Direct estimation of inhomogeneous Markov interval models of spike-trains

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A necessary ingredient for a quantitative theory of neural coding is appropriate "spike kinematics": precise description of spike trains. While summarizing experiments by complete spike time collections is clearly inefficient and probably unnecessary, also the most common probabilistic model used in neurophysiology, the inhomogeneous Poisson process, often seems too crude. Recently a more general model was considered, the inhomogeneous Markov interval model (Berry & Meister 1998, Kass & Ventura 2001), which takes into account both the current experimental time and the time from the last spike. Several techniques were proposed to estimate the parameters of these models from data. Here we propose a direct method of estimation which is easy to implement, fast, and conceptually simple. The method is illustrated with an analysis of sample data from the cat superior colliculus.

1 Introduction

The problem of information coding in sensory systems is one of the outstanding problems of neuroscience (Rieke et al. 1999, van Hemmen & Sejnowski 2006). It is particularly striking posing the variability of neural responses against the stability of our percepts. A natural approach to the problem of coding is through the theory of probability and information theory (Rieke et al. 1999). Even if the changes of membrane potential can be considered deterministic (Hodgkin & Huxley 1952) and if we neglect the synaptic noise (Faisal et al. 2008), still the multitude of synaptic contacts usually requires statistical approach in the description of spike trains.

A natural framework for the description of spiking responses is provided by the point process theory (Cox & Isham 1980, Daley & Vere-Jones 2003). It has been used in neuroscience for a long time (Perkel et al. 1967), however, two simplified approaches were most popular. Renewal processes, which could account for refractory properties of the membrane, were used to describe stationary processes. Nonstationarity has usually been described with inhomogeneous Poisson processes (Tuckwell 1988). Only in the last two decades other models started to come into use for the description of non-stationary spike trains, such as inhomogeneous renewal processes (Gerstner & Kistler 2002), inhomogeneous Markov interval (IMI) processes (Berry & Meister 1998, Kass & Ventura 2001), or time-rescaled renewal processes (Brown et al. 2002).

To estimate models from data one must balance the flexibility of the model versus estimation precision given available data. Two-parameter processes, in particular multiplicative IMI models, seem especially suitable in the neurophysiological context. They are flexible enough to account for both the structure of the receptive fields and membrane properties, yet simple enough to be reasonably estimated from typically available data. Several approaches were proposed for estimation of IMI models (Berry & Meister 1998, Kass & Ventura 2001, Truccolo et al. 2005). We propose here a simple approach which we found conceptually intuitive, easy to implement and efficient, even if not as general as the techniques based on the generalized additive models (Kass & Ventura 2001) or the generalized linear models (Truccolo et al. 2005). It is based on a direct estimation of the part of the model describing history-dependent properties of spike generation under the assumption of a constant rate followed by an estimation of the modulatory part describing the response properties.

In this note we first introduce the formal model to be estimated in the framework of general point processes (Section 2). We then discuss our estimation method and a class of experiments where it is applicable in Section 3. The technique is illustrated with analysis of sample data from the cat superior colliculus cells in Section 4. The results are summarized in Section 5.

2 Multiplicative inhomogeneous Markov interval models

Consider an experiment where a spike train is recorded from a neuron observed in time $t \in (0, T]$. We can describe the process locally in time with the conditional intensity λ, also called the hazard function (Cox & Isham 1980, Johnson 1996, Gerstner & Kistler 2002). It describes the probability density of generating a spike at time t given the whole history of the process up to t, that is

$$\begin{cases} \Pr[\text{1 event in } (t, t+\Delta t] \,|\, \text{spikes at } t_1, t_2, \ldots, s_*(t)] = \lambda(t; t_1, t_2, \ldots, s_*(t))\, \Delta t \\ \Pr[\text{more than 1 events in } (t, t+\Delta t] \,|\, \text{spikes at } t_1, t_2, \ldots, s_*(t)] = o(\Delta t) \end{cases}$$

Here t_k are times of consecutive spikes in a single realization of the process, $s_*(t)$ is the last spike time before t in this realization, and $o(\Delta t)$ denotes terms of higher order than linear in Δt.

To estimate λ from data one is forced to assume memory of no more than the last few spikes. In the simplest case of intensity depending on time only, $\lambda(t)$, this is the inhomogeneous Poisson process. If we relax the constraint and assume dependence of hazard function on the current time t and time from the previous spike $\tau = t - s_*(t)$ we

obtain the inhomogeneous Markov interval or inhomogeneous renewal process (Berry & Meister 1998, Kass & Ventura 2001, Gerstner & Kistler 2002). We shall further restrict ourselves to the multiplicative variant of the model of the form

$$\lambda(t, \tau) = \lambda_1(t) \cdot \lambda_2(\tau). \tag{1}$$

Berry & Meister (1998) proposed a simple method of estimation of these factors from data. They assumed $\lambda_2(\tau) = 0$ for τ less than the time of absolute refraction t_{abs}, and $\lambda_2(\tau) = 1$ for τ greater than the time of relative refraction, t_{rel}. The intermediate values were obtained from the probability distribution of all interspike intervals (ISI). Having thus obtained $\lambda_2(\tau)$ they used it to estimate $\lambda_1(t)$ from the mean firing rate. The apparent simplicity of this approach is hampered by several assumptions which in general need not be satisfied. For example, the assumption of the special form of $\lambda_2(\tau) = 0$ for $\tau < t_{\text{abs}}$ and 1 for $\tau > t_{\text{rel}}$, while physiologically very natural, in general is unjustified. In fact, $\lambda_2(\tau)$ can even be unbounded; cf. the typical hazard functions (Tuckwell 1988).

In response to that, alternative, more general procedures were proposed by Kass & Ventura (2001) and Truccolo et al. (2005), based on, respectively, generalized additive models and generalized linear models. There the idea is to span $\lambda_1(t)$ and $\lambda_2(\tau)$ on a spline basis with appropriately chosen knots and fit the spline parameters from data. These methods are much more universal but can be slow for large amounts of data due to substantial optimization needs.

In our analysis of data from the cat superior colliculus cells we observed that the data did not satisfy the assumptions of Berry & Meister (1998) procedure and the application of the approaches of Kass & Ventura (2001) and Truccolo et al. (2005) led to computationally intensive analysis. We found a simple variant of Berry & Meister (1998) approach which proved easy to implement, efficient, and conceptually natural, but it can only be applied to a class of experiments including recordings of stationary activity. We discuss it in the next section.

3 Estimation of IMI process from data

Consider an experiment where a stimulus s is presented N times during intervals of length T. Assume also a control recording with no stimulus and stationary activity during time $T_{\text{stationary}}$. Thus we have N spike trains of duration T and an additional spike train of duration $T_{\text{stationary}}$. We assume that the data are described by the multiplicative IMI model (1). There is an undetermined constant in the two factors and we set it by requiring $\lambda_1 = 1$ for stationary activity with no stimulus. An alternative natural normalization is to require λ_1 equal to the mean rate in this region. Thus we can easily obtain $\lambda_2(\tau)$ using the standard approach for stationary renewal processes (Cox & Lewis 1966, Perkel et al. 1967). We estimate the probability density of interspike intervals $P(\tau)$ from the control recording of background activity. From $P(\tau)$ we obtain λ_2 as

$$\lambda_2(\tau) = \frac{P(\tau)}{S(\tau)} = \frac{P(\tau)}{1 - \int_0^\tau d\tau' \, P(\tau')}, \tag{2}$$

where $S(\tau) = 1 - \int_0^\tau d\tau' P(\tau')$ is the survival function. In practice we used either nonparametric or parametric methods which have different advantages and trade-offs (Hastie et al. 2001). In the nonparametric approach we used Gaussian kernel smoothing with optimal

or scaled kernel width[1] and with positive support (Bowman & Azzalini 1997). In the parametric variant we fitted gamma distribution. The analysis was done using MATLAB (The Mathworks).

Having obtained the factor describing refractory properties of the membrane, $\lambda_2(\tau)$, we can evaluate the modulatory factor $\lambda_1(t)$ describing response properties of the cell. We divide the time of experiment, $(0, T]$, into bins of length Δt short enough that there would be at most one spike per bin. The probability to generate a spike in trial j in bin k is approximately $p_k^j = \lambda_1(t_k)\lambda_2(\tau_k^j)\Delta t$, where $t_k = (k - 1/2)\Delta t$, $\tau_k^j = t_k - s_*^j(t_k)$, and $s_*^j(t)$ is the time of the last spike before t on j-th trial. If no history of spike train is known before $t = 0$ we assume $\tau = t$ until the first spike, t_1^j. The possible error introduced by inexact timing was usually negligible for typical spike statistics. Over N repetitions, the *mean* probability to observe a spike in bin k is

$$p_k = \langle p_k^j \rangle_j = \frac{1}{N} \sum_j p_k^j = \lambda_1(t_k)\Delta t \frac{1}{N} \sum_{j=1}^{N} \lambda_2(\tau_k^j).$$

But p_k is essentially time dependent rate $p_k = r_k \Delta t = N_k/N$, where N_k is the number of trials on which we observed a spike in bin k, and the rate $r_k = (1/\Delta t)(N_k/N)$. Since we already know λ_2, we obtain an estimate for λ_1 as

$$\lambda_1(t_k) = \frac{N r_k}{\sum_{j=1}^{N} \lambda_2(\tau_k^j)}. \tag{3}$$

In practice we obtained the rate by either smoothing the PSTH with a Gaussian kernel or by spreading each individual spike with a Gaussian kernel with $\sigma = 5$ or 10 ms and averaging the sum (Nawrot et al. 1999). Usually, the results were equivalent. Since the mean $\lambda_2(\tau)$ was rather variable, to stabilize the resulting λ_1 we also smoothed the time-dependent function $\sum_{j=1}^{N} \lambda_2(\tau_k^j)$ with Savitzky-Golay filter of order 3 and width 31 ms.

The whole scheme easily generalizes to a situation where a set of stimuli s_i, $i = 1, \ldots, K$ is presented repeatedly, n_i times each. We discuss a simple example of experimental data analysis in such a case in the next section.

4 Results

To illustrate our estimation method we used data of the single unit recording from the cat's superior colliculus. Conventional experimental methods for animal preparation and extracellular single unit recording were used (Waleszczyk et al. 1999). In the experiment, spike trains of single neurons were recorded during movements of a bar of light on a screen with a fixed velocity along one axis of the receptive field and waiting periods, when the stimulus was held outside of the receptive field for 1 second between the sweeps in both directions. Single cell data consisted of multiple recordings of responses to stimuli of different velocities. Velocities ranged from 2 to 1000 degrees per second. For short sweeps with high velocities we could see the response extending to the first part of the waiting period. However, it was never noticeable during the last 0.5 s of the waiting period. We pooled all the intervals from all such periods following sweeps into a single collection of

[1] We first used `ksdensity` function with Gaussian kernel to evaluate optimal window width u. Then we used it to calculate the cdf and pdf with window width $0.5u$, u, and $1.5u$.

ISIs. This procedure was equivalent to analysis of a single long recording of background activity advocated in the previous section.

The probability distribution of ISI sampled by this collection was used to estimate $\lambda_2(\tau)$. Thus we assumed $\lambda_1(t) = 1$ in the second half of each waiting period. We used both parametric and non-parametric methods for estimation of $\lambda_2(\tau)$, as mentioned in the previous section.

Given λ_2, we analyzed responses to every stimulus separately using the procedure detailed in the previous section. On Figure 1 we show example results of such analysis. These are data from a single cell and a single stimulus ($v = 1000$ deg/s moving left to right). Figure 1A shows the distribution of all the ISI from the background activity (empirical data; bar plot), the non-parametric estimate (solid line), and the parametric fit (gamma distribution; dashed line) of the probability distribution $P(\tau)$. The main plot in log-normal coordinates shows the differences in the tails while the inset in normal-log coordinates emphasizes the differences for small intervals. Panel B shows the estimate of $\lambda_2(\tau)$ obtained from data of panel A. There is a striking difference between the non-parametric and parametric estimates for $\tau > 0.1$ s as the hazard function for gamma distribution is monotonic while the non-parametric estimate is more flexible. To test the stability of estimates we calculated λ_2 on different parts of data. We separated waiting periods following stimuli moving left to right from those following stimuli moving right to left. We also analyzed separately the intervals from the first half of the recordings and those from the second half of the recordings. In all cases for these data the obtained results were quantitatively very similar to the result obtained from all of the data (not shown). In Fig. 1C we show $\lambda_1(t)$ estimated from data as described in Section 3 using non-parametric (solid line) and parametric approach (dashed line). To compare these results with the inhomogeneous Poisson model (dash-dotted curve) they have all been normalized so that their mean value during the waiting period is equal to 1. There is an enhancement of the response profile in both IMI models as compared to the Poisson model, particularly strong for the non-parametric model, which corroborates well with the previous findings (Berry & Meister 1998, Kass & Ventura 2001). The last panel (Fig. 1D) compares the quality of different models using the Kolmogorov-Smirnov (K-S) plots (Brown et al. 2002). Each curve was obtained by appropriate rescaling of spike times (Brown et al. 2002) using conditional intensity estimated with either inhomogeneous Poisson model (dash-dotted curve), parametric IMI model (dashed curve), or nonparametric IMI model (thick solid line). Perfect model of data corresponds to diagonal (thin solid line), two parallel thin dashed lines demark 95% confidence band. We interpret the distance from the diagonal as a measure of the quality of the model. Clearly, the inhomogeneous Poisson model is describing the data rather poorly. The gamma IMI gives a much better description of the data, with non-parametric IMI model leading to the K-S curve almost within the 95% confidence band.

5 Summary

The common model of spike trains, inhomogeneous Poisson process, is very useful in its simplicity and often adequate for the description of experimental data, especially for relatively low firing rates. To account for the membrane mechanisms, such as refraction, one must go beyond the Poisson processes and the inhomogeneous Markov interval models seem good candidates for modeling spike train data. We proposed a direct method useful in the description of experimental recordings where apart from responses to repeated stimuli

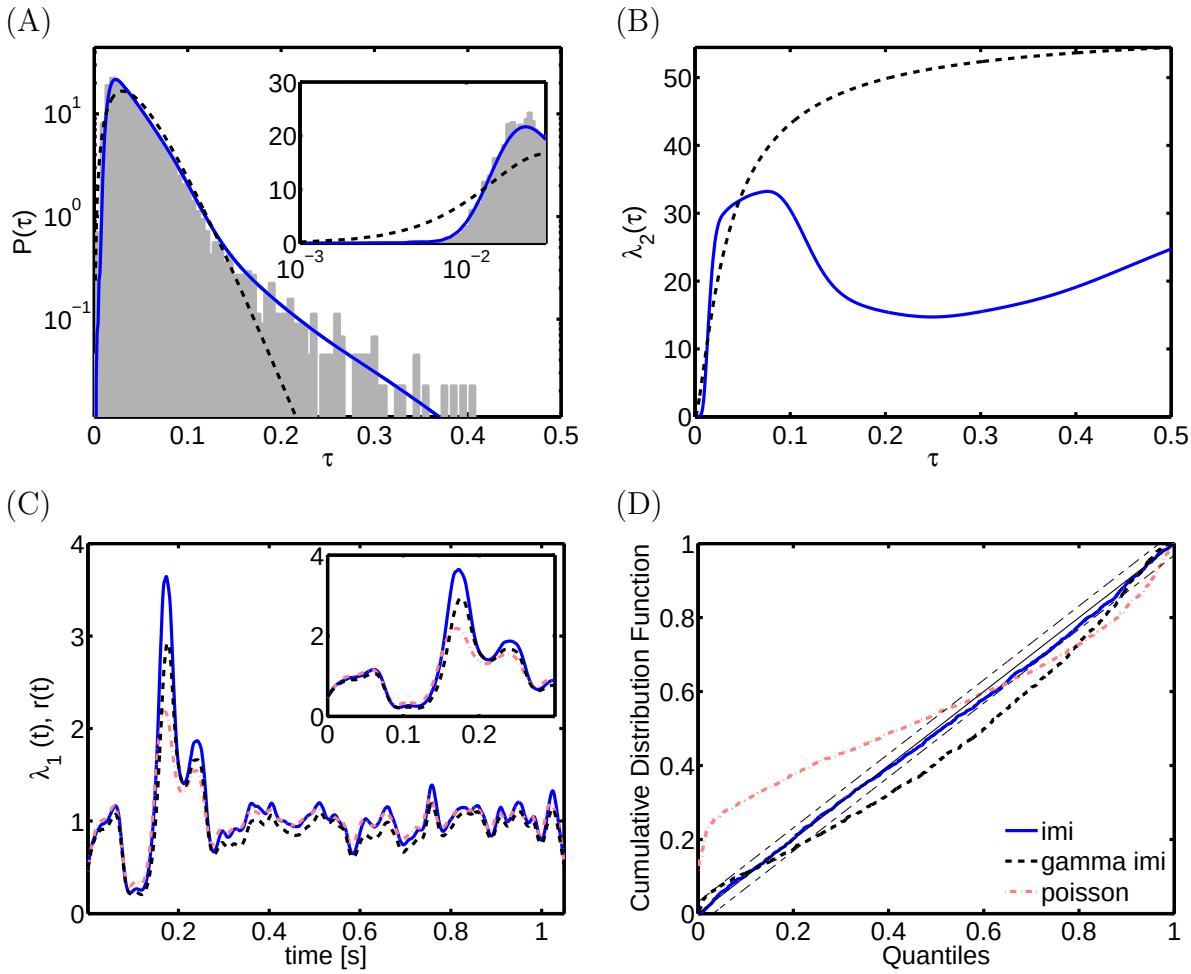

Figure 1: Estimation of IMI models from sample data: a single cell and a single stimulus (v = 1000 deg/s moving left to right). (A) Distribution of all the ISI from the background activity (bar plot), the non-parametric estimate (solid line), and the parametric fit (gamma distribution; dashed line). The main plot in log-normal coordinates shows the difference in the tails. The inset in normal-log coordinates emphasizes the differences for small intervals. (B) The estimate of $\lambda_2(\tau)$ obtained from the distribution shown in (A). (C) The modulatory factor $\lambda_1(t)$ estimated from data as described in Section 3 using non-parametric (solid line) and parametric approach (dashed line). To compare these results with the inhomogeneous Poisson model (dash-dotted curve) they have been normalized so that their mean value during the waiting period is equal to 1. (D) The quality of different models using the Kolmogorov-Smirnov plots. Each curve was obtained by appropriate rescaling of spike times using conditional intensity estimated with either inhomogeneous Poisson model (dash-dotted curve), parametric IMI model (dashed curve), or nonparametric IMI model (thick solid line). Perfect model of data corresponds to diagonal (thin solid line), two parallel thin dashed lines demark 95% confidence band.

also background activity was recorded. Our proposition was to use the stationary data from the background activity to estimate the factor of intensity describing the membrane properties, $\lambda_2(\tau)$. An estimate of $\lambda_2(\tau)$ can then be used to extract the modulatory factor taking into account the response properties of the cell, $\lambda_1(t)$. We have demonstrated a practical use of our method on data from example cell from the cat superior colliculus and showed with K-S plots the superiority of IMI model over inhomogeneous Poisson model for these data. A complete physiological analysis of the full dataset from these experiments is in preparation. We believe that the simplicity of our estimation method will make it a viable alternative to other approaches wherever it can be applied.

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References

Berry, M. J. & Meister, M. (1998), 'Refractoriness and neural precision.', *J Neurosci* **18**(6), 2200–2211.

Bowman, A. & Azzalini, A. (1997), *Applied Smoothing Techniques for Data Analysis*, Oxford University Press.

Brown, E. N., Barbieri, R., Ventura, V., Kass, R. E. & Frank, L. M. (2002), 'The time-rescaling theorem and its application to neural spike train data analysis.', *Neural Comput* **14**(2), 325–346.

Cox, D. R. & Isham, V. (1980), *Point processes*, Chapman and Hall.

Cox, D. R. & Lewis, P. A. W. (1966), *The statistical analysis of series of events*, Chapman and Hall.

Daley, D. J. & Vere-Jones, D. (2003), *An Introduction to the Theory of Point Processes*, Springer.

Faisal, A. A., Selen, L. P. J. & Wolpert, D. M. (2008), 'Noise in the nervous system.', *Nat Rev Neurosci* **9**(4), 292–303.

Gerstner, W. & Kistler, W. M. (2002), *Spiking neuron models*, Cambridge University Press.

Hastie, T., Tibshirani, R. & Friedman, J. (2001), *The elements of statistical learning*, Springer.

Hodgkin, A. & Huxley, A. (1952), 'A quantitative description of membrane current and its application to conduction and excitiation in nerve', *Journal of Physiology* **117**, 500.

Johnson, D. H. (1996), 'Point process models of single-neuron discharges.', *J Comput Neurosci* **3**(4), 275–299.

Kass, R. E. & Ventura, V. (2001), 'A spike-train probability model', *Neural Computation* **13**(8), 1713–1720.

Nawrot, M., Aertsen, A. & Rotter, S. (1999), 'Single-trial estimation of neuronal firing rates: from single-neuron spike trains to population activity.', *J Neurosci Methods* **94**(1), 81–92.

Perkel, D. H., Gerstein, G. L. & Moore, G. P. (1967), 'Neuronal spike trains and stochastic point processes. i. the single spike train.', *Biophys J* **7**(4), 391–418.

Rieke, F., Warland, D., de Ruyter van Steveninck, R. & Bialek, W. (1999), *Spikes: Exploring the Neural Code*, MIT Press.

Truccolo, W., Eden, U. T., Fellows, M. R., Donoghue, J. P. & Brown, E. N. (2005), 'A point process framework for relating neural spiking activity to spiking history, neural ensemble, and extrinsic covariate effects', *Journal Of Neurophysiology* **93**(2), 1074–1089.

Tuckwell, H. C. (1988), *Introduction to theoretical neurobiology*, Cambridge University Press.

van Hemmen, J. L. & Sejnowski, T. J., eds (2006), *23 Problems in Systems Neuroscience*, Oxford University Press.

Waleszczyk, W. J., Wang, C., Burke, W. & Dreher, B. (1999), 'Velocity response profiles of collicular neurons: parallel and convergent visual information channels.', *Neuroscience* **93**(3), 1063–1076.