξ is reversible if the components $w_e, e \in C_\infty$ of the circulation distribution of ξ satisfy the condition

$$w_e = w_{e^-}, \forall e \in C_\infty$$

i.e., The detailed balance is $\pi_i P_{ij} = \pi_j P_{ji}, \forall i, j \in S$. Hence for a continuous time Markov chain if its entropy vanishes then it is reversible.

Let $\xi = \{\xi_n\}_{n \in Z}$ is a stationary, irreducible and positive recurrent Markov chain with denumerable state space S with a transition probability $P = (P_{ij})_{i,j \in S}$ and a unique invariant distribution $\pi = (\pi_i)_{i \in S}$ then the entropy production rate is defined as

$$e_p = \lim_{n \rightarrow \infty} HP(F_0^n | P, P^- | F_0^n)$$

where $F_0^n = \sigma(\xi_k, 0 \leq k \leq n)$ and $H(P | F_0^n, P^- | F_0^n)$ is the relative entropy of P with respect to P^- restricted to the σ field F_0^n , where P and P^- are the distributions of the Markov chains and its time reversal respectively.

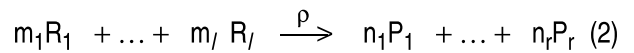
1.1 ENTROPY PRODUCTION IN MARKOV CHAINS

The study of complex systems with a large number of interacting particles requests global observables that characterize their behavior. Modern statistical mechanics has successfully identified, interpreted and applied such observables for equilibrium systems. One of these Observable is the entropy which allows for predictions of a system's behavior through the second law of thermodynamics (an isolated system's entropy cannot decrease). Entropy serves as a central observable in equilibrium thermodynamics. However, many biological and ecological systems

operate far from thermal equilibrium. Entropy production can characterize the behavior of such non equilibrium systems. Hence entropy production for a population model that displays non equilibrium behavior resulting from cyclic competition. At a critical point the dynamics exhibits a transition from large, limit-cycle like oscillations to small, erratic oscillations identifying similar principles for non-equilibrium systems, however, proves elusive. Neither a characteristic global observable nor a universal principle has been identified in a general way, While in non equilibrium the entropy production has been proposed as a useful observable [1] and different principles governing its behavior have been suggested [3] problems arise from different employed definitions of entropy and approaches to non equilibrium dynamics [2]. Random interactions between individuals and the finiteness of the population lead to intrinsic stochasticity.

II. DESIGN OF THE MARKOV MODEL

In this paper, we study a class of Continuous Time Markov chains (CTMCs) that typically emerge in the stochastic simulations with the Gillespie algorithm [4]. These models are dynamical systems where the states are populations of agents of various species, and the state transitions are updates to subpopulations of the state. For example, in a model of classical chemical kinetics, there are finitely many chemical species, and the states are finite multisets of species. Transitions are described by a finite set of reactions of the form



where the reactants are R_1, \dots, R_l and the products are P_1, \dots, P_r where each m_i is the number of instances of reactant R_i consumed by the reaction, and each n_i is the number of instances of product P_i produced by the reaction. For a particular choice of m_i reactants of species R_1, m_2 reactants of type R_2 , and so on, the probability that they react according to (2) in an infinitesimal time interval dt is ρdt and ρ is sometimes called the stochastic rate constant. Mass-action kinetics is based on the assumption that the likelihood of reaction (2) occurring during a small time interval dt is ρdt multiplied by the number of ways of choosing the reactants. There are two main ways of modeling systems governed by mass-action kinetics. The more traditional method uses ordinary differential equations to approximate the changes in population sizes. While this approach has the benefits mentioned above, it

ignores the fundamental discrete and stochastic nature of the reactions, and this can be important, especially for smaller population sizes that are frequently seen in biological systems.

Each simulation is a trajectory of a CTMC, which is a sequence of computations of the underlying transition system. The CTMC trajectory imposes a total order on the transitions of the simulation trajectory that is emphasized by the unique time stamps of the individual transition instances. In this respect, a simulation on a model can be seen as reduction of a complex structure, i.e., the model, into a simpler structure, i.e., the simulation trajectory. However, during this reduction some of the information on the model is lost, and some is made implicit. The idea here is to recover this implicit information, when these transitions are inspected from the point of view of their dependencies on one another, it is possible to relax the total order of the transitions into a partial order structure. We can then use this partial order as a representation of causal dependencies in the simulation and process it to observe the flux in the system with respect to the flow of the resource.

For a reaction occurring in an isothermal and isobaric system the chemical driving force ΔG the Gibbs free energy difference which characterizes how far a chemical reaction is away from equilibrium. If we take a simple bimolecular reaction in a dilute solution $A + B \rightleftharpoons C + D$ as an example, then ΔG is related to the concentrations of the reactants and products, as well as the equilibrium constant K_{eq} , through the well-known thermodynamic equation

$$\Delta G = -RT \ln ([A][B] K_{eq} / [C][D]) \quad (2)$$

If we further assume that the law of mass action governs the reaction's kinetics, then the forward and reverse reaction fluxes and equilibrium constant are

$$J^+ = k_{+1} [A][B], J^- = K_{-1} [C][D] \text{ then } K_{eq} = k_{+1} / K_{-1} \quad (3)$$

where k_{+1} and K_{-1} are constants that do not depend on the concentrations. Combining Equations (2) and (3) yields

$$\Delta G = -RT \ln (J^+ / J^-) \quad (4)$$

Expressing ΔG in terms of Equation (4) has many advantages as it is apparent that if $\Delta G = 0$, then $J^+ = J^-$. This equilibrium relationship is required by the principle of detailed balance, which states that at equilibrium the forward and reverse fluxes are equal for all existing independent mechanisms for the reaction $A \rightleftharpoons B$. Furthermore, Equation (4) can be generalized to many other situations. For example, for reversible enzyme reactions governed by Michaelis-Menten kinetics, although both J^+ and J^- are complex, nonlinear functions of reactant and substrate concentrations, Equation (4) still holds true.

Another nontrivial example of Equation (4) that arises in cycle kinetics in unimolecular systems is due to T.L. Hill. As in the example above, the law of mass action is assumed in all of Hill's work. The novelty of this note is to show a wide range of validity of Equation (4) based solely on conservation of mass, without invoking any assumptions of rate laws such as Equation (3). Hence, Equation (4) is in fact a fundamental relation for any chemical process operating in steady, open-system state. The relation is also intimately related to the fluctuation theorem. However, the most significant insight from the present work is that the relation between one-way-fluxes and G can be established without any supposition on the dynamics of a system. For the case of a catalytic cycle with J^+ / J^- equal to the ratio of the forward-to-reverse cycle flux and ΔG equal to the thermodynamic driving force for the cycle, Equation (4) is identical to the relationship introduced by Hill and proved by Kohler and Vollmerhaus [21] and by Qian *et al.* [1] for cycles in Markov systems. Therefore the relationship between J^+ / J^- and ΔG introduced by Hill for linear cycle kinetics is a special case of Equation (4).

The Markov chain ξ generates an infinite sequence of cycles where the cycles are the circuits represented as C . The weight w_c is the mean number of occurrences of the cycle c along almost all the sample paths of ξ . [8] provided a survey of all principle trends to cycle representation theory of Markov processes which is devoted to the study of inter connections between edge co-ordinates and the cycle-coordinates along with the corresponding implications for the study of stochastic properties of the processes. Also [1] developed the cycle representations

in terms of the entropy production, detailed balance etc. If the diagram method is translated into the language of Markov chain, the Hill's cycle weights. The detailed balance corresponds to the reversibility of the Markov chain ξ .

The probabilistic cycle representation expresses the relations between the edge coordinates $\pi_i, P_{ij}, i, j \in S$ and the cycle coordinates $w_e, e \in C_\infty$ in the sample-path-behavioral approach.

The finite or the denumerable Markov chains can be generated by the weighted circuits also. Consider a finite collection C of overlapping circuits in the state space S . Suppose that all points of S can be reached from one another following path of circuit edges. By associating the number w_e with each $e \in C$ define

$$w(i, j) = \sum_{e \in C} w_e J_e(i, j) \quad \forall i, j \in S$$

and

$$w(i) = \sum_{e \in C} w_e J_e(i) \quad \forall i \in S$$

Then define detailed balance for the Markov chain ξ as

$$\pi_i P_{ij} = \pi_j P_{ji} \quad \forall i, j \in S.$$

Also (5)

then (5) is called the probabilistic (circuit) cycle representation of and is also called as a circuit chain. Periodic motion in a stochastic (noisy) system is

$$\frac{r_0(x \rightarrow x', y)}{r_0(x \rightarrow x, y)} = \exp[-\beta \Delta G] \quad (6)$$

with ΔG as the Gibbs free energy. The concentrations of the various reactants (or, the equilibrium chemical potentials) are then obtained by differentiating G with respect to the x . Stationary non equilibrium is installed when the environment maintains a different chemical potential; the concentration of ATP can be much larger than its equilibrium value. For a particle exchange between the motor and the environment the transition rates will pick up a dependence on, the ATP concentration. It is proved that the non equilibrium transition rates are obtained by associating with each state i an energy G_i and we assume the transition rates

$r(i, j)$ and $r(j, i)$ between two such states i and j to satisfy

$$\frac{r(i, j)}{r(j, i)} = \Phi(i, j) e^{\beta(G_i - G_j)} \quad (7)$$

where β is the inverse temperature and $\Phi F(i, j) = 1/\Phi(j, i)$ will break the detailed balance condition as a consequence of the driving mechanism via the gradient in chemical potential, possibly counteracted by some external load. The above equation can be solved by the choice with μ_{ij} the chemical potential

$$r(i, j) = \frac{w_{ij} e^{\beta \mu_{ij}}}{1 + e^{\beta [\lambda_{ij} - U_{ij}]}} \quad (8)$$

of some substance α involved in the transition from state i to state j . The difference in energy is in the exponential $F_{\lambda_{ij}} - U_{ij}$ with $U_{ij} = G_i - G_j$, the free energy difference between state i and state j without load. $F_{\lambda_{ij}} = \vec{F} \cdot \vec{\lambda}_{ij}$ is the product of an external load acting from state j to state i over "distance" $\vec{\lambda}_{ij} = \vec{\lambda}_i$. Since in the motility cycle the whole configuration has shifted over the stepping distance (8 nm) we demand that $\sum_{\text{cycle}} \lambda_{ij} = \lambda$ and is further parameterized by $w_{ij} = w_{ji}$. We call w_{ij} the characteristic frequency of transition (i, j) . It can possibly be seen as a measure of the friction of the transition and may still depend on the applied load F due to some conformational change inside the kinesin head. By the symmetry $i \leftrightarrow j$, it cannot have a definite influence on the non equilibrium features of the motion. Comparing (8) with (7) we have

$$\Phi(i, j) = e^{-\beta [F \lambda_{ij} - \mu_{ij} + \mu_{ji}]} \quad (9)$$

and (8) solves (6) in equilibrium.

III. ENTROPY PRODUCTION IN KINESIN

The probability to find the system in state i at time t satisfy the Master equation

$$\frac{d\rho_t(i)}{dt} = \sum_{j \in \Omega} [r(j, i) \rho_t(j) - r(i, j) \rho_t(i)] \quad (10)$$

when $\rho_t(i) = \rho(i)$ is no longer varying with time the processes is Stationary. The model describes a non

equilibrium steady state when (9) vanishes without each term in the sum being zero. We can associate a mean entropy production rate (MEP) to it [11] as

$$MEP = \sum_{i,j} \rho(i) r(i,j) \log \frac{r(1,j)}{r(j,i)} \quad (11)$$

MEP is always non-negative and it is zero if and only if $\rho(i) r(i,j) = \rho(j) r(j,i)$ which is the detailed balance. The “current” $J_{ij}(t_1, t_2)$ over a time-interval $[t_1, t_2]$ between any two different states i and j is the random variable

$$J_{ij}(t_1, t_2) = N_{ij}(t_1, t_2) - N_{ji}(t_1, t_2) \quad (12)$$

with $N_{ij}(t_1, t_2)$ the number of transitions in (t_1, t_2) from state i to state j . When sampled over a large time-interval, we get its mean, the stationary current

$$J_{ij} = \rho(i) r(i,j) - \rho(j) r(j,i) \quad (13)$$

and another way to write the entropy production rate is

$$MEP = \frac{1}{2} \sum_{i,j} J_{ij} A_{ij} \quad (14)$$

with $A_{ij} = \log(r(i,j)/r(j,i))$ the thermodynamic force by which the system is driven away from equilibrium. Most interesting are the currents associated with the power stroke, from which the velocity and the possible dependence on load and the ATP concentration are obtained. In the same manner, since motor functioning can hardly be imagined without a cyclic component, we are concerned with Markov chains that are at least partially cyclic. We call a Markov chain as monocyclic if we can write $\Omega = \{1, 2, \dots, n\}$ and $r(i,j) = 0$ unless $i = j \pm 1$ (with the convention that $n+1 = 1$). For a monocyclic Markov chain the currents satisfy $J_{ij} = J - J_{ji}$ when $j = i+1$ and are zero otherwise. Using (4) in (10), it is easy to verify that the mean entropy production rate takes the explicit form

$$MEP = J \beta [\Delta \mu - F \lambda] \quad (15)$$

$$\text{where } \Delta \mu = \sum_{i=1}^n [\mu_{i,i+1} - \mu_{i+1,i}] \quad \text{and}$$

$$\lambda = \sum_{i=1}^n \lambda_{i,i+1}. \quad \text{We have taken the positive direction}$$

of the current opposite to that of the load. It is therefore natural to say that the stall force F_{stall} , the load at which the mean entropy production vanishes, satisfies

$$F_{\text{stall}} = \frac{\Delta \mu}{\lambda} \quad (16). \quad \text{While this monocyclic (sometimes}$$

also called linear) architecture most conveniently expresses the motion of a motor, in reality, various rate limiting steps can break the exact order of steps. Nevertheless formulae (9) and (10) remain valid if the transition rates satisfy a local detailed balance equation as in (7) with no bias or driving over internal loops except over the main motility cycle where the current is J . [27] For the case of a catalytic cycle with J^+/J^- equal to the ratio of the forward-to-reverse cycle flux and ΔG equal to the thermodynamic driving force for the cycle, Equation

$\Delta G = -RT \ln J^+/J^-$ is identical to the relationship introduced by Hill [13].

IV. CYCLES AND FLUXES

In the steady state of the model, the rate at which the transition $i \rightarrow j$ occurs is $w_{ij} p_i$, and the net transition flux along each transition is $J_{ij} = w_{ij} p_j - w_{ji} p_i = -J_{ji}$. From the master equation for the steady state, the equations for the transition fluxes into each state $\partial_t p_i(t) = 0 = \sum_{j \neq i} (w_{ij} p_j(t) - w_{ji} p_i(t)) = \sum_{j \neq i} \Delta J_{ij}$. The transition fluxes are in general not independent, but can be expressed in terms of cycle fluxes, probability currents flowing around the closed loops in the kinetic diagram. The cycles fluxes, J_C , are functions of the rate constants, and take the general form [16].

$$J_C = (\Pi C_+ - \Pi C_-) \frac{\sum c}{\Sigma} = J_{C_+} - J_{C_-},$$

$$J_{C_{\pm}} = \Pi C_{\pm} \frac{\sum c}{\Sigma}$$

Here $\sum c$ and Σ are complicated polynomials in the transition rates, C is the cycle index, and C is the product of rate constants around the cycle in the positive or negative direction. The directed cycle fluxes $J_{C_{\pm}}$ are interpreted as forward and backward components of the net cycle flux. To complete the decomposition, two more steps are needed. First, the transition fluxes can be expressed in terms of the cycle fluxes [16]

$$\Delta J_{ij} = \sum_{C \in ij} \varepsilon_{ij} C (J_{C+} - J_{C-}) \text{ where, } \varepsilon_{ij}, C = \pm 1$$

takes care of the sign, depending on in which direction the cycle C passes through the transition ij . Secondly, it is necessary to show that the directed cycle fluxes $J_{C\pm}$ really correspond to actual fluxes, i.e., describe the average frequencies of forward and backward cycle completions. The direction of each cycle flux depends on the dissipated free energy associated with the cycle.

$$\frac{J_{C+}}{J_{C-}} = \frac{\prod C+}{\prod C-} = e^{-\Delta G(C+)/RT}. \text{ Hence, it is}$$

understood that the steady state as a competition between the different cycle fluxes in the kinetic diagram. The relative magnitudes of the forward and backward component of the cycle flux are given by the dissipated free energy associated with that cycle. However, the relative magnitudes of fluxes around different loops depend in a non-trivial way on the individual rate constants. The mean steady-state one-way cycle fluxes, calculated from the diagram method are correct as long-time averages but, in general, are not valid as cycle rate constants at the detailed cycle-by-cycle level. The main ingredients of this more detailed examination of one-way cycle fluxes is based on the beginning state ν for each cycle, $J_{\nu\eta}$ and \vec{t}^{ν} and F_{ν} . The self-consistency relations with the more conventional long-time averages J_n and \vec{t} are easily seen to be

$$\vec{t} = F_1 \vec{t}^1 + F_2 \vec{t}^2 + F_3 \vec{t}^3$$

$$J_n = (F_1 \vec{t}^1 / \vec{t}) J_{n1} + (F_2 \vec{t}^2 / \vec{t}) J_{n2} + (F_3 \vec{t}^3 / \vec{t}) J_{n3}$$

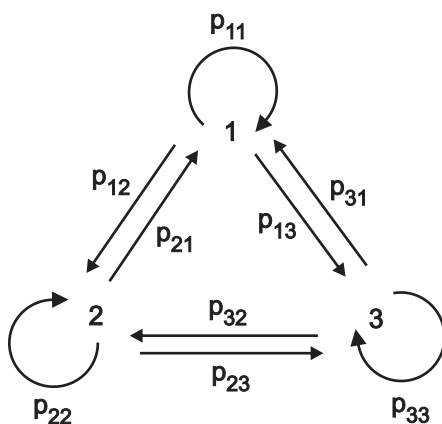


Fig. 1. Discrete-time diagram used to find the fraction of cycles F that begin from each state ν .

The cycle fluxes are subdivided into one-way cycle fluxes. These in turn are subdivided further according to their origin. (Based on the value of ν). The state probabilities and the fluxes are easily calculated based on these cycles.

In addition to application to chemical reactions, Equation (4) is directly applied to transport processes.

For example, one-dimensional transport of particles in a complex medium is governed by a Fokker-

Planck equation with spatially dependent diffusion coefficient $D(x)$ and potential function $u(x)$

$$\frac{\partial c(x, t)}{\partial t} = \frac{\partial}{\partial x} \left(\frac{D}{RT} C \frac{\partial u}{\partial x} + D \frac{\partial c}{\partial x} \right) \text{ over the domain } 0 \leq x \leq 1.$$

V. CONCLUSIONS

A living environment provides a continuous chemical energy input that sustains the reaction system in a nonequilibrium steady state with concentration fluctuations. Deterministic, nonlinear mathematical models usually based on the law of mass action have been traditionally used for modelling biological systems while nowadays stochastic fluctuations observed in most living organisms. Energy may play an important role in biological information processing and biochemical signal transduction. In biochemical reactions involved in signaling, high-grade chemical energy is reduced to low-grade heat. The energy involved in processing information must be explained in terms of entropy production, the central concept in non equilibrium steady-state (NESS) thermodynamics. This paper analyses this non equilibrium steady states of a Continuous Time Markov Chain in terms of cyclic fluxes.

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