



# Computing rates of Markov models of voltage-gated ion channels by inverting partial differential equations governing the probability density functions of the conducting and non-conducting states



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## ABSTRACT

Markov models are ubiquitously used to represent the function of single ion channels. However, solving the inverse problem to construct a Markov model of single channel dynamics from bilayer or patch-clamp recordings remains challenging, particularly for channels involving complex gating processes. Methods for solving the inverse problem are generally based on data from voltage clamp measurements. Here, we describe an alternative approach to this problem based on measurements of voltage traces. The voltage traces define probability density functions of the functional states of an ion channel. These probability density functions can also be computed by solving a deterministic system of partial differential equations. The inversion is based on tuning the rates of the Markov models used in the deterministic system of partial differential equations such that the solution mimics the properties of the probability density function gathered from (pseudo) experimental data as well as possible. The optimization is done by defining a cost function to measure the difference between the deterministic solution and the solution based on experimental data. By evoking the properties of this function, it is possible to infer whether the rates of the Markov model are identifiable by our method. We present applications to Markov model well-known from the literature.

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## 1. Introduction

Numerous mechanisms in cells are fueled by the energy contained in concentration gradients that exist across the cell membrane. One such process is the electrical signaling that results from ionic fluxes carried by specialized membrane proteins, collectively termed ion channels. Cell membranes are densely populated by ion channels, which fluctuate between different states in a stochastic manner that depends on the charge difference across the membrane (the membrane potential). These fluctuations between the various states are commonly represented by continuous-time Markov models; see e.g. [1–4]. Markov models have been successfully used for half a century and offer great flexibility for precisely describing the functional states of a channel. Given the structure and rates of the Markov model, it is straightforward to use simu-

lations to study channel behavior. But the inverse problem, which seeks to infer the structure and rates of the Markov model from single-channel recordings, is much more challenging and remains a field of active research; see e.g. [5–9].

Single channel recording was first demonstrated in the seminal work by Sakmann and Neher; see [10,11]. Many of the principles used to deduce the form and rates of Markov models based on single channel data were developed by Colquhoun and Hawkes beginning almost forty years ago; see [12,13], and are classically summarized in chapter 18 of [14]. More recently, Qin et al. [15,16] developed maximum likelihood (MLE) approaches for defining the most probable hidden Markov model for a given dataset. These algorithms form the core of the open source QuB software package, which is available to the community, and contains tools for automated Markov model construction and parameterization; see Nicolai and Sachs [17]. Furthermore, Markov chain Monte Carlo (MCMC) fitting has been used to solve the inversion problem for models of intracellular calcium channels, which poses the same mathematical problem as the gating of voltage-dependent

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channels, see [6–9,18–20]. While both the MLE and MCMC approaches have been used to good effect, each has specific shortcomings [7], and a robust method for determining hidden Markov model structure from single-channel data remains a priority for the field.

The problem of identifiability of a model based on recordings of conducting and non-conducting states is of great importance and has been addressed by many authors. Characterizations of identifiable models and non-identifiable models have been provided by e.g. Fredkin and Rice [21] and more recently by Siekmann et al. [7] and Hines et al. [8]. These results, however, address the classical problem based on voltage clamped data and the results are therefore not automatically applicable to the case under consideration in the present paper.

Prior efforts to address the problem of identifying the rates of Markov models have been based on conventional experimental procedures for recording single-channel activity. That is, by fitting the binary changes in transmembrane current associated with channel opening and closure under conditions where transmembrane potential is clamped by the experimenter. The purpose of the present paper is to describe a fundamentally different approach, which involves an analysis procedure for defining a hidden Markov model from measurements of time-varying transmembrane potential in current clamped single ion channels. To the best of our knowledge, this is the first attempt to identify Markov models based on such voltage traces of single channel data. A similar approach has previously been applied for identification of Markov models from voltage recordings made in whole-cells; see e.g. Milesescu et al. [22]. Following the tradition in the field, we present the method using simulated data. It turns out that the methodology described here also enable us to address the question of identifiability. We demonstrate use of the method to compute rates of a Markov model and we will show to determine whether the computed rates are unique.

## 2. Methods

Our aim is to devise an alternative method for inverting Markov models. The inversion will be based on time-traces of the transmembrane potential of single ion-channels. The traces used in our analysis will be pseudo-experimental data generated by a dynamical model formulated in terms of an ordinary differential equation including a stochastic term. The stochastic term is governed by a Markov model with rate-functions expressing the probability of going from one state to another state. The inversion problem is to determine these rate-functions based on observations of recordings of the time-traces of the transmembrane potential.

By running numerous Monte Carlo simulations using the stochastic differential equation, we can compute probability density functions by gathering the simulation results in histograms. The same probability density functions can be computed by solving a deterministic system of partial differential equations, see e.g. Smith [2], Bressloff [3] or Tveito and Lines [4]. In this report we will use the simulation results based on the stochastic differential equations as pseudo-experimental data in terms of time-dependent voltage traces represented by histograms. The method of inversion is to adjust the parameters of the system of deterministic partial differential equation so that the solution of this system is as close as possible to the histograms representing pseudo-experimental data. The adjustment will be performed in term of minimizing a cost-function.

The method is described for Markov models of the potassium channel, but the method is quite general and can, in principle, be applied to Markov models of any ion channel.

### 2.1. Markov models

Let us first consider a Markov model on its simplest possible form;

$$C \xrightleftharpoons[\beta]{\alpha} O. \quad (1)$$

Here  $C$  and  $O$  denote the closed and open states, respectively. The rates  $\alpha$  and  $\beta$  represent the probability of leaving a state in the sense that, for a small time-step  $\Delta t$ , we have

$$\alpha \Delta t = \text{Prob}[S(t + \Delta t) = O \mid S(t) = C]$$

and

$$\beta \Delta t = \text{Prob}[S(t + \Delta t) = C \mid S(t) = O],$$

respectively. The problem of inversion for this simple model is to find the rates  $\alpha$  and  $\beta$  such that the Markov model represents the behavior of the model as good as possible. It is well-known that the probabilities  $o = o(t)$  and  $c = c(t)$  of being in the open ( $O$ ) or closed state ( $C$ ) evolve according to the following system of ordinary differential equations (see e.g. Keener and Sneyd [1]),

$$o' = \alpha c - \beta o,$$

$$c' = \beta o - \alpha c.$$

Since the sum of the probabilities add up to one, we can reduce this system to a single equation that is easily solved. Experimental data on probability of being in the open or closed state can thus be used to find determine the rates  $\alpha$  and  $\beta$ .

In principle this approach is straightforward to generalize to much more complex Markov models involving many states. Generally, the system of ordinary differential equations governing the vector  $v$  of probabilities of occupying different states is given by

$$p' = Ap.$$

Here, the matrix  $A$  contains the rates of the Markov model and the problem is to compute these rates. For a matrix with constant coefficients, the solution of this problem can, in principle, always be found on the form

$$p(t) = \exp(A)t p_0,$$

where  $p_0$  is the vector of probabilities at time  $t = 0$ . In principle, this formula can be used to deduce the rates of the Markov model, but severe difficulties arise due to inherent instabilities in the inversion process. This approach to inversion is based on experimental data with clamped transmembrane potential. Our method is based on data where the transmembrane potential is recorded.

### 2.2. Stochastic model of the transmembrane potential

For a single channel, with the initial condition  $v(0) = v^0$ , the dynamics of the transmembrane potential  $\bar{v}$  can be modeled as follows (see e.g. [2–4]),

$$C\bar{v}' = -\gamma g_K(\bar{v} - v_K) - g_S(\bar{v} - v_S) - I_0 \quad (2)$$

where  $C$  is the specific capacitance of the preparation,  $v_K$ ,  $v_S$  are the Nernst potentials for potassium and for the seal current, respectively,  $\gamma$  is a stochastic variable depending on the state of the channel, and  $I_0 = I_0(t)$  is an applied current; note also that the bar on  $\bar{v}$  is used to indicate that this is a stochastic variable. The dynamics of  $\gamma$  are governed by a Markov model, and in the forward simulations, the rates of the Markov model are assumed to be given. Additionally, the expression for seal current is used to simulate under as realistic clamp conditions as possible, where a proportion of any applied current will be lost to ground through a conductance that exists in parallel to the membrane patch. Intuitively, this conductance represents the current leak between the

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