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A two-phase Poisson process model and its application to analysis of cancer mortality among A-bomb survivors

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ABSTRACT

We consider a two-phase Poisson process model where only early successive transitions are assumed to be sensitive to exposure. In the case where intensity transitions are low, we derive analytically an approximate formula for the distribution of time to event for the excess hazard ratio (*EHR*) due to a single point exposure. The formula for *EHR* is a polynomial in exposure dose. Since the formula for *EHR* contains no unknown parameters except for the number of total stages, number of exposure-sensitive stages, and a coefficient of exposure effect, it is applicable easily under a variety of situations where there exists a possible latency time from a single point exposure to occurrence of event. Based on the multistage hypothesis of cancer, we formulate a radiation carcinogenesis model in which only some early consecutive stages of the process are sensitive to exposure, whereas later stages are not affected. An illustrative analysis using the proposed model is given for cancer mortality among A-bomb survivors.

1. Introduction

Many chronic diseases can be characterized by stages and may be expressed mathematically by an irreversible point process. As for human cancer, Muller [21] and Nordling [23] proposed the idea of a multistage model to explain the observation that mortality rates increase proportionately to the fifth or sixth power of age. The quantitative consequences of this theory were derived by Stocks [32]. Armitage and Doll [4] considered that cancer was the end result of the accumulation in a normal cell of a critical number (k) of independent transitions through a series of intermediate states, assuming that the cancer was caused by exposure to carcinogens at a fairly constant rate throughout life, and that age is the same as the duration of carcinogenic exposure. For most cases of cancer 5–7 stages are indicated for the value of k. The multistage model has been incredibly useful as a conceptual tool to understand the role of time in carcinogenesis [7]. From the aspect of biological science, Vogelstein et al. [35] revealed that the process of colorectal cancer, for example, consists of several carcinogenic mutations of specific genes. Molecular biologists have reinterpreted the theory as the "Hallmarks of Cancer" [11,12]. Chiang [6] proposed a multistage model based on a non-stationary Poisson process to describe a chronic disease process, and derived explicit formulas for the density and distribution functions of time to event. Ohtaki and colleagues [24–26] developed a generalized Armitage–Doll model based on an approximation to Chiang's result. Applying this model, Doi et al. [10] analyzed cohort data on former workers in a poisonous gas factory and clarified that lung cancer incidence decreased with age at exposure to sulfur mustard. Pierce and Vaeth [29] showed that the effects of exposure shift the age scale instead of acting multiplicatively on cancer rates, and that those effects can be specified by age and dose. As for analyses of the effects of the radiation exposure, Pierce et al. [28], Preston et al. [30], Izumi and Ohtaki [13,14], and Ozasa et al. [27] performed detailed analyses of the data from the Life Span Study (LSS) cohort of A-bomb survivors using a model for a single point radiation exposure. These traditional multistage carcinogenesis models, however, do not explain the evidence that the incidence of many solid tumors among the A-bomb survivors requires more than 20 years of latency from the radiation exposure due to the Atomic bomb [31]. Whittemore [36] considered time and age dependence of cancer incidence resulting from various types of carcinogenic exposures, assuming that the exposure affects one of several changes necessary for malignant cell transformation. Based on these studies, we extend the generalized Armitage - Doll model with non-stationary transitions to cope with the problem of long latency.

In Section 2, we present the mathematical formulation of the point process model. In Section 3, the hazard ratio of time to event

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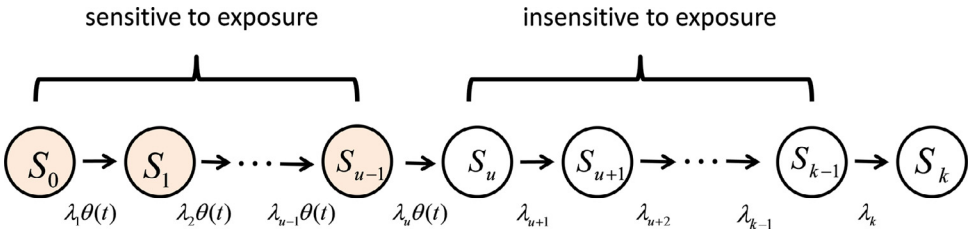

Fig. 1. Schematic diagram of the two-phase irreversible k-stage point process $M(u, k-u)$.

due to a single point exposure is considered. In Section 4, we show an application to the analysis of mortality risk from solid cancer among A-bomb survivors. In Section 5, some discussions on mathematical modeling of carcinogenesis and speculations on the results of our data analysis are given.

2. Two phase Poisson process

In this section, we modify the multistage model due to Chiang [6] such that only some early consecutive stages of the process are sensitive to the exposure of interest, whereas later stages are not affected by that exposure. In other words, we assume that there exists a stage u at which the transition becomes irreversibly insensitive to the exposure of interest (Fig. 1).

Definition 1. Suppose that there are k stages in a process, $S_0, S_1, \ldots, S_{k-1}$ and a final stage S_k and that the only possible transition in this process is $S_{j-1} \to S_j$ for $j = 1, 2, \ldots, k$. Given an element in stage S_j at time t, the intensity of the transition $S_{j-1} \to S_j$ during the interval $(t, t+dt)$ is $\lambda_j\theta(t)$ if $j \le u$ and λ_j if $j \ge u+1$, $u = 1, \ldots, k-1$ for all $0 \le t < +\infty$, where λ_j denotes a transition intensity at $S_{j-1} \to S_j$ in the case of non-exposure and $\theta(t)$ is the effect of exposure on the transition intensity at t. Let T be the time at which an element that is initially in stage S_0 at time 0 enters the final stage S_k. We call this process *the two-phase irreversible k-stage point process*, and denote it by $M(u, k-u)$ (see Fig. 1).

As for the process $M(k-1, 1)$, explicit formulas for the density and distribution functions of T were given by Chiang [6] and simple approximations with the gamma distribution were provided by Ohtaki [24]. We present them without detailed proof in the following proposition.

Proposition 1. *Let $f_k(t|\boldsymbol{\lambda}, \theta)$ and $F_{(k-1,1)}(t|\lambda, \theta)$ be the density and distribution functions of T in $M(k-1, 1)$, respectively. Let $\Theta(t) = \int_0^t \theta(z)dz$, $t \ge 0$. If $\lambda_i \ne \lambda_j$, then for $i \ne j$,*

$$f_{(k-1,1)}(t|\lambda, \theta) = \lambda_1 \ldots \lambda_k \theta(t) \sum_{i=1}^{k} \frac{1}{\prod_{\substack{j=1 \\ j\ne i}}^{k} (\lambda_j - \lambda_i)} \exp(-\lambda_i \Theta(t)), \tag{1}$$

$$F_{(k-1,1)}(t|\lambda, \theta) = \lambda_1 \ldots \lambda_k \sum_{i=1}^{k} \frac{1}{\prod_{\substack{j=1 \\ j\ne i}}^{k} (\lambda_j - \lambda_i)\lambda_i} \times \{1 - \exp(-\lambda_i \Theta(t))\}, \quad t \ge 0, \tag{2}$$

and these are approximated by the following gamma-type density and distribution functions:

$$g_k(t|\mu, \theta) = \frac{\mu^k}{(k-1)!}\theta(t)\{\Theta(t)\}^{k-1} \exp(-\mu\Theta(t)),$$

$$G_k(t|\mu, \theta) = 1 - \exp(-\mu\Theta(t)) \cdot \sum_{j=1}^{k} \frac{\mu^{j-1}}{(j-1)!}\{\Theta(t)\}^{j-1}, \tag{3}$$

respectively, where $\mu = \sqrt[k]{\lambda_1 \ldots \lambda_k}$. More precisely, we have

$$\sup_{0\le\tau\le t} \frac{|f_{(k-1,1)}(\tau|\lambda, \theta) - g_k(\tau|\mu, \theta)|}{g_k(\tau|\mu, \theta)} \le \sup_{0\le\tau\le t} \frac{|F_{(k-1,1)}(\tau|\lambda, \theta) - G_k(\tau|\mu, \theta)|}{G_k(\tau|\mu, \theta)} \le \frac{1}{2}\{\exp((\bar\lambda + \mu)\Theta(t)) - \exp(2\mu\Theta(t)) + 1 - \exp(-(\bar\lambda - \mu)\Theta(t))\}, \quad t \ge 0, \tag{4}$$

where $\bar\lambda = \max_{j=1,\ldots,k} \lambda_j$.

Proof of Proposition 1. Formulas (1) and (2) were derived by Chiang [6, Theorem 2]; the approximating formula and related inequalities were given in the theorem of Ohtaki [24].

3. Excess hazard ratio due to single point exposure

In this section we consider the excess relative hazard for arrival at the kth stage when a single point exposure exists. In the case of a single point exposure of dose D at time a, the effect of the exposure on transition can be specified as

$$\theta(t) \equiv \theta(t|D, a) = 1 + \beta_a D \cdot \delta(t-a), \tag{5}$$

where β_a is a function of a and $\delta(t-a)$ is the Dirac delta function with support a. Then the intensity of the transition $S_{j-1} \to S_j$ during the interval $(t, t+dt)$ is $\lambda_j\{1 + \beta_a D\delta(t-a)\}$ if $j \le u$ and λ_j if $j \ge u+1$. As for the probabilities of occupying the various stages, we have the following lemma.

Lemma 1. *Assume that $M(u, k-u)$ with a single point exposure of dose D at time a is given. Let X_t be the stage number at time t defined by $X_t = j$ if the stage is $j \in \{1, 2, \ldots, k\}$. Denote $\lim_{\varepsilon\downarrow 0} \Pr(X_{a-\varepsilon} = j)$ and $\lim_{\varepsilon\downarrow 0} \Pr(X_{a+\varepsilon} = j)$ by $\Pr(X_{a-0} = j)$ and $\Pr(X_{a+0} = j)$, respectively. Then*

$$\Pr(X_{a-0} = j) = \frac{\lambda_1 \ldots \lambda_j}{j!} a^j \cdot \left\{1 + o\left(\max_{m=1,\ldots j} \lambda_m\right)\right\}, \tag{6}$$

$$\Pr(X_{a+0} = j + \ell | X_{a-0} = j) = \frac{\lambda_{j+1} \ldots \lambda_{j+\ell}(\beta_a D)^\ell}{\ell!} \cdot \left\{1 + o\left(\max_{m=j+1,\ldots,j+\ell} \lambda_m\right)\right\}, \tag{7}$$

and

$$\Pr(X_t = k-1 | X_{a+0} = j+\ell) = \frac{\lambda_{j+\ell+1} \ldots \lambda_{k-1}}{(k-1-j-\ell)!}(t-a)^{k-1-j-\ell} \cdot \left\{1 + o\left(\max_{m=j+\ell+1,\ldots k-1} \lambda_m\right)\right\}, \tag{8}$$

for $\ell = 1, \ldots, u-j$, $j = 1, \ldots, u$.