Journal of Theoretical Biology 400 (2016) 129–137

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Simplification of irreversible Markov chains by removal of states with fast leaving rates

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HIGHLIGHTS

- We provide a simple technique to simplify irreversible Markov chains with a large state space.
- We provide several equivalent formulas to calculate the generator matrix and initial distribution of the effective chain.
- We study the effects of the initial distribution on model simplification.
- We study the relationship between model simplification and irreversibility.
- The technique is illustrated by several examples from biology.

ARTICLE INFO

Article history:
Received 26 December 2015
Received in revised form
26 February 2016
Accepted 2 April 2016
Available online 9 April 2016

Keywords:
Model reduction
Time scale
Fast state
Entropy production rate
Reversibility

ABSTRACT

In the recent work of Ullah et al. (2012a), the authors developed an effective method to simplify reversible Markov chains by removal of states with low equilibrium occupancies. In this paper, we extend this result to irreversible Markov chains. We show that an irreversible chain can be simplified by removal of states with fast leaving rates. Moreover, we reveal that the irreversibility of the chain will always decrease after model simplification. This suggests that although model simplification can retain almost all the dynamic information of the chain, it will lose some thermodynamic information as a trade-off. Examples from biology are also given to illustrate the main results of this paper.

1. Introduction

Markov chains are widely used to model various stochastic biochemical systems, such as chemical reaction networks (Kurtz, 1972), single-molecule enzyme kinetics (Qian and Elson, 2002), allostery of proteins and ion channels (Sakmann, 1995), and phenotypic switching of cell populations (Gupta et al., 2011). In practice, it often occurs that the Markov model of a biochemical system has a large number of states. This raises a natural question of whether we can simplify a Markov model to a simpler but effective one that will lose very little dynamic and thermodynamic information of the original model.

The simplification of Markov models is of crucial importance in many applications. It not only helps us gain a clearer understanding of the dynamic properties of the system, but also allows us to perform a deeper theoretical analysis on the model. In addition, there is another important advantage of model simplification. In practical biological problems, we often need to fit experimental data with a Markov model and hope to obtain a robust estimation of all the model parameters. This enables us to explain experimental phenomena and make model predictions to guide the designs of future experiments. However, if the state space of the Markov model is too large, there will be a huge number of model parameters so that none of them could be estimated robustly from experimental data. For example, Markov chains and hidden Markov chains play an important role in deriving the possible side effects of biological therapies. In this case, the presence of a large number of states and the resulting large number of fitting parameters may seriously weaken the approach (Wallis et al., 2004; Agliari et al., 2013). Thus an effective simplification approach will improve the statistical significance of data fitting to a large extent.

So far, the simplification techniques of Markov chains have been studied by many authors. Most of these approaches are based

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http://dx.doi.org/10.1016/j.jtbi.2016.04.003
0022-5193/

on the fact that the state transitions of Markov chains possess multiple different time scales. In applications, state aggregation is perhaps the most straightforward way to deal with Markov chains with a large state space when some states have relatively fast transition rates between them (Stewart, 1994). This idea has been recently developed into a rigorous mathematical theory based on the model of singularly perturbed Markov chains (Yin and Zhang, 2012). The spectral method has become popular for aggregating states in numerical computations (Huisinga et al., 2004). However, the requirement to compute the eigenvectors of the generator matrix of a very large Markov chain makes this method difficult to be carried out.

Recently, Ullah et al. (2012a) developed a simpler but effective method to simplify reversible Markov chains. Their idea is to identify those states that have relatively low probability to be occupied, which add unnecessary complexity to a Markov chain. They found that it is possible to simplify a reversible chain by removal of states with low equilibrium occupancies. Furthermore, they pointed out that a reversible chain is equivalent to a resistor-capacitor (RC) circuit and the procedures to discard the low-occupancy states from a reversible chain is equivalent to the steps to remove the capacitors with low capacitance from an RC circuit.

For a reversible chain, it is easy to calculate the equilibrium occupancies of all states and carry out further theoretical analysis. That is why Ullah et al. 2012a focuses on the simplification of reversible chains. However, recent studies on nonequilibrium statistical mechanics show that a reversible chain can only describe a thermodynamic equilibrium state in which the system does not consume energy (Seifert, 2012; Zhang et al., 2012). However, as Schrödinger pointed out in his famous book "What is life?" (Schrodinger, 1944), a thermodynamic equilibrium state can only be the "death state" of a living system and the reason why a living system has ordered structures and functions is because the system constantly exchanges materials and energy with its environment. In order to realize a particular biological function, a biochemical system usually exists in a nonequilibrium steady state that should be modeled as an irreversible Markov chain (Seifert, 2012; Zhang et al., 2012).

Now that nonequilibrium steady states are of fundamental importance in living systems, it is natural to ask whether a similar approach can be established to simplify irreversible Markov chains, which is the main subject of this paper. It turns out that the low-occupancy states for reversible chains correspond to the states with fast leaving rates for irreversible chains. We show that an irreversible chain can be simplified to an effective chain by removal of those fast states. Moreover, we provide several equivalent formulas to calculate the generator matrix and initial distribution of the effective chain.

We next study the effects of the initial distribution on model simplification. We find that if the original chain starts from a slow state, then the probability distributions of the original and effective chains will agree with each other over the whole time axis. However, if the original chain starts from a fast state, then model simplification may cause large errors within a very short time, but the probability distributions of the two chains will coincide with each other afterwards.

Inspired by the simplification approach for reversible chains (Ullah et al., 2012a), we find that the transition rates of the effective chain can be obtained by a series of transformations which is different but similar to the so-called $Y-\Delta$ transformations in the circuit theory (Akers, 1960). By parameterizing the original transition rates with steady-state occupancies and fluxes, we show that our formula for the effective transition rates reduces to the formula given in Ullah et al. (2012a) when the original chain is reversible. This shows that the simplification technique for reversible chains proposed in Ullah et al. (2012a) is a special case of our approach.

In addition, we also discuss the connection between model simplification and irreversibility. We reinforce the previous discovery that the effective chain of a reversible chain must be also reversible (Ullah et al., 2012a). Furthermore, we reveal that the entropy production rate, as a characterization of irreversibility, of a Markov chain will always decrease after the fast states are removed. This shows that although model simplification can retain almost all the dynamic information of the Markov chain, it will lose some thermodynamic information as a trade-off.

Finally, we use three specific biological examples that we think might be of general interest to illustrate the main results of this paper. It turns out that our simplification technique can introduce nontrivial ligand dependence into the transition rates of the effective model.

2. Model

Markov chains provide an effective way to model various stochastic biochemical systems in living cells. In this paper, we consider a biochemical system modeled by a continuous-time Markov chain with generator matrix $Q=(q_{ij})$, where q_{ij} with $i\neq j$ denotes the transition rate from state i to j and $q_{ii}=-\sum_{j\neq i}q_{ij}$. We assume that the system can exist in N different states, denoted by $1, \ldots, N$. Let $p(t)=(p_1(t), \ldots, p_N(t))$ denote the probability distribution of the system at time t. Then the dynamics of the system is governed by the master equation

$$\begin{cases} \dot{p}(t)=p(t)Q, \\ p(0)=\pi, \end{cases} \tag{1}$$

where $\pi=(\pi_1, \ldots, \pi_N)$ is the initial distribution of the system.

Following standard notations, let $q_i=-q_{ii}=\sum_{j\neq i}q_{ij}$ denote the rate at which the system leaves state i. In practice, it often occurs that some states of the system have relatively fast leaving rates compared to other states. In this case, the state transitions of the system will have two separate time scales.

We next introduce a definition that will be used frequently in the sequel. If state i has a relatively fast leaving rate q_i compared to other states, then i is referred to as a fast state. Otherwise, i is called a slow state. Intuitively, the probability distribution of a fast state will change very fast and that of a slow state will change very slowly.

3. Results

3.1. Simplification of general Markov chains

If i is a fast state, then its leaving rate q_i will be very fast and thus the time that the system stays in state i will be very short. Intuitively, we may except that the system could be simplified by removal those fast states. Here, we shall use the method of averaging to achieve this aim.

Let A denote the set of all the slow states and let B denote that of all the fast states. We assume that the system has M fast states and $N-M$ slows states. By relabeling the states, we can always assume that $A=\{1, \ldots, N-M\}$ and $B=\{N-M+1, \ldots, N\}$. Thus the probability distribution $p(t)$ can be represented as a block vector $p(t)=(p_A(t), p_B(t))$ and the generator matrix Q can be represented as a block matrix

$$Q=\begin{pmatrix} Q_{AA} & Q_{AB} \\ Q_{BA} & Q_{BB} \end{pmatrix}.$$