Mathematical Biosciences 251 (2014) 30–39

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Comparison of multi-stage dose–response mixture models, with applications ☆

Eva María Ortega [a,*], José Alonso [b]

[a] Residencia Universitaria Oblatas, Murcia 30001, Spain
[b] Clínica Virgen Caridad, Cartagena 30204, Spain

ARTICLE INFO

Article history:
Received 24 June 2013
Received in revised form 21 January 2014
Accepted 4 February 2014
Available online 15 February 2014

Keywords:
Dose–response
Multi-stage models
Mixed Bernoulli
Stochastic orderings
Upper and lower bounds
Cancer models

ABSTRACT

This article concerns the analysis of a stochastic model that we propose for the population that generates a response (response measure) to the dose with the multi-stage model. The parameter uncertainty is dealt with via random dose and random size of the population at risk. The response measure is modeled by a random sum of mixed Bernoulli random variables with arbitrary distribution for the mixing parameters. Some extensions of the model are defined by functionals of the infection probability, fulfilling some convexity properties. We analyze the response by stochastic comparisons under different stochastic relations on the random dosages and the random sizes of the population at risk; or on the random infection rates. We provide stochastic exact bounds of the mixture model for the response, using inequalities and the positive quadrant dependence. Numerical bounds of the response by a dose having a scalar value or having an exponential or uniform distributions are obtained. Some conclusions are derived: the lower estimation of the response measure in the increasing convex order sense by replacing the dosages by their means; effects of the variation of the dose on the magnitude of the probability distribution of the response; effects of parameter correlation on the degree of variability of the response to any random dose; the low-dose region assessment; and also, the classical multi-stage model is compared versus the mixture model featuring independence and versus that with positive quadrant dependence.

1. Introduction and motivation

The dose–response models have been used for several decades in the field of toxicology, and more recently, in clinical oncology, radiology, microbiology, and ecology, to study the response of the individuals to a dose of ingested microorganisms or of pathogen or of received treatment, in water or food, or by other routes, from the exposure to the agents. Some applications can be seen, for example in [24,27,17,43,44]. A dose–response model describes the probability of infection or of a specified response, to a given dose, in a specific population, as a mathematical function of the dose. The biological, exposure and clinical aspects of the pathogen-host (cancer-tissue) interactions should be considered to generate a plausible model, apart of the empirical data, because different functionals have been proved to describe the same data (equally well). When only major effects can be distinguished, the high dosages are considered, however, other scenarios to be studied for assessing risks, usually include those with low-dose exposures (see [9]). Modeling the parameter uncertainty of different dose–response models has been dealt with, from several approaches, e.g. in [16,45,4,19,2,8].

The hit models are special dose–response models which consider that the stages in the infection process can be viewed as Poisson events (hits) that characterize the changes (see e.g., [6,37]). The multi-stage model (see [1]) is an extension of the so-called single-hit model by considering different infection rates for each stage of the process. The multi-stage family of models describe the initiation, progress and outcome of cancer, developmental and other diseases as a function of the dose. These models include the linearized multi-stage model (LMS) used in regulatory risk assessment in which the probabilistic transitions are used to model the events turning non-cancerous cells into cancer. In this context, some analytical methods of probability have been studied for random

☆ The contributions of this paper were presented in an extended paper published in the Proceedings of XXXII National Conference on Statistics and Operations Research 2010, in A Coruña, Spain and in the 10th International Conference on Ordered Statistical Data and Their Applications, OSDA12 in Murcia, Spain, and other international workshops in 2010. EM Ortega is supported by the research project MTM2009-13433, Ministerio Economía y Competitividad, Spain.

* Corresponding author. Address: C/Plaza de Universidad, s.n., Murcia 30001, Spain. Tel.: +34 669603351.
E-mail address: emariaop@gmail.com (E.M. Ortega).

http://dx.doi.org/10.1016/j.mbs.2014.02.004
0025-5564/

variables that measure the response. These methods have been applied to assess acceptable or tolerable dosages, and to correct some treatment or some diagnosis indicators in experimental studies. For instance, the moment distributions, the survival function, the hazard rates of the infected population for some cancer models have been studied in [23,46,30,28,38]. Some hit models with time-dependent dose were proposed by Crump and Howe [7], Kodell et al. [22] and Murdoch and Krewski [31] and the Moolgavkar–Venzon–Knudsen model (MVK) (see [29]) is a more complex cancer model than the multi-stage model, based on a stochastic birth–death process.

This article concerns the analysis of a stochastic model which we propose for describing the population that generates a response (called the response measure) to the dose with the multi-stage model. The exact distribution of the response with the classical multi-stage model having scalar parameters belongs to the binomial family. This response measure plays an important role in theory and in practice, and its exact distribution and its asymptotic behaviour, have received considerable attention in the literature. We derive some stochastic directional convexity properties (for these concepts we refer to [26]) of the parameterized Bernoulli family that is used to define the response measure, as well as, some monotonicity properties of the hazard rates and the reversed hazard rates of the Bernoulli sequence used for the response. We propose to deal with parameter uncertainty via random dose $D > 0$ and random size of the population at risk $N(\Theta) > 0$, that depends on a parameter $\Theta > 0$; or via a random vector of infection rates $(A_1, \ldots, A_m) \in \mathbb{R}_+^m$. For any fixed scalar vector of infection rates $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m) \in \mathbb{R}_+^m$, the response measure denoted by $C_{\boldsymbol{\alpha},D,\Theta}$ in Eq. (3.3) is modeled by a random sum of mixed Bernoulli random variables with an arbitrary distribution for the mixing parameters $(D, \Theta) \in \mathbb{R}_+^2$. This mixture model allows us, both to deal with heterogeneity that can not be explained by observable covariates, and to incorporate positive correlations between the dose and the size of the population at risk or between other parameters. These positive correlations emerge naturally in the process of infection or of the treatment. For instance, when some factors that affect the population at risk are only expressed once the bacterial population reaches a certain size, that depends on the dose, then positive correlations between the size of the population at risk and the dose arise. The positive correlations between the infection rates at each stage correspond to situations in which some exposure or clinical or virulence factors may affect simultaneously all the stages of the infection process. The infection capacity is often correlated with the dose level and/or the population at risk, when the larger the neoplasm of the tissue is, the higher dose of the treatment becomes.

As far as we know, modeling the parameter correlations and analyzing their effect on multi-stage models have not yet been discussed within a nonparametric framework, and there is not any probabilistic study for such models that uses the theory of stochastic orderings. To analyze the response to the dose, we provide stochastic orderings of the mixture model for the response under different stochastic relations on the random dosages and the random sizes of the population at risk; or on the random infection rates. This new methodology also provides a unified approach to the comparison of multi-stage models. Stochastic orderings are risk assessment based methods, which play an essential role in identifying and ranking the alternative choices while accounting for uncertainty, average and variability of the response.

First, we study the effect of the positive correlation between the dose and the size of the population at risk, that determine a bivariate mixing parameter vector and we assume an arbitrary distribution. For that, we consider the response measure under two scenarios described by two mixing parameter vectors, that are connected with a dependence ordering, and we compare the response measure using the variability order. Then, we conclude on the effect of increasing the positive dependence of the components of the mixing parameters, using the increasing directionally convex order. Secondly, we study just the effect of the variation of the random dose with an arbitrary mixing distribution, and by taking the size of the population at risk having scalar value or fixed probability distribution. For that, we consider the response measure under two scenarios described by two random dosages. We compare the response measure using some magnitude orders (likelihood ratio, hazard rate, stochastic, reversed hazard rate, mean residual life), and we conclude on the effect of increasing the magnitude of the dose using an univariate stochastic order. Thirdly, we study the effect of the positive correlation between the random infection rates for each stage of the infection process with fixed dose and fixed size of the population at risk. The mixing parameters are given by the random infection rates, with an arbitrary joint distribution. In such a case, we compare the response using the increasing concave order. Unlike the previous literature on multi-stage models, such as [14], neither a particular joint distribution for the mixing parameter vector, nor a marginal distribution for the dose are required to state our results. The effects of the parameter correlation on the degree of variability of the response measure to any random dose, jointly with the effect of the variation of the dose on the magnitude of the probability distribution of the response measure are analyzed and some conclusions are established.

Furthermore, assuming that the mixing parameters are positively correlated via the concepts of comonotone, mutually exclusive and positive quadrant dependent (for the dependence notions, we refer to Joe [18]) and using the relationship between these concepts and the increasing directionally convex order, from our main results, several bounds of the variability of the response measure can be derived. In this article, we focus on stochastic exact bounds of the mixture model for the response, using some mathematical inequalities or using the positive quadrant dependence denoted *PQD*. The Kibble's bivariate gamma, the Marshall–Olkin's bivariate exponential, and the bivariate extreme-value are *PQD* bivariate distributions. Also, stochastic exact bounds of the response are obtained assuming that the dose fulfills the new better than used in expectation property, denoted by *NBUE* (for this ageing notion we refer to [3]). The stochastic bounds are used to compare the classical multi-stage model (scalar parameters) versus the mixture model featuring independence or versus the mixture model featuring positive correlation via *PQD* parameters.

In practice, it is not easy to assign prior distributions to the mixing parameters, due to incomplete data, thus the exact distribution of the response measure cannot be calculated in general. It is therefore of great interest to obtain lower and upper bounds that can be effectively calculated. The aforementioned theoretical procedures of bounding, allow us to obtain some numerical bounds of the response measure, by a dose having a scalar value or a fixed specified distribution: exponential or uniform. Furthermore, in some experimental studies, the dosages are approximated by their means. From our main results, replacing the dosages by their means lowerestimates the response measure in the increasing convex order sense, and the error of this approximation can be evaluated with bounds in terms of the moment distributions. Also, the numerical bounds of the response that are obtained by fixing the dose can be used in the low-dose region assessment.

To finish, it is worth to mention that the multi-stage model relies on a rather specific parametric form for the probability to generate a response for an individual exposed to d microorganisms, or the infection probability of an individual exposed to the dose d, but the main results of the present study can be extended to the case of such an infection probability being an increasing convex function of the dose $d > 0$, or an increasing directionally concave function of the vector of the infection rates $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m) \in \mathbb{R}_+^m$.