Stochastic Models for Ion Channels: Introduction and Bibliography

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Technical Report No. 327
October 1991

[1]Supported by a grant from the UK Science and Engineering Research Council
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Abstract

We provide an introduction to and overview of the use of stochastic models and statistical analysis in the study of ion channels in cell membranes. An extensive bibliography is included.

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October 24, 1991

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1 Introduction

Ion channels are large proteins that span cell membranes; in certain conformations these macromolecules form pores, allowing electric current in the form of ions to pass across the membrane. The current through a single channel is quite small, on the order of picoamperes. The structure and function of these fundamental units of the nervous system are only partly understood. There is a large variety of such channels, including calcium channels, sodium channels, and acetylcholine receptors, to mention but a few. Their interrelationships shape the electrical signals of the nervous system. The openings and closings of some types of channels ("agonist gated" channels) are in response to binding and unbinding of stimulatory molecules; other types of channels open and close in response to changes in the transmembrane potential and are termed "voltage gated." Hille (1984) provides a broad review of ion channels.

Patch clamp recordings are one of the principal sources of information about ion channels. A glass micropipette with an extremely narrow tip is placed against a cell membrane and suction is applied to form a high resistance seal around the edge of the tip. Current flowing across the tip can then be recorded. In the case that only a single channel or a small number of channels are present in the portion of the membrane surrounded by the tip, the measured current typically has a quantal character, alternating seemingly at random between a small number of levels as the channels open and close. Many channels have only two levels—conducting and non-conducting.

The quantal nature of the underlying signal in a patch clamp recording is obscured by noise and by low-pass filtering which is applied before digitization. The signal to noise ratios vary considerably depending on seal resistance, electronics, and channel conductance. The durations of some quantal events may be short relative to the sampling rate or to the impulse response function of the low pass filter and will thus appear as transitions of less than full amplitude in the experimental record. Transitions between openings and closures are also rounded off by the filtering. Typically, the sampling interval is of the order of 100 microseconds and durations of openings are of the order of milliseconds. A good experiment can last several minutes, thus giving rise to a large quantity of data. Depending on the type of channel and the experimental preparation, the channel's activity is recorded in equilibrium or in response to perturbation such as a voltage jump. Discussions and examples of patch clamp recordings can be found in Sakmann and Neher (1983).

2 Models

Stochastic models are used extensively in the study of ion channels. A model can serve a number of functions: it can provide a conceptual framework, it can explain specific observations, it can stimulate and direct measurements, and it can provide a framework for data summary and analysis. The most commonly used models of channel dynamics are Markovian. The channel makes transitions between a small number of states (corresponding to hypothetical conformational states of the protein) as a Markov process. As an example, a tentative model of the acetylcholine receptor might consist of three closed states (resting, one agonist molecule bound, two agonist molecules bound), one open state, and allowable transition pathways between the states as indicated by the diagram $C_0 \rightleftharpoons C_1 \rightleftharpoons C_2 \rightleftharpoons O$. An alternative model might allow opening with only one agonist bound and one might wish to judge the relative plausibilities of these models on the basis of experimental data.

Predictions generated from such a model can be compared to experimental observations, leading to its validation or modification. Those aspects of Markov models which have been most extensively used are predicted stochastic properties of the sequence of open and closed dwell times (sojourns) such as marginal and joint probability density functions and correlation functions (e.g. Colquhoun and Hawkes, 1981; Fredkin et al., 1985). Questions of statistical inference are discussed in a later section.

An important feature of such a model is that the underlying Markov process is not directly observable. Thus, in the example mentioned above, the patch clamp recording can at best reveal only at what times the channel was open or closed (current or no current) through the course of the recording, but cannot reveal the sequence of closed states actually visited. The basic observable data is thus a function of a finite state Markov process, giving rise to a number of related questions concerning identifiability: In general what can be learned about a Markov process from observations of a function of it? For example, what aspects of the graph structure (states and pathways) of the Markovian model can in principle be determined? Can the number of closed states and the number of open states be determined? Can the number of pathways joining open and closed states be determined? How can classes of indistinguishable models be characterized? Can all the transition rates of a given model be estimated?

Identifiability problems can be classified broadly as (i) structural; (ii) over-parameterisation and (iii) time interval omission induced. Structural unidentifiability arises from the fact that two or more distinct underlying process can yield aggregated processes with identical probabilistic properties; see Kienker (1989) who, following Gilbert (1959), provides necessary and sufficient conditions in terms of the generators of the underlying processes. As an example of a structural identifiability problem, it can be seen fairly easily that the two models $C_1 \rightleftharpoons C_2 \rightleftharpoons O$ and $C_1 \rightleftharpoons O \rightleftharpoons C_2$ are indistinguishable. (However, by varying experimental conditions such as voltage and noting the effect on estimated rate constants, it may be possible to distinguish between these models by a series of experiments) Some single channel models depend on many unknown parameters and clearly there are likely to be problems in their joint estimation. Fredkin et al. (1985) showed that for a two level channel a model is not identifiable if it depends on more than $2n_o n_c$ independent parameters, where n_o and n_c are respectively the numbers of open and closed states in the underlying process. This can be sharpened to $n_o n_c + n_o + n_c - 1$ if the underlying process is time reversible. This result can be generalized to channels having more than two levels and further sharpened if the number of pathways between open and closed states are taken into account (Fredkin and Rice, 1986). Finally, time interval omission (discussed below) can induce identifiability problems. This has been explored by several authors within the context of a two state Markov model; see Yeo et al. (1988) for a detailed investigation.

Several alternatives to Markov models for ion channel gating mechanisms have been proposed recently. The two that have received the most attention are fractal models (Liebovitch et al., 1987) and diffusion models (Millhauser et al., 1988). Fractal models are actually alternating renewal processes with Weibull sojourn time distributions. Liebovitch and his co-workers found that fractal models provide an improved fit to some single channel recordings, for example from the corneal endothelium. However, subsequent analyses have shown that this is not generally the case (eg Korn and Horn (1988), McManus et al. (1988) and Sansom et al. (1989)). Moreover, the results of analyses based on fractal models are difficult to interpret as the models have no clear physical basis. In contrast, diffusion models attempt to model the dynamics of the channel protein more directly. They are in fact still Markov models, usually with one open state and a large number of closed states with very similar kinetics. The simplest such model (Millhauser et al, 1988) contains a linear array of closed states with constant transition rates between neighbouring pairs of states. More complicated models are based, for example, on a three-dimensional cubic structure of closed states. Although comparative studies that have been carried out to date (eg Sansom et al., 1989) suggest that these diffusion models do not fit observed channel data as well as the traditional Markov models, it is clearly of upmost importance to develop models that aid our understanding of channel gating at a molecular level.

3 Time Interval Omission

Limitations in the electronic recording system and the need for filtering result in very brief (typically less than ca. 100 microseconds) open and closed sojourns being absent from experimental data. This phenomenon is known as time interval omission, or limited time resolution. It is usually modelled by assuming that any sojourn of length less than some critical value, τ say, fails to be detected. Thus an observed open sojourn will consist of an actual open sojourn of length at least τ, followed by a number of pairs of closed and open sojourns with the closed sojourns all having length less than τ, and terminates as soon as there is a closed sojourn of length at least τ. An observed closed sojourn is defined in the same fashion.

A general semi-Markov framework for analysing single channel data incorporating time interval omission was developed by Ball et al. (1991a,b). This framework includes Markov, fractal and diffusion models as special cases and generalises previous approaches based on Markov models (e.g. Roux and Sauvé (1985), Ball and Sansom (1988) and Hawkes et al. (1990)) and alternating renewal processes (Milne et al, 1988). It is based upon an embedded semi-Markov process that records the lengths and entry states of successive observed open and closed sojourns. The properties of the observed single channel record incorporating time interval omission are then completely determined by the associated semi-Markov kernel. Unfortunately, only the Laplace transform of this kernel is readily available. Although several observed channel properties, such as moments and correlations of observed sojourns, can be derived from this Laplace transform, the kernel itself is required to calculate probability density functions of observed open and closed sojourns. It is also required for most likelihood based parameter estimation procedures.

We now concentrate on the case when the underlying single channel process is Markovian. Then an exact recursive expression for the time interval omission kernel has been derived by Hawkes et al. (1990). However, there may be numerical problems in implementing it for large sojourn times. Several approximations to the kernel have been considered in the literature. They include (i) ignoring the lengths of undetected closed (open) sojourns within an observed open (closed) sojourn (Roux and Sauve, 1985); (ii) ignoring undetected open (closed) sojourns that occupy more than one open (closed) state (Blatz and Magleby, 1986); (iii) assuming that the length of minimum detectable sojourns, τ, follows a negative exponential or a gamma distribution with integer shape parameter (Ball, 1990); (iv) the use of virtual open and closed states corresponding to undetected sojourns (Crouzy and Sigworth, 1990) and (v) the use of Tauberian theorems (Jalali and Hawkes, 1991a,b). Approximations (i)-(iv) essentially model the observed process by an appropriate continuous time Markov chain so methods developed in the absence of time interval omission can be applied. Some of these approximations are compared in Hawkes et al. (1990). Numerical inversion of the Laplace transform of the kernel has been considered by some authors, e.g. Roux and Sauvé (1985) and Wilson and Brown (1985). An alternative approach based on numerical solution of a system of renewal type integral equations, derived by exploiting a regenerative structure in observed sojourns, is described in Ball and Yeo (1991).

4 Inference

Statistical inference for ion channel gating mechanisms usually proceeds in two distinct stages. Firstly, the forms of open and closed time probability densities and auto- and cross-correlation functions are used, together with biophysical considerations, to postulate an underlying model. Secondly, the parameters of that model are estimated in some fashion. Both stages are thwart with identifiability problems and are affected by time interval omission. Structural inferences based on correlation functions are robust to time interval omission (Ball and Sansom, 1988), whilst those on probability density functions are less so (Ball, 1990).

When time interval omission is ignored it is relatively straightforward to derive the likelihood of a sequence of sojourn times (Fredkin et al., 1985), which can then be maximised numerically (see eg Horn and Lange (1983), Chay (1988) and Ball and Sansom (1989)). This has been applied successfully to even quite large state space models (Bates et al, 1990). Yang and Swenberg (1988) consider an alternative to maximum likelihood which can be more efficient computationally. The difficulty in extending maximum likelihood to incorporate time interval omission is that it is no longer easy to compute the likelihood, owing to the absence of a simple form for the associated semi-Markov kernel. Thus it seems sensible to consider approximations to the likelihood based upon various approximations to the kernel described earlier. Alternative methods of inference, such as Laplace transform based inference (Feigen et al, 1983) and deriving parameter estimates from the forms of observed two-dimensional (open-closed and closed-open) sojourn time probability functions (Magleby and Weiss, 1990a,b) are very attractive.

Recently approaches to inference based on the theory of "Hidden Markov Models" (Baum et al., 1970; Rabiner and Juang, 1986) have been developed. These approaches are based on the digitized data rather than on the restored sequence of sojourn times and, if filtering is taken into account, thus avoid the problems of time interval omission. Fredkin and Rice (1989) and Chang et al. (1990) use these techniques to restore sojourn sequences from digitized data. Fredkin and Rice (1991) go further and compute maximum likelihood estimates of kinetic parameters directly from digitized data.

5 Multiple Channels

Patch clamp recordings often reveal the presence of more than one channel, as the currents through the channels superimpose. In such a record one cannot always tell when a particular individual channel opens and closes, which complicates the analysis. There may be multiple channels of a given type present in the record or mixtures of different types of channels. The constituent channels may not operate independently (Yeramian et al., 1986).

Kijima and Kijima (1987b) derive the density functions of sojourn times at different conductance levels under the assumption that the constituent channels follow independent and identically distributed Markov processes; see also Jackson (1985). Yeo et al. (1989) and Fredkin and Rice (1990) consider this problem when the constituent channels follow more general stochastic processes. In particular, Fredkin and Rice (1990) show how to extract the open and closed time distributions of an individual channel.

If more than one channel is believed to be present, it may be of interest to estimate how many channels there are and to test whether they are independent (Dabrowski et al., 1989; Dabrowski and McDonald, 1990; Horn, 1991). Although there may be no direct evidence of more than one channel (no superpositions being observed), it may be difficult to rule out the possibility that different channels are active in the record at different times, as many types of channels are known to go through states of sustained deactivation (Colquhoun and Hawkes, 1990).

6 Concluding Remarks

We have attempted to give an introduction and overview of the facets of this fascinating area of research. Only a few illustrative references to the literature have been made in the sections above. In compiling the more extensive bibliography that follows, we have categorized the literature according to the section headings above; in doing so we have had to make some arbitrary decisions, as many of the papers touch on a variety of subjects. We do hope that this categorized bibliography will aid those who wish to read further in this area. We are undoubtedly guilty of oversights and we apologize in advance to those researchers whose work we have inadvertently slighted.

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