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On the Limiting Joint Distribution of Semi-Markov Processes with Finite Number of States, with an Application

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ABSTRACT. We derive expressions for $\lim_{t\to\infty}$ Prob $\{Z_t = i, Z_{t+z} = j\}$ for a semi-Markov process with a finite number of states. As an application of the resuts, we obtain the autocorrelation function of the process of recorded current flowing through a single channel, for two Markovian models of the behavior of drug-operated ion-channels. The additional information provided by the autocorrelation function would facilitate the task of identifying the model which is more consistent with the observed record.

1. Introduction

We are concerned with the probability that a semi-Markov process arrives in state i at time t, and then after a further period z, it is in state j, *i.e.*, Prob $\{Z_t = i, Z_{t+z} = j\}$. In particular, we consider the case when $t \to \infty$. It is to be noted that this probability does not depend on the states visited between the times t and t + z.

Limits of transitional probabilities of semi-Markov processes have been considered by various authors, notably by Pyke (1961a, b), Taga (1963) and Çinlar (1965, 1975). However, joint distributions in the sense stated here are yet to be considered as they may be of interest in their own right.

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In Section 2 we introduce some notations and state some known results which will be used later. Section 3 presents the main results of the paper. In Sub-section 3.3 the results for a two state semi-Markov process are derived. We conclude the paper with an applied example (Section 4) in which, for two separate models, we obtain expressions for the autocovariance and autocorrelation functions for the process of recorded current flowing through a single ion-channel.

2. Preliminaries

Consider a stoachastic process, which moves from one state to another of a number of N+1 possible states. Successive states visited form a discrete time Markov chain, with an $(N+1) \times (N+1)$ transition probability matrix $\mathbf{P}$ or $\{p_{ij}\}$. Let X_0 denote the initial state of the process and X_n, $n = 0,1,2, \ldots$, the states immediately following the n^{th} transition, so that $X_n \in \{0,1,2,\ldots, N\}$. In addition, let the inter-transition times $\{T_n, n = 0,1,2, \ldots\}$ be positive random variables such that

$$\text{Prob}\{T_n < t \mid X_0, X_1,\ldots,X_{n-1} = i, X_n = j, T_1, T_2,\ldots,T_{n-1}\} = H_{ij}(t) \text{ for all } n, i \neq j. \quad (2.1)$$

Definition.

Let $S_n = \sum_{k=1}^{N} T_k$, $S_0 = 0$, define $Z_t = X_n$ for $S_n \leq t < S_{n+1}$, and suppose $S_n \to \infty$ a.s. Then the process $\{Z_t, t \geq 0\}$ is called a semi-Markov process (Pyke 1961a).

With F_{ij} defined as $F_{ij}(t) = p_{ij}H_{ij}(t)$, $i \neq j$ and $F_{ii} = 0$, the unconditional distribuion function of the sojourn time in state i is $W_i(t) = \sum_{j=0}^{N} F_{ij}(t)$, postulated to have a finite mean μ_i. Here $F_{ij}(t)$ represents the probability that a process presently in state i will next be in state j a time t later. N may be either finite or infinite, but we shall assume N to be finite. Also $\lim_{t \to \infty} F_{ij}(t) = p_{ij}$, $i,j=0,1,2,\ldots,N$, where p_{ij} is the stationary transition probability that a process in state i will next be in state j.

Let $\phi_{ij}(t)$ be defined as $\phi_{ij}(t) = \text{Prob}\{Z_t = j \mid Z_0 = i\}$, for all i,j, and $t > 0$. These conditional probabilities are expressible in the following recursive form (Pyke 1961b, Çinlar 1969);

$$\phi_{ij} = \delta_{ij}\,[1 - W_i(t)] + \sum_{k=0}^{N} \int_0^t \tau\, dF_{ik}(\tau)\phi_{kj}(t - \tau) \quad (2.2)$$

where δ_{ij} is the usual Kronecker delta function. The Laplace transform of $\phi_{ij}(.)$ in matrix notation, derived from (2.2), is of the form

$$\boldsymbol{\Phi}(\theta) = (1/\theta)[\mathbf{I} - \theta\mathbf{F}(\theta)]^{-1}[\mathbf{I} - \theta\mathbf{W}(\theta)], \qquad \theta>0 \tag{2.3}$$

where **I** is an (N+1)×(N+1) identity matrix and $\mathbf{F}(\theta)$ and $\mathbf{W}(\theta)$ are the matrices of the Laplace transforms of **F**(.) and **W**(.) respectively. If **F**(.) and **W**(.) are absolutely continuous then (2.3) can be written as

$$\boldsymbol{\Phi}(\theta) = (1/\theta)[\mathbf{I} - \mathbf{f}(\theta)]^{-1}[\mathbf{I} - \mathbf{w}(\theta)], \tag{2.4}$$

with $\mathbf{f}(\theta)$ and $\mathbf{w}(\theta)$ being the matrices of the Laplace transforms of the density function **f**(.) and **w**(.) of **F**(.) and **W**(.) respectively.

For an irreducible persistent and aperiodic semi-Markov process, it is know that $\phi_{ij}(t) \to \eta_j$ as $t \to \infty$, where $\eta_j = (\pi_j\mu_j)/\sum_{l=0}^{N} \pi_l\mu_l$, and π_j are elements of the row vector Π, which is the unique solution of $\Pi = \Pi P$, with $\sum_{j=0}^{N} \pi_j = 1$ and $\mathbf{P} = \lim_{t\to\infty} \mathbf{F}(\mathbf{t})$.

Futhermore, let $P_j(.) = \mathrm{Prob}\{.|X_0=j\}$, $n(t) = \sup\{n, S_n<t\}$, $V_t^+ = S_{n(t)+1} - t$ and $Z_t^+ = X_{n(t)+1}$. Then it is known that (ibd) as $t \to \infty$

$$P_j\{Z_t = j, Z_t^+ = k, V_t^+ \leq y\} \to (\eta_j/\mu_j) \int_0^y [p_{jk} - F_{jk}(u)]du \quad i,j = 0,1,2,\ldots,N. \tag{2.5}$$

It is to be noted that the limit is independent of the initial state i.

3 The Limiting Joint Distribution

3.1 Special Case of a Markov Process

For illustrative purpose, let us assume that Z_t, $t \geq 0$, is in fact a time homogeneous Markov process with matrix of transition $\mathbf{Q} = (q_{ij})$. The distribution $H_{ij}(t)$ is then exponential with mean $\mu_i = (-1/q_{ii})$ for each i = 1,2, …, N independently of j. The relationship between **P** and **Q** is given by

$$p_{ik} = q_{ik}/(-q_{ii}), \qquad i\neq k,$$

and

$$p_{ii} = 0.$$

It then easily follows that

$$\mathbf{Q} = \mu^{-1}(\mathbf{P} - \mathbf{I}) \tag{3.1.1}$$

where μ is a diagonal matrix with diagonal elements μ_i, i = 1, 2. …, N.

Let $R_{ij}(z) = \lim_{t\to\infty} P(Z_t = i, Z_{t+z} = j)$, and put $\mathbf{R(z)} = (R_{ij}(z))$. Then we have the following theorem.

Theorem. The Laplace transform of $\mathbf{R(z)}$ satisfies

$$\theta\mathbf{R}^*(\theta) = \eta[\mathbf{I} + \mathbf{Q}\Phi^*(\theta)] \tag{3.1.2}$$

where η is a diagonal matrix with diagonal elements η_i, i = 1,2, …, N and $\mathbf{Q}$ is given by (3.1.1), and $\mathbf{R}^*(\theta)$ and $\Phi^*(\theta)$ are the Laplace transforms of $\mathbf{R}(.)$ and $\Phi(.)$ respectively.

Proof. $\text{Prob}(Z_t = i, Z_{t+z} = j) = \text{Prob}(Z_{t+z} = j \mid Z_t = i)\ \text{Prob}(Z_t = i)$.

Taking limits we get

$$R_{ij}(z) = \eta_i \varphi_{ij}(z)$$

which in matrix notation is

$$\mathbf{R(z)} = \eta\Phi(z). \tag{3.1.3}$$

The Kolmogorov backward equation of the process is

$$\frac{d\Phi(t)}{dt} = \mathbf{Q\Phi(z)}. \tag{3.1.4}$$

Taking Laplace transforms of both sides leads to

$$\theta\Phi^*(\theta) = I + \mathbf{Q}\Phi^*(\theta) \tag{3.1.5}$$

which in turn leads to

$$\Phi^*(\theta) = (\theta I - \mathbf{Q})^{-1}. \tag{3.1.6}$$

The Laplace transform of R (z) can be expressed as

$$\theta\mathbf{R}^*(\theta) = \eta\theta\Phi^*(\theta).$$

The Laplace transform of (3.2.6) is easily obtained as

$$R_{ij}(\theta) = (\eta_i/\mu_i)\{(\delta_{ij}\mu_i)/\theta + \sum_{k=0}^{N} p_{ik}\phi_{ij}(\theta) - \phi_{ij}\theta)\} \qquad i,j=0,1,2,\ldots,N. \qquad (3.2.10)$$

In matrix notation these become

$$\mathbf{R}^*(\theta) = \eta[\mathbf{I}/\theta + \mu^{-1}(\mathbf{P}-\mathbf{I})\Phi^*(\theta)]. \qquad (3.2.11)$$

3.3 Two-state semi-Markov Process

As an example, for a two state semi-Markov process we have

$$\mathbf{P}=\begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}.$$

Hence $w_0(t) = f_{01}(t) = f_0(t)$ and $w_1(t) = f_{10}(t) = f_1(t)$, so that

$$\mathbf{w(t)} = \begin{bmatrix} w_0(t) & 0 \\ 0 & w_1(t) \end{bmatrix}, \text{ and } \mathbf{f(t)} = \begin{bmatrix} 0 & f_0(t) \\ f_1(t) & 0 \end{bmatrix}.$$

Hence, by substituting for $\mathbf{w}(\theta)$ and $\mathbf{f}(\theta)$ in equation (2.4) and simplifying, we obtain

$$\Phi^*(\theta) = [\theta(1 - f_0^*(\theta)\, f_1^*(\theta))]^{-1} \begin{bmatrix} 1-f_0^*(\theta) & f_0^*(\theta)(1-f_1^*(\theta)) \\ f_1^*(\theta)(1-f_0^*(\theta)) & 1-f_1^*(\theta) \end{bmatrix}.$$

It follows that

$$(\mathbf{P}-\mathbf{1})\,\Phi^*(\theta) = \theta|\Phi^*(\theta)|\,(\mathbf{P}-\mathbf{I}).$$

This leads to

$$\mathbf{R}^*(\theta) = \eta\,[I/\theta + \mu^{-1}\,(\mathbf{P}-\mathbf{I})\,|\,\Phi^*(\theta)|]. \qquad (3.3.1)$$

4. Application

4.1 Models of Drug-Operated Ion-Channels

We consider two models of drug-operated ion-channels. The membranes of cells such as those found in heart and nerve tissue contain molecular structures known as ion-channels. Some of these molecules are capable of pumping ions across the cell membrane and producing a detectable unit of current. The current produced by an ion-channel in a cell has been modeled as a finite state-space Markov process (Colquhoun and Hawkes 1977, 1981, 1982, 1983, Milne *et al.* 1988).

The simplest such model assumes that a channel becomes open immediately after it is bound to a molecule of the agonist drug (acetylcholine, for example). When a channel is open it allows a rectangular pulse of current, that can be recorded, to pass through. The reaction is reversible, and once the channel is free again the current ceases to flow. Denoting the free channel by **T,** the open channel by **AR** and agonist drug molecule by **A,** we can write symbolically the model in the form of a reversible reaction

$$\mathbf{A} + \mathbf{T} \Leftrightarrow \mathbf{AR}\,. \tag{4.1}$$

A slightly more complicated model assumes that a bound channel has to undergo a conformation change before it opens up. The reaction can be represented as

$$\mathbf{A} + \mathbf{T} \Leftrightarrow \mathbf{AT} \Leftrightarrow \mathbf{AR}\,. \tag{4.2}$$

For the latter model we have therefore three states for the channel, namely, free, bound and open. However the observed record of current will only show whether the channel is open or closed (*i.e.* free or bound). Other models have also been suggested (Dabrowski *et al.* 1990).

In this example we obtain expressions for the autocovariance and the autocorrelation functions of the process of recorded current flowing through a single ion-channel under each of models (4.1) and (4.2). These functions provide additional tool for investigating which of the two models is more consistent with the observed record. Our main objective here is to demonstrate the usefulness of the results derived here.

We denote states **T, AT,** and **AR** of the ion-channel by 0, 1 and 2 respectively. For the sake of computational convenience we assume that the state of the channel under model (4.2) follows a Markov process with matrix of transition rates **Q**

$$\begin{array}{c} 0 \\ 1 \\ 2 \end{array} \begin{bmatrix} -2 & 2 & 0 \\ 1 & -2 & 1 \\ 0 & 2 & -2 \end{bmatrix}$$

We first derive the distributions of sojourn times in the bound and the open states. Note that the sojourn in the closed state starts immediately after leaving state

$$1 - f_0^*(\theta)f_1^*(\theta) = \frac{\theta(\theta+4)}{\theta^2+4\theta+2}.$$

Hence

$$|\Phi^*(\theta)| = \frac{\theta+3}{\theta(\theta+2)(\theta+4)}$$

$$= \frac{3}{8}\frac{1}{\theta} - \frac{1}{4}\frac{1}{\theta+2} - \frac{1}{8}\frac{1}{\theta+4}. \tag{4.5}$$

Substituting (4.5) in (4.4) we obtain the following expression for $\mathbf{R}^*(\theta)$

$$\mathbf{R}^*(\theta) = \frac{1}{\theta}\begin{bmatrix} 3/4 & 0 \\ 0 & 1/4 \end{bmatrix} + \frac{1}{2}\left\{\frac{3}{8\theta} - \frac{1}{4(\theta+2)} - \frac{1}{8(\theta+4)}\right\}\begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}. \tag{4.6}$$

In particular, after inverting we get

$$R_{11} = \frac{1}{16} + \frac{e^{-2z}}{8} + \frac{e^{-4z}}{16}. \tag{4.7}$$

For model (4.1) it is easier to proceed by noting that

$$|\Phi^*(\theta)| = |\theta\,\mathbf{I} - \mathbf{Q}|^{-1}.$$

Since $|\theta\,\mathbf{I} - \mathbf{Q}| = \begin{vmatrix} \theta+2/3 & -2/3 \\ -2 & \theta+2 \end{vmatrix} = \frac{1}{3}\theta(3\theta+8)$,

we have $|\Phi^*(\theta)| = \dfrac{3}{\theta(3\theta+8)} = \dfrac{3}{8\theta} - \dfrac{9}{8(3\theta+8)}$.

Hence $$\mathbf{R}^*(\theta) = \frac{1}{\theta}\begin{bmatrix} 3/4 & 0 \\ 0 & 1/4 \end{bmatrix} + \frac{1}{2}\left[\frac{3}{8\theta} - \frac{9}{8(3\theta+8)}\right]\begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}. \tag{4.8}$$

Again, after inverting we obtain

$$R_{11}(z) = \frac{1}{16} + \frac{3e^{-\frac{8z}{3}}}{16}. \tag{4.9}$$

If Z_t is in equilibrium then $\mathrm{Prob}(Z_t = 0) = \eta_0 = 3/4$ and $\mathrm{Prob}(Z_t = 1) = \eta_1 = 1/4$, so that we have $E(Z_t) = 1/4$ and $\mathrm{Var}(Z_t) = 3/16$. The autocovariance function, denoted by $\gamma(.)$, is given by

$$\gamma(z) = E(Z_t Z_{t+z}) - \eta_1^2 = R_{11}(z) - 1/16. \tag{4.10}$$

Hence, under model (4.1) the expression (4.9) becomes

$$\gamma(z) = \frac{3e^{-8z/3}}{16},$$

while under model (4.2) the autocovariance function becomes

$$\gamma(z) = \frac{e^{-2z}}{8} + \frac{e^{-4z}}{16}.$$

Note that, in both models, $\gamma(0) = 3/16$, as it should be. The autocorrelation function, which we denote by $\rho(.)$ is given by

$$\rho(z) = \gamma(z)/\gamma(0)$$

$$= e^{-8z/3} \quad \text{for modle (4.1),} \tag{4.11a}$$

$$\text{and} = \frac{2e^{-2z}}{3} + \frac{e^{-4z}}{3} \quad \text{for model (4.2).} \tag{4.11b}$$

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حول التوزيعات المشتركة النهائية للتعليمات شبه الماركوفيه بعدد محدود من الحالات مع مثال تطبيقي

شارلس ساكي بخيت و الفضل خليفة الشيخ

قسم الرياضيات والإحصاء - كلية العلوم - جامعة السلطان قابوس
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نستنتج تعابير رياضية $\lim\limits_{t\to\infty} \text{Prob}\,\{Z_t = i, Z_{t+z} = j\}$ لعملية شبه ماركوفيه بعدد متناهي من الحالات . كمثال نستخدم نتائجنا للوصول لدالة معاملات الارتباط الذاتية لعملية مرور تيار عبر قناة واحدة بافتراض كل من نموذجين ماركوفيين لتصرف القنوات الأيونية المحفزة بعقار . المعلومات الإضافية المستقاة من دالة الارتباط الذاتي يمكن أن تستخدم لتحديد النموذج الأكثر اتساقاً مع البيانات .