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Maximum Caliber Analysis of Ion-Channel Gating

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Introduction

The principle of maximum caliber, MaxCal, is a generalization to nonequilibrium statistical mechanics of the principle of maximum entropy, MaxEnt. E. T. Jaynes introduced the MaxEnt approach to equilibrium statistical mechanics in 1957 [1] and its MaxCal generalization in 1980 [2]. MaxCal has recently been used to derive dynamical laws of transport, analyze single particle two-state dynamics, and study few state models of non-equilibrium processes. [3 – 7] We use MaxCal to analyze hidden Markov models of ion-channel gating and make logical inferences concerning the underlying dynamics. MaxCal is used to determine model parameters; test the adequacy of a model; and predict unmeasured quantities from the trajectory probability distribution.

The Principle of Maximum Caliber

The principle of maximum caliber is to non-equilibrium systems as the principle of maximum entropy is to equilibrium systems.

Equilibrium Principle of Maximum Entropy	Non-Equilibrium Principle of Maximum Caliber
Let p_i be the probability that the system is in state i.	Let p_Γ be the probability that the system follows trajectory Γ, where a trajectory is a time sequence of states
Maximize the entropy	Maximize the caliber
$S = -k_B \sum_i p_i \log(p_i)$	$C = -k_B \sum_\Gamma p_\Gamma \log(p_\Gamma)$
subject to the constraints	subject to the constraints
$\sum_i p_i = 1$	$\sum_\Gamma p_\Gamma = 1$
$\langle A_m \rangle = \sum_i p_i A_{mi}$	$\langle A_m(t) \rangle = \sum_\Gamma p_\Gamma A_{m\Gamma}(t)$
where the $\langle A_m \rangle' s$ are known expectation values.	where the $\langle A_m \rangle' s$ are known expectation values.

The probabilities can be used to determine unknown expectation values

$$\langle B_m \rangle = \sum_i p_i B_{mi}$$

The partition function

$$Z = \sum_i \exp(-\sum_m \lambda_m A_m)$$

where the λ's are Lagrange multipliers, can be used to calculate expectation values

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

The probabilities can be used to determine unknown expectation values

$$\langle B_m(t) \rangle = \sum_\Gamma p_i B_{m\Gamma}(t)$$

The dynamic partition function

$$Z_d(T) = \sum_i \exp(-\sum_m \int_0^T \lambda_m(t) A_{m\Gamma}(t)dt)$$

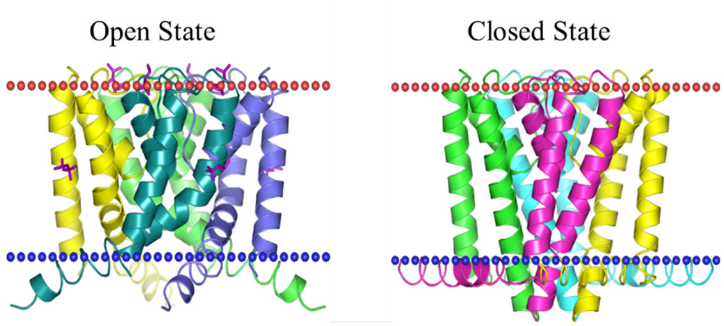
where the λ's are Lagrange multipliers, can be used to calculate expectation values

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

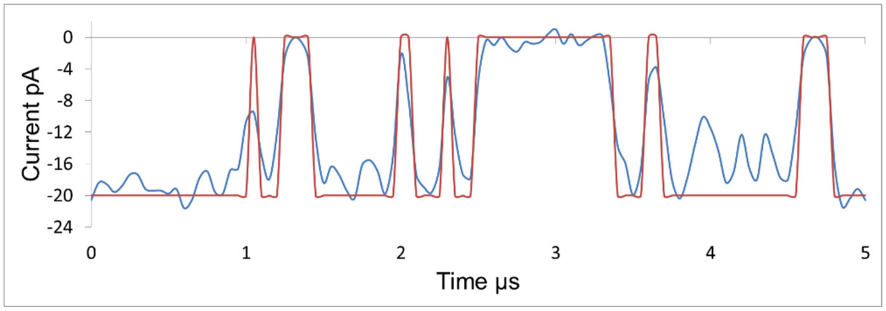
The probabilities calculated using the principle of maximum caliber are the least biased probabilities consistent with the constraints. Observed $\langle A_m \rangle's$ are used to make unbiased inferences concerning the values of the $\langle B_m \rangle's$. This point of view is faithful to the original spirit of the principle of maximum entropy put forward by Jaynes in 1957 [1].

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.



NaK potassium channel, (*Bacillus cereus)* [8]

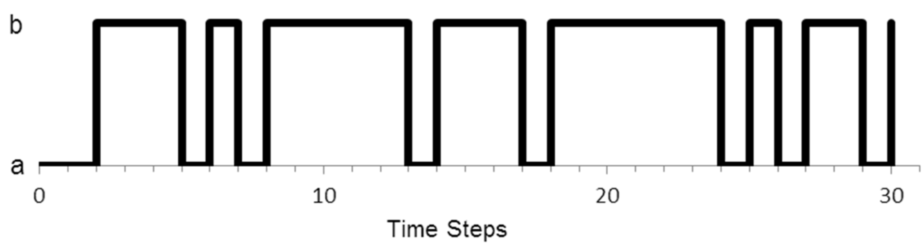


5 microseconds of patch-clamp data for an inositol triphosphate receptor [9]

Two-State Model

$$C_a \underset{\gamma_{ba}}{\overset{\gamma_{ab}}{\leftrightharpoons}} O_b$$

State a is a closed state, state b is an open state and γ_{ab} is a transition probability.



An example of a two-state trajectory.

The caliber for an N-step time interval is calculated by summing over all possible N-step trajectories. Observables such as the average number of closed state to open state transitions in N time steps, $\langle N_{10} \rangle$, can be measured using single channel gating data. These observables are used to constrain the trajectory probability distribution during the maximization of caliber. Following Ghosh et. al. [3], [4], [5], the partition function when the system is initially in state a can be written as

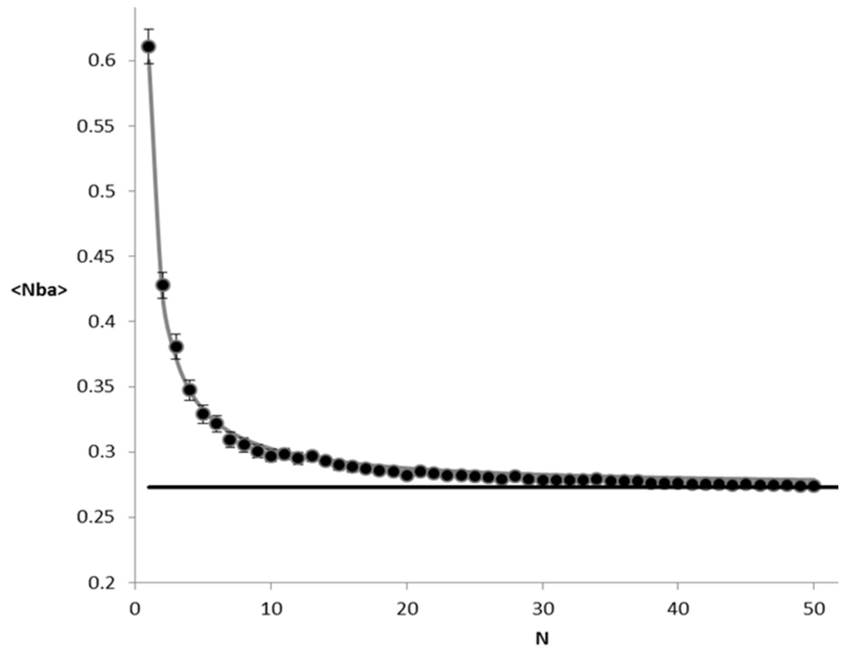
$$Z_a(N) = (1 \quad 1)\, G^N \begin{pmatrix} 1 \\ 0 \end{pmatrix}$$

where

$$G = \begin{bmatrix} \gamma_{aa} & \gamma_{ab} \\ \gamma_{ba} & \gamma_{bb} \end{bmatrix}$$

and N is the number of time steps in the trajectories.

Two-State Results

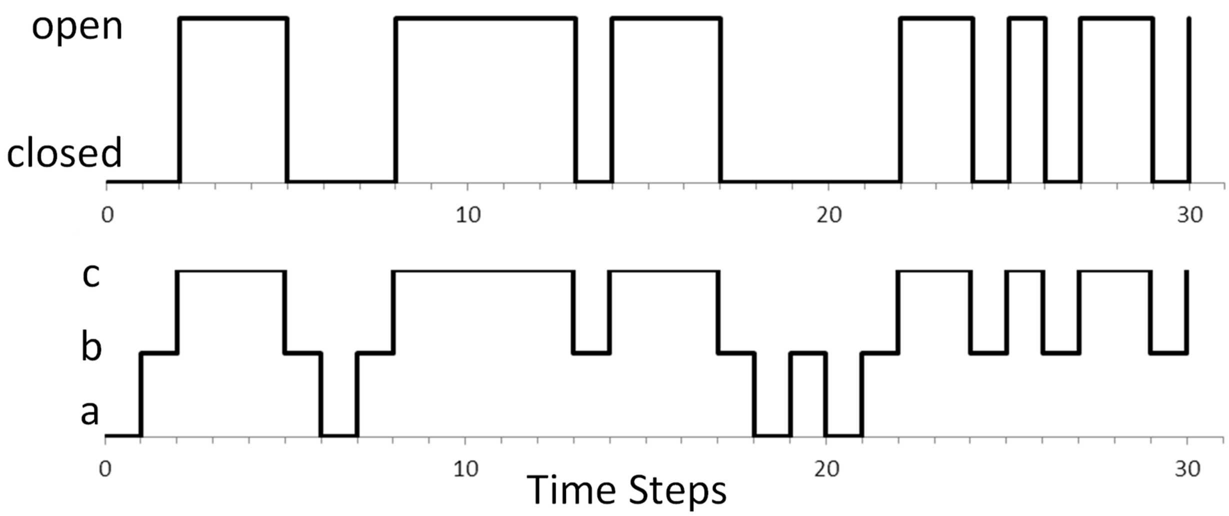


The expected fractional number of state a to state b transitions verses the number of time steps with $\gamma_{ab} = 0.5$, $\gamma_{ba} = 0.6$, and an initial state a. The solid line is the MaxCal prediction and the points are Monte Carlo simulation results.

Hidden States

$$C_a \underset{\gamma_{ba}}{\overset{\gamma_{ab}}{\leftrightharpoons}} C_b \underset{\gamma_{cb}}{\overset{\gamma_{bc}}{\leftrightharpoons}} O_c$$

In this simple model there are two closed states, one open state, and transitions between states a and c are not allowed. Since a closed channel can either be in state a or state b we call these hidden states. We solved the problem of applying MaxCal to a model with hidden states by considering multiple-time-step observables such as $\langle N_{000} \rangle$, the expected number of times the system will make a transition from a closed state to another closed state and then to another closed state.



A three-state trajectory showing a time sequence of transitions between states a, b and c and the corresponding sequence of open and closed transitions.

The partition function for this system can be written as

$$Z_d(N) = (1 \quad 1 \quad 1) G^N \begin{pmatrix} p_a \\ p_b \\ 0 \end{pmatrix} \qquad G = \begin{bmatrix} \gamma_{aa} & \gamma_{ab} & 0 \\ \gamma_{ba} & \gamma_{bb} & \gamma_{bc} \\ 0 & \gamma_{cb} & \gamma_{cc} \end{bmatrix}$$

where N is the number of time steps in a trajectory and p_a and p_b are the equilibrium occupation probabilities for states a and b when the system is initially in a closed state.

Hidden-State Results

The results of our analysis with

$$G = \begin{bmatrix} 0.7 & 0.2 & 0 \\ 0.3 & 0.5 & 0.3 \\ 0 & 0.3 & 0.7 \end{bmatrix}$$

are given in the table below. We first tried to analyze the simulated three-state data with a two-state model. The values of $\langle N_{10} \rangle$ and $\langle N_{01} \rangle$ were used to fix the parameters of the model then the observables $\langle N_{000} \rangle$ and $\langle N_{0001} \rangle$ were calculated. The disagreement between the actual values for these observables and the two-state model prediction is a flag that tells us that two states are not enough. When the correct number of states were used, MaxCal gave us the correct model parameters.

Observable	Simulation	Two-State Results	Three-State Model Results
$\langle N_{10} \rangle$	0.180 ± 0.001	0.180 ± 0.001	0.180
$\langle N_{01} \rangle$	0.300 ± 0.001	0.300 ± 0.001	0.300
$\langle N_{000} \rangle$	**0.694 ± 0.002**	**0.672 ± 0.001**	0.694
$\langle N_{0001} \rangle$	**0.166 ± 0.001**	**0.121 ± 0.001**	0.165

Observables calculated from the MaxCal analysis of simulated three-state data. Note the disagreements (bold).

Conclusions

For Markov models of Ion-channel gating, including hidden Markov models, the principle of maximum caliber can be used to:

1. determine model parameters,
2. test the adequacy of the model, (i.e. Do we need to add states?), and
3. predict unmeasured quantities from the trajectory probability distribution.

References

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