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

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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

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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 $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m) \in \mathbb{R}_+^m$.

The article is structured as follows. Section 2 provides the mathematical methodology: some concepts on stochastic orderings, dependence orderings, and stochastic convexity. Section 3 recalls the mathematical description of the multi-stage model, and provides the mixture model for the response measure and their extensions and their structural properties. Section 4 studies the effects of the correlation between the dose and the size of the population at risk, using the variability order. Section 5 studies the effects of the variation of the dose, using some magnitude orders (likelihood ratio, hazard rate, stochastic, reversed hazard rate, mean residual life). Section 6 focuses on the effects of the correlation among the infection rates at each stage, using the increasing concave order. The proofs of the main results are given in the Appendix. The contributions of this article were presented at the XXXII National Conference on Statistics and Operations Research, A Coruña, Spain, and [33] is a summary in their Proceedings.

Throughout the article, given a measure space (Ω, A, λ) and for a probability density function f on A with respect to λ, we will assume that f belongs to the space of functions defined on $A \subset \mathbb{R}$, whose derivative $\frac{d}{dx}f(x)$ exists and is continuous in A, whenever required. All the random variables used in the article are non-negative. The notation Pr stands for a probability function on a probability space; $=_{st}$ stands for equality in law; a.s., as a shorthand for almost surely; and *iid* for independent and identically distributed. For any random variable X and an event E, $[X|E]$denotes a random variable whose distribution is the conditional distribution of X given E. The non-negative semiaxis of real numbers is denoted by $\mathbb{R}_+$. The concepts of directionally convex (directionally concave) functions are denoted by $dcx(dcv)$, and adding the monotonicity, $idcx(idcv)$ stands for a function that is increasing and directionally convex (increasing and directionally concave). We will write "increasing" and "decreasing" in wide sense.

2. Mathematical methodology

In this section, we recall some definitions of the concepts used to state and to prove our results. For the definitions, properties and relationships between the stochastic orders, we refer to [25,42].

2.1. Stochastic univariate orders

Definition 2.1. Given two non-negative random variables X and Y, then X is said to be smaller than Y in the

(i) **stochastic order**, denoted by $X \leqslant_{st} Y$, if $E[\phi(X)] \leqslant E[\phi(Y)]$, for every increasing real-valued function ϕ for which the expectations exist;
(ii) **increasing convex order**, denoted by $X \leqslant_{icx} Y$, if $E[\phi(X)] \leqslant E[\phi(Y)]$, for every increasing convex real-valued function ϕ for which the expectations exist;
(iii) **increasing concave order**, denoted by $X \leqslant_{icv} Y$, if $E[\phi(X)] \leqslant E[\phi(Y)]$, for every increasing concave real-valued function ϕ for which the expectations exist.

The increasing convex order is commonly known as variability order. If $X \leqslant_{icx} Y$ and the non-negative random variables have equal means, then it is written $X \leqslant_{cx} Y$, that implies $Var(X) \leqslant Var(Y)$, where Var denotes the variance of the random variable. The comparison $X \leqslant_{icx} Y$ provides bounds for the mean and the higher-order moments of the non-negative random variables, and for the variances as mentioned above. Mathematical inequalities based on some parametric families may be applied to obtain other bounds. The increasing concave order characterizes the comparison of the expected utility for risk averse agents in economics.

We recall that for an absolutely continuous random variable X with density function f and survival function $\overline{F}$, the hazard rate at x is defined by $r(x) = \frac{f(x)}{\overline{F}(x)}$, for any x such that $\overline{F}(x) > 0$. For a discrete integer-valued non-negative random variable, with distribution function F, the hazard rate is defined as $r(k) = \frac{F(k)-F(k-1)}{1-F(k)}$, for any $k \in \mathbb{N}$ (see [41]). The hazard rate, also known as failure rate, has been broadly applied in survival and actuarial science where is identified with the mortality rate of a lifetime.

Definition 2.2. Given two non-negative random variables X and Y with hazard rates r and s, respectively, X is smaller than Y in the **hazard rate order**, denoted by $X \leq_{hr} Y$ if $r(x) \geqslant s(x)$ for all $x \in \mathbb{R}$.

The reversed hazard rate has been applied in epidemiology, survival analysis and demography (see e.g., [21]). Given a non-negative random variable X, with distribution function F, the reversed hazard rate at x is defined as $a(x) = \frac{d}{dx} log(F(x))$, provided the derivative exists. It can be used to predict the occurrence of events since $a(x)dx$ represents the probability of failing in the interval $(x - dx, x)$, when a lifetime is found failed at time x. For a distribution function F of a discrete integer-valued non-negative random variable, the reversed hazard rate is defined by $a(k) = \frac{F(k)-F(k-1)}{F(k)}$, for any $k \in \mathbb{N}$ (see e.g., [40]).

Definition 2.3. Given two non-negative random variables X and Y with reversed hazard rates a and a^*, respectively, X is smaller than Y in the **reversed hazard rate order**, denoted by $X \leq_{rhr} Y$ if $a(x) \leqslant a^*(x)$ for all $x \in \mathbb{R}$.

The mean residual life function, also known as biometric function (see [15]) has been applied in medicine and biotechnology. For a non-negative random variable X with finite mean μ, and survival function $\overline{F}$, the mean residual life at x is defined by $\mu(x) = E[X - x|X > x]$, for any x such that $\overline{F}(x) > 0$. The **mean residual life order** is defined by the comparison of the corresponding functions of the random variables in the same direction as that of the ordering.

A stronger stochastic comparison, is given next.

Definition 2.4. Let X and Y be two absolutely continuous non-negative random variables, with density functions f and g, respectively, then X is said to be smaller than Y in the **likelihood ratio order**, denoted by $X \leq_{lr} Y$, if $\frac{f(x)}{g(x)}$ is decreasing in x such that $g(x) > 0$.

An analogous definition can be given in the discrete case by replacing the density function by the probability mass function. Note that the likelihood ratio order is a magnitude type order and implies the hazard rate order, which implies the increasing convex order, which implies the stochastic order, thus it ranks the survival functions of the non-negative random variables.

2.2. Stochastic directional convexity

The stochastic directional convexity for families of parameterized random variables plays a relevant role in the variability analysis of mixture models (see [10,34]). For its definition, the directionally convex functions are used, taking into account that the directional convexity does not imply, nor is implied by, convexity in higher-dimensional spaces. We recall these concepts, according to [26] for a general space.

Definition 2.5. Let $\mathcal{T}$ be a sublattice of either $\mathbb{R}^n$ or $\mathbb{N}^n$. A family $\{\boldsymbol{X}(\boldsymbol{\theta})|\boldsymbol{\theta} \in \mathcal{T}\}$ of parameterized multivariate random variables is said to be:

(i) stochastically increasing (denoted by $\{\boldsymbol{X}(\boldsymbol{\theta})|\boldsymbol{\theta}\in\mathcal{T}\}\in SI$) if for any $\boldsymbol{\theta}_i\in\mathcal{T}, i=1,2, \boldsymbol{\theta}_1\leqslant\boldsymbol{\theta}_2$, then there exist random variables $\boldsymbol{X}_i$, such that $\boldsymbol{X}_i=_{st}\boldsymbol{X}(\boldsymbol{\theta}_i), i=1,2$, defined on a common probability space, then $\boldsymbol{X}_1\leqslant\boldsymbol{X}_2$ almost surely;
(ii) stochastically increasing and directionally convex (denoted by $\{\boldsymbol{X}(\boldsymbol{\theta})|\boldsymbol{\theta}\in\mathcal{T}\}\in SI-DCX$) if $\{\boldsymbol{X}(\boldsymbol{\theta}),\boldsymbol{\theta}\in\mathcal{T}\}\in SI$ and $\mathbf{E}[\phi(\boldsymbol{X}(\boldsymbol{\theta}))]$ is increasing and directionally convex in $\boldsymbol{\theta}$ for any $\phi\in idcx$;
(iii) stochastically increasing and directionally concave (denoted by $\{\boldsymbol{X}(\boldsymbol{\theta})|\boldsymbol{\theta}\in\mathcal{T}\}\in SI-DCV$) if $\{\boldsymbol{X}(\boldsymbol{\theta}),\boldsymbol{\theta}\in\mathcal{T}\}\in SI$ and $\mathbf{E}[\phi(\boldsymbol{X}(\boldsymbol{\theta}))]$ is increasing and directionally concave in $\boldsymbol{\theta}$ for any $\phi\in idcv$;
(iv) stochastically increasing and linear (denoted by $\{\boldsymbol{X}(\boldsymbol{\theta})|\boldsymbol{\theta}\in\mathcal{T}\}\in SIL$) if both $\{\boldsymbol{X}(\boldsymbol{\theta})|\boldsymbol{\theta}\in\mathcal{T}\}\in SI-DCV$ and $\{\boldsymbol{X}(\boldsymbol{\theta})|\boldsymbol{\theta}\in\mathcal{T}\}\in SI-DCX$.

A family is called stochastic increasing convex ($SI-CX$) if both the parameter and random variables are univariate. Similar notation $SI-CV$ is used for the stochastic concave case.

The Poisson, the Gamma, and the Log-Normal distributions are examples of families fulfilling some stochastic convexity properties.

Finally, in the proofs of the results, we will also apply some properties of functions that are defined by composition of functions. Next, we state an assertion that will be of interest.

Lemma 2.1. *Let $f:\mathbb{R}_+^m\mapsto\mathbb{R}_+$ and $\phi:\mathbb{R}_+\mapsto[0,1]$. Then, the following composition rule holds: if f is increasing directionally concave and ϕ is increasing concave, then $\phi\circ f$ is increasing directionally concave.*

Proof. The result follows from Lemma 2.6 in [26]. □

2.3. Directionally convex orders

The stochastic directional convexity becomes the key point of some of the proofs, since it allows us to link the structure of the family of parameterized random variables with the increasing convex comparison of the mixture model defined by unconditioning on the mixing parameters. This arises when the mixing parameters are compared by a directional convex ordering, that we recall next.

Definition 2.6. Given $\mathbf{X}=(X_1,\ldots,X_n)$ and $\mathbf{Y}=(Y_1,\ldots,Y_n)$ two n-dimensional random vectors, then $\mathbf{X}$ is said to be smaller than $\mathbf{Y}$ in the directionally convex (directionally concave, increasing directionally convex, increasing directionally concave) order (denoted by $\boldsymbol{X}\leqslant_{dcx,dcv,idcx,idcv}\boldsymbol{Y}$) if $\mathbf{E}[\phi(\boldsymbol{X})]\leqslant\mathbf{E}[\phi(\boldsymbol{Y})]$, for all directionally convex (directionally concave, increasing directionally convex, increasing directionally concave) real-valued functions ϕ defined on $\mathbb{R}^n$ for which the expectations exist.

3. Mixture model for the response and structural properties

3.1. The multi-stage model

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 infection process. The single-hit models are determined by a linear dose–response function. According to them, when a host ingests exactly one cell of a pathogenic microorganism, then the probability that this pathogen will infect (survive all barriers and colonize the host) is a scalar value $0<\alpha<1$ (thus, the probability of the host not being infected is $1-\alpha$). If the host ingests an actual dose d of pathogens, then the number of microorganisms that will infect the host (survive the beginning of an infectious foci) has the binomial distribution, with the number of trials d and the success probability α. If each of the d ingested microorganisms has an equal individual infection probability α, then the probability of infection (or to generate a response) of a host that ingests exactly d pathogens is given by

$$p(\alpha,d)=1-(1-\alpha)^d. \tag{3.1}$$

This model is called the conditional dose–response model, and observe that Eq. (3.1) corresponds to the infection probability in the Reed-Frost model (see recent results in [35]).

The multi-stage model with m stages is characterized by different rates $\alpha_i>0, i=1,\ldots,m$ for each stage, such that the probability to generate a response for an individual who ingests d microorganisms depends also on $\alpha_i>0, i=1,\ldots,m$ and is given by

$$p(\boldsymbol{\alpha},d)=1-\exp\left(-\sum_{i=1}^m\alpha_i d^i\right)=1-\prod_{i=1}^m\exp(-\alpha_i d^i). \tag{3.2}$$

Observe that for any $d\in\mathbb{R}_+$, the function $p(d)=p(\boldsymbol{\alpha},d)$ defined in Eq. (3.2) is increasing convex in $d\in\mathbb{R}_+$.

Since the multi-stage model assumes a polynomial relationship for the probability of infection with respect to the dose, the model is often expected to behave as if it were a linear model in the low-dose region. Taking $\alpha_1>0$, (that is required by spontaneous transition rates), this response approximates a single hit model at low-dose, that is, $p(\alpha,d)\approx 1-\exp(-\alpha d)$. Often the infection probability is linear ($m=1$) or quadratic ($m=2$) for practical purposes.

3.2. The response measure

The response measure being focus of this article is a random variable that measures the population that generates a response with the multi-stage model. Since the observed human, plant or animal populations, are usually heterogeneous, and some biological, clinical, and environmental factors determine variations on the response of the individuals to a given dose, a stochastic model for the response should incorporate a method of modeling the parameter uncertainty. Here we will use randomization of some parameters.

Consider the multi-stage model with m stages, as described earlier. The probability of infection for an individual who ingests d microorganisms is given by Eq. (3.2). Assume that the dose d is a scalar value of a continuous non-negative random variable D. Also, assume that the size of the population of susceptible individuals, or of the population at risk, denoted by $N(\theta)$, is an integer-valued non-negative random variable, that depends on a random parameter having on values $\theta\in\mathcal{T}$ over a sublattice $\mathcal{T}\subseteq\mathbb{R}_+$. Consider that $\boldsymbol{\alpha}=(\alpha_1,\ldots,\alpha_m)\in\mathbb{R}_+^m$ is a scalar vector.

3.2.1. Exact distribution

If we consider that each of the susceptible individuals is exposed to a given ingested dose d, conditioning on $N=N(\theta)$ fixed and $D=d$ fixed, the conditional distribution of the response measure (or equivalently, the number of infected individuals) belongs to the binomial family, with the number of trials N and the success probability in Eq. (3.2). Formally, the population that generates a response is described by the random variable

$$C_{\boldsymbol{\alpha},d,\theta}=\sum_{j=1}^{N(\theta)}I_j(p(\boldsymbol{\alpha},d)) \tag{3.3}$$

with $\{I_j(p(\boldsymbol{\alpha},d)), j\in\mathbb{N}\}$ being a sequence of *iid* Bernoulli random variables with parameter given in Eq. (3.2). Thus, the exact

distribution of the population that generates a response $C_{\boldsymbol{\alpha},d,\theta}$ given by Eq. (3.3) is Binomial.

3.2.2. Mixture model for the response, with random dose

Unconditioning, consider that $I_j(p(\boldsymbol{\alpha},d)), j\in\mathbb{N}$ and $N(\theta)$ are independent for any fixed values of the parameters $d>0$ and $\theta\in\mathcal{T}$, that is, they are conditionally independent, then $C_{\boldsymbol{\alpha},D,\Theta}$ is a random sum of mixed Bernoulli random variables, with mixing parameters $(D,\Theta)\in\mathbb{R}_+^2$ (since $\{I_j(p(\boldsymbol{\alpha},D)), j\in\mathbb{N}\}$ is a sequence of identically distributed mixed Bernoulli random variables with parameter $p(D)=p(\boldsymbol{\alpha},D)$ being a transform of D given in Eq. (3.2)). Since (D,Θ) exhibits statistical dependence, in general, there is not any expression of the distribution function for the mixture model $C_{\boldsymbol{\alpha},D,\Theta}$ of the response measure.

3.2.3. Mixture model for the response, with random infection rates

Consider now the multi-stage model with random infection rates A_i $i=1,\ldots,m$ that characterize the response at each stage of the infection for the population at risk. As mentioned in Section 1, recall that m may be interpreted as the number of transitions in the infection process. Assume that the fixed dose is scalar. The response measure is given by

$$C_{\boldsymbol{A},d}=\sum_{j=1}^{N} I_j(p(A_1,\ldots,A_m,d)), \tag{3.4}$$

with $\{I_j(p(A_1,\ldots,A_m,d)), j\in\mathbb{N}\}$ being a sequence of identically distributed mixed Bernoulli random variables with parameter $p(A_1,\ldots,A_m,d)$ being a transform of the random vector $(A_1,\ldots,A_m)$ given by Eq. (3.2). We notice that for any fixed scalar vector $\boldsymbol{\alpha}\in\mathbb{R}_+^m$, the function $p(\boldsymbol{\alpha})=p(\boldsymbol{\alpha},d)$ given in Eq. (3.2) is increasing directionally concave in $\boldsymbol{\alpha}\in\mathbb{R}_+^m$.

The random variable defined in Eq. (3.4) is a mixture of the family of parameterized random variables $\{\sum_{j=1}^{N} I_j(p(\alpha_1,\ldots,\alpha_m,d)) \,|(\alpha_1,\ldots,\alpha_m)\in\mathbb{R}_+^m\}$ with mixing parameters $(A_1,\ldots,A_m)\in\mathbb{R}_+^m$. In general, there is not any expression of the distribution function for this model.

3.2.4. Structural properties and extensions

Some structural properties of some parameterized families of random variables that are used to define the stochastic models in this article are given next. First, we state some useful properties of the hazard rates and the reversed hazard rates of the Bernoulli variables.

Lemma 3.1. *Consider $\{I_j(p(\boldsymbol{\alpha},d)), j\in\mathbb{N}\}$ being a sequence of Bernoulli random variables with parameter $p_{\boldsymbol{\alpha}}(d)=p(\boldsymbol{\alpha},d)$ given in* Eq. (3.2) *with $\boldsymbol{\alpha}$ scalar, and assume that $(I_j(p(\boldsymbol{\alpha},d)), I_j(p(\boldsymbol{\alpha},d'))), j=1,\ldots,n$ are independent pairs of random variables, for any fixed $0<d\leqslant d'$. Then, for any $0<d\leqslant d'$*

(i) $r_{I_j(p_{\boldsymbol{\alpha}}(d))}(x)\geqslant r_{I_j(p_{\boldsymbol{\alpha}}(d'))}(x)$, *for all $x\geqslant 0$, where r_X denotes the hazard rate of X,*

(ii) $a_{I_j(p_{\boldsymbol{\alpha}}(d))}(x)\leqslant a_{I_j(p_{\boldsymbol{\alpha}}(d'))}(x)$, *for all $x\geqslant 0$, where a_X denotes the reversed hazard rate of X.*

Proof. A direct proof of the first assertion comes from the fact that the quotient of survival functions $\frac{\overline{G}_{I_j(p(\boldsymbol{\alpha},d'))}(x)}{\overline{G}_{I_j(p(\boldsymbol{\alpha},d))}(x)}$ is an increasing function, where $\overline{G}_{I_j(p(\boldsymbol{\alpha},d))}$ denotes the survival function of a Bernoulli random variable $I_j(p(\boldsymbol{\alpha},d))$ as above. For that, observe that for any $0<d\leqslant d'$ and $x\in[0,1)$,

$$\frac{\overline{G}_{I_j(p(\boldsymbol{\alpha},d'))}(x)}{\overline{G}_{I_j(p(\boldsymbol{\alpha},d))}(x)}=\frac{1-\exp\left(-\sum_{i=1}^{m}\alpha_i d'^i\right)}{1-\exp\left(-\sum_{i=1}^{m}\alpha_i d^i\right)}>1$$

and for $x<0$

$$\frac{\overline{G}_{I_j(p(\boldsymbol{\alpha},d'))}(x)}{\overline{G}_{I_j(p(\boldsymbol{\alpha},d))}(x)}=1.$$

The second assertion arises from the fact that for all $j=1,\ldots,n$, and for any $0<d\leqslant d'$

$$\frac{G_{I_j(p(\boldsymbol{\alpha},d'))}(x)}{G_{I_j(p(\boldsymbol{\alpha},d))}(x)} \text{ is an increasing function,} \tag{3.5}$$

where $G_{I_j(p(\boldsymbol{\alpha},d))}$ denotes the distribution function of a Bernoulli random variable $I_j(p(\boldsymbol{\alpha},d))$ as above. □

Now, from Example 5.3.8 by Chang et al. [5] the Bernoulli family is *SIL*, as it is stated in the following lemma.

Lemma 3.2. *Let $\{I(p)|p\in(0,1)\}$ denote a family of Bernoulli random variables, then*

$\{I(p)|p\in(0,1)\}\in SIL$.

Theorem 3.2 in [26] deals with the stochastic directional convexity or the stochastic directional concavity of families of random variables defined by composition. Some parameterized Bernoulli variables defined by composition are used to define the response measure. We study them in the next theorem, whose assertions are used in some main results.

Lemma 3.3. *Let $\{I(p)|p\in(0,1)\}$ denote a family of Bernoulli random variables.*

(i) *If $p:\mathbb{R}_+\mapsto(0,1)$ is an increasing convex function on its domain, then*

$\{I(p(d))|d>0\}\in SI-CX$,

(ii) *If $p:\mathbb{R}_+^m\mapsto(0,1)$ is an increasing directionally concave function on its domain, then*

$\{I(p(\boldsymbol{\alpha}))|\boldsymbol{\alpha}\in\mathbb{R}_+^m\}\in SI-DCV$.

Proof. Using Lemma 3.2, the Bernoulli family is $SI-CX$ in its parameter. Then, the assertion (i) is a consequence of Theorem 3.2 in [26] since the family of random variables is obtained by composition of a $SI-CX$ family and an increasing convex function.

Now, the assertion (ii) comes from the fact that the Bernoulli family is $SI-CV$ in its parameter (from Lemma 3.2 again), and Theorem 3.2 in [26], because the family of random variables comes from the composition of a $SI-CV$ family and an increasing directionally concave function. □

Furthermore, these earlier properties allow us to extend the main results in the article for a more general formula of the probability to generate a response for an individual who receives a dose d, under the multi-stage model. The main results in Sections 4 and 5 hold for a multi-stage model characterized by the response measure in Eq. (3.3) with $\{I_j(p(\boldsymbol{\alpha},d)), j\in\mathbb{N}\}$ being a sequence of identically distributed Bernoulli random variables with parameter $p(d)=p(\boldsymbol{\alpha},d)$ given by an increasing convex function $p:\mathbb{R}_+\mapsto(0,1)$. Also, the main results in Section 6 hold for a multi-stage model characterized by the response in Eq. (3.4) with $\{I_j(p(\alpha_1,\ldots,\alpha_m,d)), j\in\mathbb{N}\}$ being a sequence of identically distributed Bernoulli random variables with parameter $p(\boldsymbol{\alpha})=p(\boldsymbol{\alpha},d)$ given by an increasing directionally concave function $p:\mathbb{R}_+^m\mapsto(0,1)$.

A time-dependent multi-stage model can be defined by adding the time t as a parameter in the function $p(t,d) = p(\boldsymbol{\alpha}, t, d)$ given by an increasing directionally convex function $p : \mathbb{R}_+^2 \mapsto (0,1)$.

3.3. An application of the multi-stage model

Carcinogenesis involves the accumulation of genetic changes within a single cell and the initial clonal expansion of an initiated cell that starts the tumour promotion stages until the final development of cancer, after a series of sudden and irreversible changes which must take place in a specific order. The hit models have been applied mainly in clinical oncology to study the tumour incidence when a tissue have N cells that can potentially experience carcinogenic transformations. In particular, the model described by Eq. (3.2) is analogous to that studied in [6], where m is the number of mutations in the process of tumour incidence, which are dose dependent and characterized by the rates $\alpha_i > 0, i = 1,\ldots,m$. Other studies proposing hit models for the cancer process are given e.g., by Moolgavkar and Venzon [29], Owens et al. [36], Ritter et al. [39], Morgenthaler et al. [30] and Gsteiger and Morgenthaler [14]. The last article proposed a two-stage hit model for cancer process using a mixture modeling for the population that generates a response and a Bayesian approach, and their model consists of an initiation stage (where the mutations transform stem cells into intermediate states) and a promotion stage (that includes clonal expansion and final malignant tumour cell transformation).

The critical volume models (see [32]) have been developed to study the response of organs or tissues to the radiation dosages by (oncological) treatments. This model assumes that a normal organ (or tissue) is composed of functional subunits (FSUs) (or equivalently, a tumour consists of clonogenic tumour cells) that are submitted to a radiation dose. Given the number of these structural elements, there exists a critical number of them that must be damaged to cause a failure in the whole tissue (or destroy the tumour). Under homogeneous radiation, the probability of damaging a FSU (or a tumour cell) due to the dose d, is given by $p(d) = (1 - \exp(-\alpha d))^{n_0}$, where it depends functionally on the dose d, the number n_0 of cells in the FSU and other parameters, as the radiosensitivity α. The total number of FSUs damaged after radiation with dose d in the tissue is a response measure that is given by a random sum with identically distributed Bernoulli random variables of parameter $p(d)$, as above.

In the following sections, we compare the population that generates a response under different scenarios described by mixing parameters, that are related via stochastic orderings.

4. The effect of the correlation between the dose and the size of the population at risk

In this section, we consider the positive correlations between the size of the population at risk and the dose. We consider a multi-stage model characterized by the response measure $C_{\boldsymbol{\alpha},D,\Theta}$ given by Eq. (3.3), and we study the random variable $C_{\boldsymbol{\alpha},D,\Theta}$ with mixing parameters (D,Θ).

4.1. Variability comparison of the response measure

In this section, we assume that $m \in \mathbb{N} \cup \{0\}$ and $\alpha_i \geqslant 0, i = 1,\ldots,m$ are fixed values, and $N(\theta), I_1(p(\boldsymbol{\alpha},d)), \ldots, I_n(p(\boldsymbol{\alpha},d))$ are independent random variables for any fixed values of $\theta > 0$ and $d > 0$.

Theorem 4.1. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.3). Assume that $N(\theta)$ is stochastically increasing and convex in $\theta > 0$. For two random vectors (D,Θ) and (D',Θ'), such that $(D,\Theta) \leq_{idcx} (D',\Theta')$, then $C_{\boldsymbol{\alpha},D,\Theta} \leq_{icx} C_{\boldsymbol{\alpha},D',\Theta'}$.*

The earlier result means that the more positively dependent the dose and the size of the population at risk are, then the more variable and the more larger in average the response becomes. When the behaviour of the parameters is such that as the larger the population at risk is, the higher required dose level becomes, then the dispersion of the response is higher. Therefore, the exposure factors that make the individuals being more susceptible to the infection influence on the overdispersion of the response.

4.2. Stochastic exact bounds of the response measure

The next result provides a lower exact bound of the probability distribution of the response.

Theorem 4.2. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.3), with a finite fixed size of the population at risk n. For a random dose D, then*

$$C_{\boldsymbol{\alpha},D,n} \geqslant_{cx} n\left(1 - E\left[\prod_{i=1}^{m} \exp(-\alpha_i D^i) | D\right]\right),$$

where $C_{\boldsymbol{\alpha},d,n} = \sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha},d))$ with $I_j(p(\boldsymbol{\alpha},d)), j = 1,\ldots,n$ being iid Bernoulli random variables with parameter $p(\boldsymbol{\alpha},d)$ given by Eq. (3.2), for any fixed $d > 0$.

Theorem 4.2 leads to numerical bounds just by using a prior distribution for the dose D, and is useful for determining a threshold dose with respect to the convex order.

The following result provides lower bounds when the mixing parameter vector is *PQD*.

Theorem 4.3. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.3). Assume that $N(\theta)$ is stochastically increasing and convex in $\theta > 0$. If (D,Θ) is PQD, then for any random vector (D^i,Θ^i) with identical marginal distributions than (D,Θ), but independent components, then $C_{\boldsymbol{\alpha},D,\Theta} \geqslant_{icx} C_{\boldsymbol{\alpha},D^i,\Theta^i}$.*

Remark 4.1. Observe that if D and Θ are mutually exclusive (i.e., $Pr(D > 0, \Theta > 0) = 0$), for any random vector (D',Θ') with identical marginal distributions than (D,Θ), then $C_{\boldsymbol{\alpha},D,\Theta} \leq_{icx} C_{\boldsymbol{\alpha},D',\Theta'}$. Analogously, if D and Θ are comonotone (i.e., their joint distribution function is given by $F_+(d,\theta) = \min\{F_D(d), F_\Theta(\theta)\}$ with F_D and F_Θ being the corresponding marginals), for any random vector (D',Θ') with identical marginal distributions than (D,Θ), then $C_{\boldsymbol{\alpha},D,\Theta} \geqslant_{icx} C_{\boldsymbol{\alpha},D',\Theta'}$.

Both of the earlier results allow one to compare the response measure with the multi-stage model with independent parameters and the mixture model for the response measure with positively correlated parameters, via the variability order of the response measure.

Other results in the literature on stochastic orders of convolutions and of random sums of Bernoulli random variables can be used to derive other bounds (see for instance, [12,13]).

4.3. Bounds determined by an Exponential dose

Another consequence of Theorem 4.1 is given next, where the effect of the ageing property of the dose on the variability of the response measure is explored. In particular, for an *NBUE* dose, an upper bound of the variability of the response can be computed from an Exponential dose.

Theorem 4.4. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.3) with $\theta > 0$ fixed.*

(i) *If* $D \leq_{icx} D'$, *then* $C_{\boldsymbol{\alpha},D,\theta} \leq_{icx} C_{\boldsymbol{\alpha},D',\theta}$.
(ii) *If* D *is NBUE with mean* μ_D *then* $C_{\boldsymbol{\alpha},D,\theta} \leq_{icx} C_{\boldsymbol{\alpha},Exp(\mu_D),\theta}$, *where* $Exp(\mu_D)$ *has exponential distribution with mean* μ_D.

The following example provides an upper bound for the expected value of the response, when the dose is *NBUE*.

Example 1. Consider a multi-stage model as above with three stages with $\boldsymbol{\alpha} = (\alpha_1, \alpha_2, \alpha_3)$ fixed. Let the population at risk $N(\Theta) = n$ having a scalar value. Let the dose D be a random variable exponentially distributed with mean $\mu_D = d$. Straighforward calculation and extrapolation to the single-hit model lead to

$$E[C_{\boldsymbol{\alpha},D,\theta}] \approx n\left(1 - \frac{1}{1 + d\alpha_1}\right).$$

Let the dose D' being *NBUE*, then by applying the earlier theorem,

$$E[C_{\boldsymbol{\alpha},D',\theta}] \leqslant n\left(1 - \frac{1}{1 + d\alpha_1}\right).$$

The results stated in Theorem 4.4 also lead to compare the response from the classical multi-stage model (that is characterized by scalar parameters), and from the mixture model for the response having independent parameters (and also to connect them with the mixture model with positive dependent parameters as this in Theorem 4.3). This result is stated next.

Theorem 4.5. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.3) with* $\theta > 0$ *fixed. Let* D *have exponential distribution with mean* $\mu_D = d$, *then from Theorem 4.4 and Eq.* (3.A.48) *in* [42], $C_{\boldsymbol{\alpha},d,\theta} \leq_{icx} C_{\boldsymbol{\alpha},D,\theta}$.

The constant dose minimizes the variability of the response measure, with respect to an Exponential dose with the same mean (notice that for a given mean, the constant dose constitutes the less variable dose). As a conclusion, replacing the dosages by their means leads to lowerestimating the response measure in the increasing convex order sense.

In addition, Theorem 4.5 allows us to deal with the low-dose risk assessment problem, when such an scenario holds, just by comparing the response with that having the scalar dose $0 < d < 1$.

4.4. Bounds determined by an Uniform dose

The uniform dose leads to a lower bound for the response measure.

Theorem 4.6. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.3) with* $\theta > 0$ *fixed. Let* D *have density function being decreasing on* $[0, +\infty)$, *with mean* μ_D. *Denote* $U(0, 2\mu_D)$ *a random variable with uniform distribution on the interval* $(0, 2\mu_D)$. *Then,* $C_{\boldsymbol{\alpha},D,\theta} \geqslant_{icx} C_{\boldsymbol{\alpha},U(0,2\mu_D),\theta}$.

Another example of numerical bound is given next for the response.

Example 2. Consider a multi-stage model as above with two stages with $\boldsymbol{\alpha} = (\alpha_1, \alpha_2)$ fixed. Let the population at risk $N(\Theta)$ have Poisson distribution with mean Θ, with mean $\mu_\Theta > 0$. Let the dose D be a random variable uniformly distributed in the interval (l_1, l_2), such that (D, Θ) is *PQD*. Then, by extrapolation to the single hit model and with $p_i = \exp(-\alpha_i)$, for $i = 1, 2$,

$$\begin{aligned} E[C_{\boldsymbol{\alpha},D,\Theta}] &\geqslant E[N(\Theta)|\Theta]E[p(\boldsymbol{\alpha},D)|D] = E[\Theta](1 - E[p_1^D p_2^{D^2}|D]) \\ &\geqslant \mu_\Theta(1 - E[p_1^D|D]) \end{aligned}$$

and by elemental calculation

$$\mu_\Theta(1 - E[p_1^D|D]) = \mu_\Theta\left(1 - \frac{p_1^{l_2} - p_1^{l_1}}{(l_2 - l_1)\log(p_1)}\right).$$

5. The effect of the variation of the dose

In this section, we analyze just the effect of a random dose on the population that generates a response, by assuming that the size of the population at risk is a scalar (also it holds for a random variable with a fixed probability distribution). Our results involve other stochastic orders related to the magnitude of the probability distribution of the random variable.

From now on, we denote by $C_{\boldsymbol{\alpha},d,n} = \sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d))$ the number of individuals that generate a response for a multi-stage model as above with scalar size of the population at risk n, with $I_j(p(\boldsymbol{\alpha}, d))$ $j = 1, \ldots, n$ being *iid* Bernoulli random variables with parameter $p(\boldsymbol{\alpha}, d)$, given by Eq. (3.2), for any fixed value of $d > 0$.

We start with a result for the likelihood ratio order, that requires stronger assumptions for the comparison of the dosages.

Theorem 5.1. *Let* $m \in \mathbb{N} \cup \{0\}$ *and* $\alpha_i \geqslant 0, i = 1, \ldots, m$ *be fixed values, and consider a multi-stage model characterized by the response measure in Eq. (3.3), with a fixed size of the population at risk* n. *Assume that* $(I_j(p(\boldsymbol{\alpha}, d)), I_j(p(\boldsymbol{\alpha}, d'))), j = 1, \ldots, n$ *are independent pairs of random variables, for any fixed* $d \leqslant d'$. *If* $D \leq_{lr} D'$, *then* $C_{\boldsymbol{\alpha},D,n} \leq_{lr} C_{\boldsymbol{\alpha},D',n}$.

A consequence of the previous result is a comparison of the response measure in the sense of the hazard rate order (that will be studied next), in the stochastic order (that compares the survival functions of the random variables), as well as, comparison of the conditional probabilities of the population that generates a response being larger than a given fixed level.

The following result is a comparison of the hazard rate of the response measure, from a finite population at risk. This is stated in terms of the hazard rate order between the dosages.

Theorem 5.2. *Let* $m \in \mathbb{N} \cup \{0\}$ *and* $\alpha_i \geqslant 0, i = 1, \ldots, m$ *be fixed values, and consider a multi-stage model characterized by the response measure in Eq. (3.3), with a fixed size of the population at risk* n. *Assume that* $(I_j(p(\boldsymbol{\alpha}, d)), I_j(p(\boldsymbol{\alpha}, d'))), j = 1, \ldots, n$ *are independent pairs of random variables, for any fixed* $d \leqslant d'$. *If* $D \leq_{hr} D'$, *then* $C_{\boldsymbol{\alpha},D,n} \leq_{hr} C_{\boldsymbol{\alpha},D',n}$.

A similar result can be stated for the stochastic order and the reversed hazard rate order.

Theorem 5.3. *Let* $m \in \mathbb{N} \cup \{0\}$ *and* $\alpha_i \geqslant 0, i = 1, \ldots, m$ *be fixed values, and consider a multi-stage model characterized by the response measure in Eq. (3.3), with a fixed size of the population at risk* n. *Assume that* $(I_j(p(\boldsymbol{\alpha}, d)), I_j(p(\boldsymbol{\alpha}, d'))), j = 1, \ldots, n$ *are independent pairs of random variables, for any fixed* $d \leqslant d'$. *If* $D \leq_{st} D'$, *then* $C_{\boldsymbol{\alpha},D,n} \leq_{st} C_{\boldsymbol{\alpha},D',n}$.

Theorem 5.4. *Let* $m \in \mathbb{N} \cup \{0\}$ *and* $\alpha_i \geqslant 0, i = 1, \ldots, m$ *be fixed values, and consider a multi-stage model characterized by the response measure in Eq. (3.3), with a fixed size of the population at risk* n. *Assume that* $(I_j(p(\boldsymbol{\alpha}, d)), I_j(p(\boldsymbol{\alpha}, d'))), j = 1, \ldots, n$ *are independent pairs of random variables, for any fixed* $d \leqslant d'$. *If* $D \leq_{rhr} D'$, *then* $C_{\boldsymbol{\alpha},D,n} \leq_{rhr} C_{\boldsymbol{\alpha},D',n}$.

Remark 5.1. Result 5.2 implies the comparison of the mean residual life functions of the random variables (see Theorem 2.A.1 in [42]). In particular, assuming again that $(I_j(p(\boldsymbol{\alpha},d)),I_j(p(\boldsymbol{\alpha},d')))$, $j=1,\ldots,n$ are independent pairs of random variables, for any fixed $d\leqslant d'$; then $D\leq_{lr}D'$ implies $C_{\boldsymbol{\alpha},D,n}\leq_{mr}C_{\boldsymbol{\alpha},D',n}$, where $\leq_{mr}$ denotes the mean residual life order.

6. The effect of the correlation between the infection rates

In this section, we consider the stochastic model for the response measure given in Eq. (3.4), when the infection rates are the only source of uncertainty. We assume that $m\in\mathbb{N}\cup\{0\}$ and $d>0$ are fixed values, and a random size of population at risk N with a fixed probability distribution, and that N and $I_1(p(\boldsymbol{\alpha},d))$, …, $I_n(p(\boldsymbol{\alpha},d))$ are independent random variables for any fixed values of $\boldsymbol{\alpha}\in\mathbb{R}^m_+$ and $d>0$. The following result states comparisons of the expected utility under risk aversion, for the response measure, by the increasing concave order.

Theorem 6.1. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.4). For two random vectors of infection rates* $\boldsymbol{A}=(A_1,\ldots,A_m)$ *and* $\boldsymbol{A}'=(A'_1,\ldots,A'_m)$ *such that* $(A_1,\ldots,A_m)\leq_{idcv}(A'_1,\ldots,A'_m)$, *then* $C_{\boldsymbol{A},d}\leq_{icv}C_{\boldsymbol{A}',d}$.

Observe that the earlier result can be proved using similar arguments as those in Theorem 3.5 in [10].

Remark 6.1. The previous result implies the comparison of the Laplace transforms of the random variables, since the *icv* order implies the Laplace transform order (see Theorem 5.A.16 in [42]). This result is useful since inversion techniques for Laplace transforms can be applied for the calculation of bounds for the distribution function of the response measure.

Remark 6.2. Other complementary results can be established as follows. The influence of a common parameter for the number of summands and the summands in the random sum can be studied just from Corollary 3.3 in [11].

The next result assumes statistical independence between the rates $A_i, i=1,\ldots,m$ and provides a bound for the risk averse utility of the response in terms of exponentially distributed rates.

Theorem 6.2. *Consider a multi-stage model as above characterized by the response measure in Eq. (3.4). Let* $\boldsymbol{A}=(A_1,\ldots,A_m)$ *and* $\boldsymbol{A}'=(Exp(\mu_{A_1}),\ldots,Exp(\mu_{A_m}))$ *be random vectors, both having independent components with means* μ_{A_i}, *and being NBUE and exponentially distributed, respectively, for* $i=1,\ldots,m$. *Then, for any fixed* $d>0, C_{\boldsymbol{A},d}\geqslant_{icv}C_{\boldsymbol{A}',d}$.

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Appendix

Proof of Theorem 4.1.

Proof. Consider the random variable $C_{\boldsymbol{\alpha},D,\Theta}$ defined in Eq. (3.3), with random $D>0$ and random $\Theta>0$. Observe that the function $p_{\boldsymbol{\alpha}}(d):=p(\boldsymbol{\alpha},d)$ defined in Eq. (3.2) is increasing and convex in d, for any fixed $\boldsymbol{\alpha}=(\alpha_1,\ldots,\alpha_m)\in\mathbb{R}^m_+$. From Lemma 3.3 i), then for any $j\in\mathbb{N}$,

$$\{Y_j(d)=I_j(p(\boldsymbol{\alpha},d))|d>0\}\in SI-CX.$$

Now, notice that the assumptions of Theorem 3.2 in [11] hold for $C_{\boldsymbol{\alpha},D,\Theta}$, that is, $N(\theta)$ and $Y_j(d), j=1,\ldots,n$ are independent for any fixed values of the parameters, $\{N(\theta)|\theta\in\mathcal{T}\}\in SI-CX$, and $\{Y_j(d)|d>0\}\in SI-CX$, thus, the $SI-DCX$ property holds for the random sum, i.e.,

$$\{C_{\boldsymbol{\alpha},D,\Theta}|(d,\theta)\in\mathbb{R}^2_+\}=\left\{\sum_{j=1}^{N(\theta)}Y_j(d)|(d,\theta)\in\mathbb{R}^2_+\right\}\in SI-DCX.$$

For any increasing convex function u, consider the function $\phi(d,\theta)=E[u(C_{\boldsymbol{\alpha},d,\theta})]$ for any scalar $(d,\theta)\in\mathbb{R}^2_+$. Then, $\phi(d,\theta)$ is increasing and directionally convex in any $(d,\theta)\in\mathbb{R}^2_+$.

To prove the result, we need to see that

$$E[u(C_{\boldsymbol{\alpha},D,\Theta})]\leqslant E[u(C_{\boldsymbol{\alpha},D',\Theta'})].$$

Using the conditional expected value,

$$E[u(C_{\boldsymbol{\alpha},D,\Theta})]=E[E[u(C_{\boldsymbol{\alpha},D,\Theta})|(D,\Theta)]]=E[\phi(D,\Theta)].$$

The result follows since $E[\phi(D,\Theta)]\leqslant E[\phi(D',\Theta')]$ from the assumption $(D,\Theta)\leq_{idcx}(D',\Theta')$. □

Proof of Theorem 4.2

Proof. By applying Theorem 3.A.20 in [42], then

$$\begin{aligned}I_1(p(\boldsymbol{\alpha},D))+\cdots+I_n(p(\boldsymbol{\alpha},D))&\geqslant_{cx}E[I_1(p(\boldsymbol{\alpha},D))|D]+\cdots+E[I_n(p(\boldsymbol{\alpha},D))|D]\\&=nE[I_j(p(\boldsymbol{\alpha},D))|D]\end{aligned}\tag{7.1}$$

and by using Eq. (3.2) and the expected value of the Bernoulli random variable

$$nE[I_j(p(\boldsymbol{\alpha},D))|D]=nE\left[1-\prod_{i=1}^{m}\exp(-\alpha_iD^i)|D\right]$$

and the result follows. □

Proof of Theorem 4.4

Proof. The assertion (i) is a consequence of Theorem 4.1. for $\theta>0$ fixed. To prove the assertion (ii), notice that from Theorem 3.A.55 in [42] if D is *NBUE* with mean μ_D then, $D\leq_{cx}Exp(\mu_D)$ and then the result follows from assertion (i). □

Proof of Theorem 4.6

Proof. By applying Theorem 3.A.46 in [42], then $D\geqslant_{cx}U(0,2\mu_D)$. Then the result follows from Theorem 4.4. □

Proof of Theorem 5.1

Proof. Consider the random variable $C_{\boldsymbol{\alpha},D,\theta}$ defined in Eq. (3.3), with random $D>0$. Consider $N(\theta)=n\in\mathbb{N}$ having a scalar value. Consider an arbitrary $j\in\mathbb{N}$.

Recall that the function $p_{\boldsymbol{\alpha}}(d):=p(\boldsymbol{\alpha},d)$ defined in Eq. (3.2) is increasing. First, let $I_j:=I_j(p(\boldsymbol{\alpha},d))$ denote a Bernoulli random variable with parameter $p(\boldsymbol{\alpha},d)$ that has the following probability mass function $p_1=Pr(I_j=1)=p_{\boldsymbol{\alpha}}(d)$ and $p_0=Pr(I_j=0)=1-p_{\boldsymbol{\alpha}}(d)$, and $p_k=0$, for any $k=2,3,\ldots$. Since $\frac{p_1}{p_0}\geqslant\frac{p_2}{p_1}$, then I_j has logconcave density (also called PF_2 density, see e.g., [20]).

By using the characterization 1.C.3. for the likelihood ratio order in [42], $I_j(p_{\boldsymbol{\alpha}}(d))\leq_{lr}I_j(p_{\boldsymbol{\alpha}}(d'))$, for any $0<d\leqslant d'$ taking into account that $p_{\boldsymbol{\alpha}}(d)$ is increasing in $d>0$.

Now, observe that the assumptions of Theorem 1.C.9. in [42] hold, that is, $(I_j(p(\boldsymbol{\alpha},d)),I_j(p(\boldsymbol{\alpha},d')))$, $j=1,\ldots,n$ are independent pairs of random variables, for any $0<d\leqslant d'; I_j(p_{\boldsymbol{\alpha}}(d))\leq_{lr}I_j(p_{\boldsymbol{\alpha}}(d'))$,

for any $0 < d \leqslant d'$; and $I_j(p(\boldsymbol{\alpha}, d))$ has logconcave density for any $j = 1, \ldots, n$, and $d > 0$; thus

$$\sum_{j=1}^{n} I_j(p_{\boldsymbol{\alpha}}(d)) \leq_{lr} \sum_{j=1}^{n} I_j(p_{\boldsymbol{\alpha}}(d')). \tag{7.2}$$

Finally, the result follows from Eq. (7.2), and the assumption $D \leq_{lr} D'$ by applying Theorem 1.C.17 in [42] on the preservation of the likelihood ratio order by mixtures, for the mixture of the family of random variables $\{\sum_{j=1}^{n} I_j(p_{\boldsymbol{\alpha}}(d)) | d > 0\}$, with mixing parameter D, that determines the random variable $C_{\boldsymbol{\alpha},D,\theta}$. □

Proof of Theorem 5.2

Proof. Consider the function $p_{\boldsymbol{\alpha}}(d) := p(\boldsymbol{\alpha}, d)$ defined in Eq. (3.2). First, observe that from the proof of Theorem 5.1, the Bernoulli random variables $I_j(p(\boldsymbol{\alpha}, d))$ are clearly *IFR* (increasing hazard rate), for all $j = 1, \ldots, n$; and in addition, $I_j(p_{\boldsymbol{\alpha}}(d)) \leq_{lr} I_j(p_{\boldsymbol{\alpha}}(d'))$, for any $0 < d \leqslant d'$ and therefore, $I_j(p_{\boldsymbol{\alpha}}(d)) \leq_{hr} I_j(p_{\boldsymbol{\alpha}}(d'))$, for any $0 < d \leqslant d'$. The earlier assertion alternatively comes directly from Lemma 3.1.

Now, observe that the assumptions of Theorem 1.B.4 in [42] hold, since $(I_j(p(\boldsymbol{\alpha}, d)), I_j(p(\boldsymbol{\alpha}, d'))), j = 1, \ldots, n$ are independent pairs of random variables, for any $0 < d \leqslant d'; I_j(p_{\boldsymbol{\alpha}}(d)) \leq_{hr} I_j(p_{\boldsymbol{\alpha}}(d'))$, for any $0 < d \leqslant d'$; and all the random variables $I_j(p_{\boldsymbol{\alpha}}(d))$ are *IFR* for any $j = 1, \ldots, n$ and $d > 0$; thus, we have that, for any $0 < d \leqslant d'$,

$$\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d)) \leq_{hr} \sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d')). \tag{7.3}$$

Finally, notice that from the earlier inequality and from the assumption $D \leq_{hr} D'$, then the assumptions of Theorem 1.B.14. in [42] (on preservation by mixtures of the hazard rate order) hold for the mixture $\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, D))$ with mixing parameter D. Thus,

$$\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, D)) \leq_{hr} \sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, D')),$$

and the result follows. □

Proof of Theorem 5.3

Proof. Consider the function $p_{\boldsymbol{\alpha}}(d) := p(\boldsymbol{\alpha}, d)$ defined in Eq. (3.2). First, observe that from the proof of Theorem 5.1, the Bernoulli random variables $I_j(p(\boldsymbol{\alpha}, d))$ are clearly *IFR* for all $j = 1, \ldots, n$; and in addition, $I_j(p_{\boldsymbol{\alpha}}(d)) \leq_{st} I_j(p_{\boldsymbol{\alpha}}(d'))$, for any $0 < d \leqslant d'$.

From the last inequality and Theorem 1.A.3 in [42] on the preservation of the stochastic order by partial sums, for any $0 < d \leqslant d'$,

$$\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d)) \leq_{st} \sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d')). \tag{7.4}$$

Finally, the result follows from the earlier inequality, from the assumption $D \leq_{st} D'$ and from Theorem 1.A.6 in [42] on the preservation by mixtures of the stochastic order, for the mixture $\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, D))$ with mixing parameter D, which determines $C_{\boldsymbol{\alpha},D,\theta}$. □

Proof of Theorem 5.4

Proof. We notice that the Bernoulli random variables have decreasing reversed hazard rate.

Also, from the proof of Theorem 5.1 $I_j(p(\boldsymbol{\alpha}, d)) \leq_{rhr} I_j(p(\boldsymbol{\alpha}, d'))$, for any $0 < d \leqslant d'$. This assertion alternatively comes directly from Lemma 3.1.

Now, the assumptions of Theorem 1.B.45 in [42] hold, since $(I_j(p(\boldsymbol{\alpha}, d)), I_j(p(\boldsymbol{\alpha}, d'))), j = 1, \ldots, n$ are independent pairs of random variables, for any $0 < d \leqslant d'; I_j(p(\boldsymbol{\alpha}, d)) \leq_{rhr} I_j(p(\boldsymbol{\alpha}, d'))$, for any $0 < d \leqslant d'$; and all the random variables $I_j(p(\boldsymbol{\alpha}, d))$ have decreasing reversed hazard rates for any $j = 1, \ldots, n$, and for any $d > 0$. Thus, we have that, for any $0 < d \leqslant d'$,

$$\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d)) \leq_{rhr} \sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d')). \tag{7.5}$$

Finally, the result follows from the assumption $D \leq_{rhr} D'$, and from the earlier inequality and Theorem 1.B.52 in [42] on preservation by mixture of the reversed hazard rate order, for the mixture $\sum_{j=1}^{n} I_j(p_{\boldsymbol{\alpha}}(D))$, with mixing parameter D. □

Proof of Theorem 6.1

Proof. Observe that by Eq. (3.4), $C_{\boldsymbol{A},d} = \sum_{j=1}^{N} I_j(p(A_1, \ldots, A_m, d))$. Consider an arbitrary scalar $n \in \mathbb{N}$ and any increasing concave function v.

By the independence between the random variable N and the random variables $I_j(p(A_1, \ldots, A_m, d)), j = 1, \ldots, n$ for any fixed values of the parameters, the result holds if we see that

$$E\left[v\left(\sum_{j=1}^{n} I_j(p(A_1, \ldots, A_m, d))\right)\right] \leqslant E\left[v\left(\sum_{j=1}^{n} I_j(p(A'_1, \ldots, A'_m, d))\right)\right]. \tag{7.6}$$

For any $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_m) \in \mathbb{R}_+^m$, let the function $g(\boldsymbol{\alpha})$ defined by

$$g(\boldsymbol{\alpha}) = E\left[v\left(\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d))\right)\right].$$

Now, by the conditioned expected value,

$$\begin{aligned} E\left[v\left(\sum_{j=1}^{n} I_j(p(A_1,\ldots,A_m,d))\right)\right] &= E\left[E\left[v\left(\sum_{j=1}^{n} I_j(p(A_1,\ldots,A_m,d))\right) | (A_1,\ldots,A_m)\right]\right] \\ &= E[g(A_1,\ldots,A_m)] \end{aligned} \tag{7.7}$$

thus, the inequality (7.6) is equivalent to

$$E[g(A_1, \ldots, A_m)] \leqslant E[g(A'_1, \ldots, A'_m)].$$

From the assumption $(A_1, \ldots, A_m) \leq_{idcv} (A'_1, \ldots, A'_m)$, if the function $g(\boldsymbol{\alpha})$ is increasing and directionally concave for any $\boldsymbol{\alpha} \in \mathbb{R}_+^m$, then the result follows.

To state $g(\boldsymbol{\alpha}) \in idcv$ for any $\boldsymbol{\alpha} \in \mathbb{R}_+^m$, we just need to prove that the random variable $\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d))$ fulfills the $SI - DCV$ property for any $\boldsymbol{\alpha} \in \mathbb{R}_+^m$. Let us prove this assertion next.

On the other hand, observe that the function $p_d(\boldsymbol{\alpha}) := p(\boldsymbol{\alpha}, d)$ defined in (3.2) is increasing and directionally concave in $\boldsymbol{\alpha} \in \mathbb{R}_+^m$. This assertion follows by Lemma 2.1, because the function $f_d(\boldsymbol{\alpha}) = \sum_{i=1}^{m} \alpha_i d^i$ is increasing and linear, thus in particular is increasing directionally concave for any fixed $d > 0$, and

$$p_d(\boldsymbol{\alpha}) = 1 - \exp(-f_d(\boldsymbol{\alpha})).$$

Furthermore, using Lemma 3.3 (ii),

$$\{I_j(p(\boldsymbol{\alpha}, d)) | \boldsymbol{\alpha} \in \mathbb{R}_+^m\} \in SI - DCV.$$

To finish, by applying Corollary 3.5 in [26] by recursive way,

$$\left\{\sum_{j=1}^{n} I_j(p(\boldsymbol{\alpha}, d)) | \boldsymbol{\alpha} \in \mathbb{R}_+^m\right\} \in SI - DCV$$

and the result holds. □

Proof of Theorem 6.2

Proof. From Theorem 3.A.55 in [42], then for any $i = 1, \ldots, m$, $A_i \geqslant_{cv} Exp(\mu_{A_i})$, that implies $A_i \geqslant_{icv} Exp(\mu_{A_i})$

and by the closure of the *idcv* order by conjunction for independent random variables, we have that $\boldsymbol{A} \geqslant_{idcv} \boldsymbol{A}'$. Now, the result is a consequence of Theorem 6.1. □

References

[1] P. Armitage, R. Doll, The age distribution of cancer and a multi-stage theory of carcinogenesis, Br. J. Cancer 8 (1954) 1.
[2] A.J. Bailer, R.B. Noble, M. Wheeler, Model uncertainty and risk estimation for quantal responses, Risk Anal. 25 (2005) 291.
[3] R.E. Barlow, F. Proschan, Statistical Theory of Reliability and Life Testing: Probability Models, Holt Rinehart and Winston, New York, 1975.
[4] C.D. Carrington, Logical probability and risk assessment, Hum. Ecol. Risk Assess. 2 (1996) 62.
[5] C-S. Chang, J.G. Shanthikumar, D.D. Yao, Stochastic convexity and stochastic majorization, in: D.D. Yao (Ed.), Stochastic Modeling and Analysis of Manufacturing Systems, Series in Operations Research, Springer-Verlag, 1994.
[6] K.S. Crump, Dg. Hoel, C.H. Langley, R. Peto, Fundamental carcinogenic processes and their implications for low dose risk assessment, Cancer Res. 36 (1976) 2973–2979.
[7] K.S. Crump, R. Howe, The multistage model with a time dependent dose pattern: application to carcinogenic risk assessment, Risk Anal. 4 (1984) 163.
[8] G.E. Dinse, D.M. Umbach, Parameterizing dose–response models to estimate relative potency functions directly, Toxicol. Sci. 129 (2012) 447.
[9] L. Edler, A. Kopp-Schneider, H. Heinzl, Dose–response modelling, in: L. Edler, C.P. Kitsos (Eds.), Recent Advances in Quantitative Methods in Cancer and Human Health Risk Assessment, John Wiley and Sons, Chichester, 2005, pp. 5–23.
[10] L.F. Escudero, E.M. Ortega, J. Alonso, Variability comparisons for some mixture models with stochastic environments in biosciences and engineering, Stochastic Environ. Res. Risk Assess. 24 (2010) 199.
[11] J.M. Fernández-Ponce, E.M. Ortega, F. Pellerey, Convex comparisons for random sums in random environments and applications, Probab. Eng. Inf. Sci. 22 (2008) 389.
[12] E. Frostig, Comparison of portfolios which depend on multivariate Bernoulli random variables with fixed marginals, Insurance Math. Econ. 29 (2001) 319.
[13] E. Frostig, On risk dependence and MRL ordering, Stat. Probab. Lett. 76 (2006) 231.
[14] S. Gsteiger, S. Morgenthaler, Heterogeneity in multistage carcinogenesis and mixture modeling, Theor. Biol. Med. Modell. 5 (2008) 13, http://dx.doi.org/10.1186/1742-4682-5-13.
[15] R.C. Gupta, On characterization of distributions by conditional expectations, Commun. Stat. Theory Methods 4 (1975) 99.
[16] D.G. Hoel, Incorporation of background in dose–response models, Fed. Proc. 39 (1980) 73.
[17] D.L. Holcomb, M.A. Smith, G.O. Ware, Y. Hung, R.E. Brackett, M.P. Doyle, Comparison of six dose–response models for use with food-borne pathogens, Risk Anal. 19 (1999) 1091–1100.
[18] H. Joe, Multivariate models and dependence concepts, Chapman and hall, london, 1997.
[19] S.H. Kang, R.L. Kodell, J.J. Chen, Incorporating model uncertainties along with data uncertainties in microbial risk assessment, Regul. Toxicol. Pharm. 32 (2000) 68.
[20] S. Karlin, Total Positivity, Stanford University Press, Stanford, 1968.
[21] N. Keiding, R.D. Gill, Random truncation models and random processes, Ann. Stat. 18 (1990) 582.
[22] R.L. Kodell, D.W. Gaylor, J.J. Chen, Using average lifetime dose rate for intermittent exposures to carcinogens, Risk Anal. 7 (1987) 339.
[23] A. Kopp-Schneider, C.J. Portier, C.D. Sherman, The exact formula for tumor incidence in the two-stage model, Risk Anal. 14 (1994) 1079.
[24] D. Krewski, Y. Zhu, Applications of multinomial dose–response models in development toxicity risk assessment, Risk Anal. 14 (1994) 613–627.
[25] A.W. Marshall, I. Olkin, Life Distributions, Structure of non-Parametric, Semiparametric and Parametric Families, Springer, 2007.
[26] L.E. Meester, J.G. Shanthikumar, Stochastic convexity on general space, Math. Oper. Res. 24 (1999) 472.
[27] E. Montesinos, A. Bonaterra, Dose–response models in biological control of plant pathogens: an empirical verification, Phytopathology 86 (1996) 464.
[28] S.H. Moolgavkar, Commentary: fifty years of the multistage model: remarks on a landmark paper, Int. J. Epidemiol. 33 (2004) 1182.
[29] S.H. Moolgavkar, D.J. Venzon, Two-event model for carcinogenesis: incidence curves for childhood and adult tumours, Math. Biosci. 47 (1979) 55.
[30] S. Morgenthaler, P. Herrero, W.G. Thilly, Multistage carcinogenesis and the fraction at risk, J. Math. Biol. 49 (2004) 455.
[31] D.J. Murdoch, D. Krewski, Carcinogenic risk assessment with time-dependent exposure patterns, Risk Anal. 8 (1988) 521.
[32] A. Niemierko, M. Goitein, Modeling of normal tissue response to radiation: the critical volume model, Int. J. Radiat. Oncol. Biol. Phys. 25 (1993) 135.
[33] E.M. Ortega, I. Ortega, J. Alonso, Epidemics in structured populations and multi-stage hit models: a Bayesian approach and stochastic comparisons of mixtures of parametric families (binomial, gamma, geometric and others), in: Proceedings of XXXII National Conference on Statistics and Operations Research, A Coruña, Spain, 2010. ISBN: 978-84-693-6152-8.
[34] E.M. Ortega, J. Alonso, I. Ortega, Stochastic comparisons of mixtures of parametric families in stochastic epidemics, Math. Biosci. 243 (2012) 18.
[35] E.M. Ortega, L. Escudero, Variability for carrier-borne epidemics and Reed–Frost models incorporating uncertainties and dependencies from susceptibles and infectives, Probab. Eng. Inf. Sci. 24 (2010) 303.
[36] D.M. Owens, S. Wei, R.C. Smart, A multihit, multistage model of chemical carcinogenesis, Carcinogenesis 20 (1999) 1837.
[37] R. Peto, Epidemiology, multistage models, and short-term mutagenicity tests, in: H.H. Hiatt, J.D. Watson, J.A. Winsten (Eds.), Origins of Human Cancer. Book C Human Risk Assessment, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1977, pp. 1403–1428.
[38] W.W. Piegorsch, D.K. Nitcheva, R.W. West, Excess risk estimation under multistage model misspecification, J. Stat. Comput. Simul. 76 (2006) 423.
[39] G. Ritter, R. Wilson, F. Pompei, D. Burmistrov, The multistage model of cancer development: some implications, Toxicol. Ind. Health 19 (2003) 125.
[40] D. Roy, R.P. Gupta, Characterizations and model selections through reliability measures in the discrete case, Stat. Probab. Lett. 43 (1999) 197.
[41] A.A. Salvia, R.C. Bollinger, On discrete hazard functions, IEEE Trans. Reliab. R-31 (1982) 458–459.
[42] M. Shaked, G.J. Shanthikumar, Stochastic Orders, Springer, New-York, 2007.
[43] M.A. Smith, K. Takenchi, Dose–response models for Listeria monocytogenes induced stillbirths in nonhuman primates, Infect. Immun. 76 (2008) 726.
[44] S. Tamrakar, C.N. Haas, Dose–response models for Lassa virus, Hum. Ecol. Risk Assess. 14 (2008) 742.
[45] W.Y. Tan, K.P. Singh, A mixed model of carcinogenesis with applications to retinoblastoma, Math. Biosci. 98 (1990) 211.
[46] Q. Zheng, On the exact hazard and survival functions of the MVK stochastic carcinogenesis model, Risk Anal. 14 (1994) 1081.