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Maximum Path-Entropy Analysis of Aggregated Markov Models

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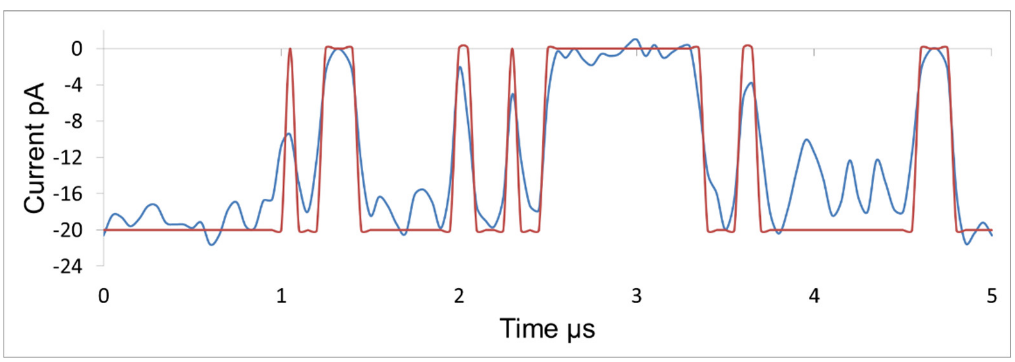
Introduction

The principle of maximum path-entropy, which is also known as the principle of maximum caliber, is a generalization of the principle of maximum entropy to systems not necessarily close to equilibrium [1,2]. The principle of maximum path-entropy has recently been used to derive dynamical laws of transport, analyze single particle two-state dynamics, study few-state models of non-equilibrium processes, analyze the dynamics and fluctuations in biochemical reactions and cycles, and analyze ion-channel gating [3-7]. It has been shown that when a system such as an ion channel is modeled using an aggregated Markov model, methods that use steady-state gating statistics can typically find several models with different topologies that fit the data equally well [8]. We explore the use of the principle of maximum path-entropy to distinguish between different aggregated Markov models that all fit the steady-state gating data but have different topologies.

Ion Channel Gating

An Ion channel is a membrane protein that can be open, letting a particular species of ion pass through, or closed, blocking the passage of ions. The gating can respond to external voltage, solute concentration, pressure, ligand interactions, etc.



5 microseconds of patch-clamp data for an inositol trisphosphate receptor [9]

$$C_1 \underset{P_{12}}{\overset{P_{21}}{\leftrightharpoons}} O_2$$

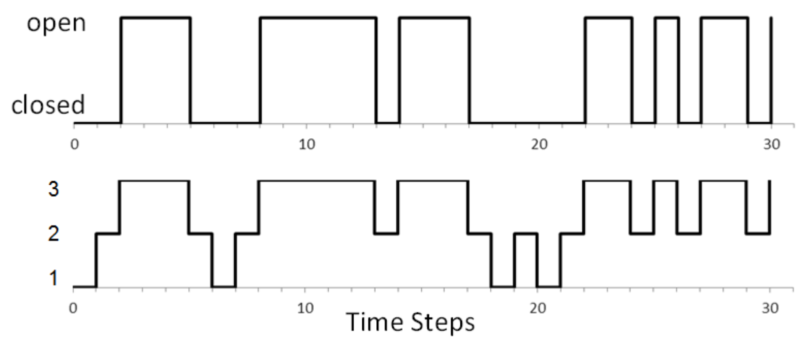
The above graph represents a simple two-state Markov model of an ion channel. State C_1 is a closed state, state O_2 is an open state and P_{ij} is the probability that the ion channel will make a transition from state i to state j in a time interval Δt.

Aggregated States

Markov models of ion channels usually have more than one closed state and one open state. Consider an ion-channel model represented by the following graph.

$$C_1 \underset{q_{12}}{\overset{q_{21}}{\leftrightharpoons}} C_2 \underset{q_{23}}{\overset{q_{32}}{\leftrightharpoons}} O_3$$

In this simple model there are two closed states, one open state, and transitions between states 1 and 3 are not allowed. In general, if Markov model states can have the same observable output they are called hidden states and if there is only one possible output for a state they are called aggregated states. So states 1 and 2 are aggregated states.



The above is a plot of a three-state trajectory showing a time sequence of transitions between states 1, 2, and 3 and the corresponding sequence of open and closed transitions.

Equivalent Models

Consider the two models:

Model CCO

$$C_1 \underset{q_{12}}{\overset{q_{21}}{\leftrightharpoons}} C_2 \underset{q_{23}}{\overset{q_{32}}{\leftrightharpoons}} O_3 \qquad Q^{CCO} = \begin{bmatrix} q_{11} & q_{12} & 0 \\ q_{21} & q_{22} & q_{23} \\ 0 & q_{32} & q_{33} \end{bmatrix}$$

Model COC

$$C_1 \underset{q_{13}}{\overset{q_{31}}{\leftrightharpoons}} O_3 \underset{q_{32}}{\overset{q_{23}}{\leftrightharpoons}} C_2 \qquad Q^{COC} = \begin{bmatrix} q_{11} & 0 & q_{13} \\ 0 & q_{22} & q_{23} \\ q_{31} & q_{32} & q_{33} \end{bmatrix}$$

If Q^{CCO} is the transition rate matrix for the first model and Q^{COC} is the rate matrix for the second model. Kienker [8] derived a similarity transformation such that if

$$Q^{COC} = S^{-1} Q^{CCO} S$$

then both rate matrices give the same steady state open-time and closed-time distributions. In the sense that the steady-state distributions cannot be used to choose one model over the other, the models are said to be equivalent.

Principle of Maximum Path Entropy

Let p_Γ be the probability that the system follows path Γ, where Γ is a time sequence of states. To calculate the least biased probability distribution from observables we maximize the path entropy

$$C = -\sum_\Gamma p_\Gamma \log(p_\Gamma)$$

subject to the constraints

$$\sum_\Gamma p_\Gamma = 1 \quad \text{and} \quad \sum_\Gamma p_\Gamma A_{m\Gamma} = \langle A_m \rangle$$

where the $\langle A_m \rangle$'s are known expectation values and are observables.

A dynamical partition function for trajectories of length T (= N·t) can be defined

$$Z_d(T) = \sum_\Gamma \exp(\sum_m \lambda_m A_{m\Gamma})$$

where the λ_m's are the Lagrange multipliers associated with the constrained maximization of C. Expectation values can be calculated from Z_d .

$$\langle A_m \rangle = \frac{1}{Z_d}\frac{\partial Z_d}{\partial \lambda_m}$$

Transients

The principle of maximum path-entropy does not assume equilibrium or steady-state behavior and provides a general method of inference for non-equilibrium processes. [6] We now consider the question of whether or not the principle of maximum path-entropy can be used to distinguish between models which are equivalent – in the sense that they give the same steady-state open and closed time distributions – by applying it to the transient behavior of the model.

An Example

For a sufficiently small-time step, Kienker's transformation can be applied to the probability matrix for finite time step Markov models.

$$P^{CCO} = \begin{bmatrix} p_{11} & p_{12} & 0 \\ p_{21} & p_{22} & p_{23} \\ 0 & p_{32} & p_{33} \end{bmatrix}$$

where p_{ij} is the probability that a transition from state i to state j occurs in time step Δt.

Consider the specific probability matrix for the CCO model.

$$P^{CCO} = \begin{bmatrix} 0.6 & 0.4 & 0 \\ 0.2 & 0.5 & 0.3 \\ 0 & 0.3 & 0.7 \end{bmatrix}$$

By applying Kienker's transformation, we get the probability matrix for the equivalent COC model

$$P^{COC} = \begin{bmatrix} 0.2628 & 0 & 0.7372 \\ 0 & 0.8372 & 0.1628 \\ 0.0717 & 0.2283 & 0.7 \end{bmatrix}$$

Following Stock, et.al [4] we can write the partition function for a three-state model in when the path length is N time steps and the initial state is state 3 (the open state) as

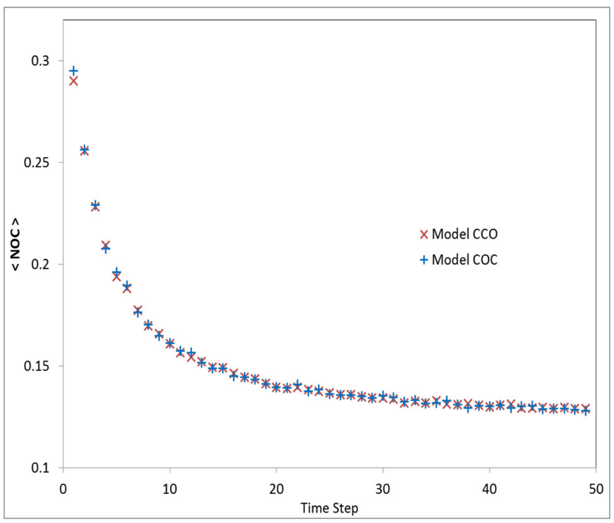
$$Z_d(N) = (1\ 1\ 1)(P)^N \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$$

For the CCO model

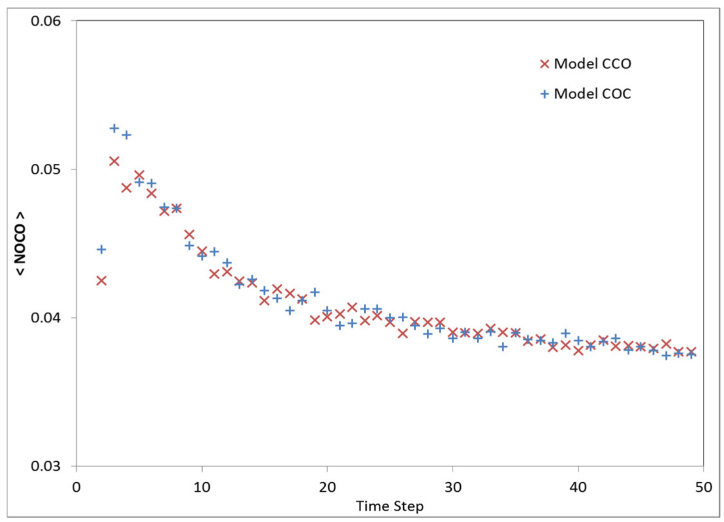
$$\langle N_{OC} \rangle = \frac{1}{Z_d} \frac{\partial Z_d}{\partial \lambda_{32}}$$

where $\lambda_{32} = \ln(P_{32})$.

Results



The average number of O to C, open to closed transitions, per time step when the initial state is open using the example probability matrix.



The average number of O to C to O transitions per time step when the initial state is the open state using the example probability matrix.

Conclusions

As illustrated in the above figures, not only is the steady-state behavior of the CCO model and the COC model the same when the COC model parameters are calculated using Kienker's transformation, but the transient behavior is also the same. Therefore, even though Kienker's transformation was derived using the steady-state properties and principle of maximum path-entropy applies when the system is not in a steady state, the principle of maximum path-entropy cannot be used to distinguish between equivalent aggregated states.

References

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