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COMPARISON OF TAILS OF DISTRIBUTIONS IN MODELS FOR ESTIMATING SAFE DOSES

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Summary

Heaviness of tail of distributions is compared each other analytically and systematically. Distributions under the study are the lognormal, loglogistic, Weibull, gamma, exponential-polynomial distributions. The beta loglogistic, which covers some of these distributions as its limits, is also discussed.

Heaviness of tail is an important notion in life-test, robust estimation and rank test. Here the notion is studied to examine models for estimating safe doses. Some results about heaviness of tail are given, and a new notion of heaviness of tail at the origin is defined and discussed.

1. Introduction

During this decade many procedures for estimating safe doses of possible hazardous chemical compounds have been proposed. Most procedures are based on dose response relationships and extrapolation from higher doses to lower doses. This extrapolation presents serious problems, one of which is the need for an assumption of a dose response curve. For example, suppose that we want to estimate a dose for which a corresponding incidence probability is very small, say 10^{-8}. The assumption of a dose response curve is then essential. In this case, the probit model and the logit model give quite different estimators, although it is well known that both models give close estimators in the usual bioassay. The difference in estimation comes mainly from differences of tail of distributions in these models. This situation was previously noted, and numerical examples were given [4], [7].

Selection of a reasonable distribution in a model depends on that of a reasonable tail of a distribution. If the model can be fixed by biological reasoning, it is the best. But, at present, there are too many biologically reasonable models.

In this paper we compare analytically tail of distributions which are used as models for risk assessment, expecting the result to be useful for selecting a model. The notion of heaviness of tail of distributions plays an important role in life test [3], robust estimation [20], and scoring of rank test [9], as well as estimation of safe doses.

Distributions under study are the lognormal, loglogistic, Weibull, gamma, exponential and exponential-polynomial distributions. In addition, the beta loglogistic distribution family introduced by Prentice is also discussed. The loglogistic is a special case of this family, and the lognormal, Weibull, and gamma are limits of distributions of this family.

General comparisons of tail of distributions for systematically varying definitions of tail will be presented in a subsequent paper [19].

This paper is constructed as follows: In Section 2 some properties of heaviness of tail are discussed as preparation. Section 3 presents main results of comparisons of distributions. An outline of the proof of these results is presented in Section 7. The beta loglogistic distribution family is studied in Section 4. The results in Section 4 aid in understanding those in Section 3. Tail ordering at the origin is defined and studied in Section 5. In the case of risk assessment our attention is usually limited to low doses; that is, to tail at the origin of a distribution. Supplemental remarks and discussions are given in Section 6.

2. Heaviness of tail

Let X and Y be random variables with their distribution functions $F(x)$ and $G(x)$ respectively. Throughout this paper, a distribution function is assumed to have a positive density function on $(0, \infty)$, unless specified otherwise. In general, for a distribution function $H(x)$, $h(x)$ and $H^{-1}(u)$ denote respectively the density function and the inverse function.

DEFINITION 1. Y is called to have heavier tail than X, iff $G^{-1}(u)/F^{-1}(u)$ is non-decreasing in u $(0<u<1)$, and the condition is denoted by $Y \succ X$ $(\mathcal{T})$.

For convenience, we do not distinguish between a random variable, its distribution, and its distribution function, unless confusion occurs. Thus, we write like $G(x) \succ F(x)$ $(\mathcal{T})$. The definition was introduced in [6], and discussed in subsequent papers; for example [9], [20], [21].

PROPOSITION 1. The following two conditions are equivalent to $G(x) \succ F(x)$ $(\mathcal{T})$.

(i) $G^{-1}(F(x))/x$ is increasing in $x>0$.

(ii) $g(G^{-1}(u))G^{-1}(u) \leqq f(F^{-1}(u))F^{-1}(u)$ for any u, $0<u<1$.

The condition (ii) is convenient for computation, so we define

$$S(u; f)=f(F^{-1}(u))F^{-1}(u)=f(x)x ,$$

where the parameter f can be replaced by F or X.

A family of distributions $\mathcal{F}$ is often closed with respect to the scale and the power transformations; that is, if $F(x)$ is in $\mathcal{F}$, then both $F(\alpha x)$ and $F(x^{\beta})$ are in $\mathcal{F}$ for any positive numbers α and β. For the present study the power parameter β is important, though the scale parameter α is irrelevant, as stated by the following proposition.

PROPOSITION 2.
(i) Let α be a positive value and $G(x)=F(\alpha x)$. Then $G(x)\succ F(x)$ $(\mathcal{T})$ and $G(x)\prec F(x)$ $(\mathcal{T})$. Conversely, if $G(x)\succ F(x)$ $(\mathcal{T})$ and $G(x)\prec F(x)$ $(\mathcal{T})$, then there exists a positive number α such that $G(x)=F(\alpha x)$ for any x.
(ii) If $G(x)\succ F(x)$ $(\mathcal{T})$ and $\beta\leqq\beta'$, then $G(x^{\beta})\succ F(x^{\beta'})$ $(\mathcal{T})$.

The next proposition indicates close relation between the notion of heaviness of tail and that of dispersion.

PROPOSITION 3 [21]. Let $F^*(x)=F(e^x)$ and $G^*(x)=G(e^x)$. Then $F^*(x)$ and $G^*(x)$ have a support $(-\infty, \infty)$. $G(x)\succ F(x)$ $(\mathcal{T})$ iff for any $0<u<v<1$ it holds that

$$G^{*-1}(v)-G^{*-1}(u)\geqq F^{*-1}(v)-F^{*-1}(u) . \tag{1}$$

When (1) is satisfied $G^*(x)$ is called to be more "spread out" than $F^*(x)$ [8].

This notion represents a partial ordering of dispersion among distributions. Note that the power parameter in heaviness of tail corresponds to the scale parameter in largeness of dispersion. In conventional dose response analyses like the probit and the logit, dose data are initially log-transformed. Transformed dose data are called metameters. In this case a response curve represented by $F(x)$ is apparently changed into that by $F^*(x)$.

The following theorem is useful in actual comparison of distributions.

THEOREM 1. *Suppose a distribution function* $F(x)$ *satisfies a condition*

$$S(u; f)=f(F^{-1}(u))F^{-1}(u) \quad \textit{is concave in } u,\ 0<u<1 \tag{2}$$

and suppose $F(x)\prec G_1(x)$ $(\mathcal{T})$ *and* $F(x)\prec G_2(x)$ $(\mathcal{T})$. *Let* $G(x)$ *be a mixture of* $G_1(x)$ *and* $G_2(x)$, *that is,* $G(x)=\lambda G_1(x)+(1-\lambda)G_2(x)$ *for* λ $(1\geqq\lambda\geqq 0)$. *Then* $F(x)\prec G(x)$ $(\mathcal{T})$.

PROOF. Put $x=G^{-1}(u)$. Proposition 1-(ii) means that we have only to show for any x

$$(3) \qquad S(G(x); f)=f(F^{-1}(G(x)))F^{-1}(G(x))\geqq g(x)x .$$

Using (2), it follows that

$$\begin{aligned} S(G(x); f) &\geqq \lambda S(G_1(x); f)+(1-\lambda)S(G_2(x); f) \\ &\geqq \lambda S(G_1(x); g_1)+(1-\lambda)S(G_2(x); g_2) \\ &=\lambda g_1(x)x+(1-\lambda)g_2(x)x=g(x)x . \end{aligned}$$

This completes the proof.

Remark. Put $F^*(x)=F(e^x)$ and $f^*(x)=e^x f(e^x)$, $-\infty<x<\infty$. The condition (2) is equivalent to that

$$(4) \qquad -\log f^*(x) \text{ is convex in } x ,$$

since the right derivative of $-\log f(e^x)$ is increasing iff the right derivative of $S(u; f)$ is decreasing. The density $f^*(x)$ is strongly unimodal, when (4) is satisfied.

COROLLARY 1. *Suppose that $f^*(x)$, $-\infty<x<\infty$, is strongly unimodal, and that both $G_1(x)$ and $G_2(x)$ are more spread out than $F^*(x)$. Let $G(x)=\lambda G_1(x)+(1-\lambda)G_2(x)$ for $0\leqq\lambda\leqq 1$. Then $G(x)$ is more spread out than $F^*(x)$.*

COROLLARY 2. *Let X and Z be two independent random variables, and let X have a distribution satisfying* (2), *and $Y=XZ$ or $Y=X/Z$. Then $Y\succ X$ $(\mathcal{T})$.*

Example 1.

(i) Let X and Z be independent random variables with the common distribution function $1-e^{-x^\gamma}$ $(\gamma>0)$, that is, they are distributed according to the Weibull distribution with its parameter γ. Then $Y=X/Z$ has the distribution function $1-1/(1+y^\gamma)$, i.e. the loglogistic distribution with its parameter γ, and $Y\succ X$ $(\mathcal{T})$. This proves $LL(\gamma)\succ Wb(\gamma)$ $(\mathcal{T})$, one case of Theorem 2.

(ii) [20] Let X and Y be distributed according to the standard normal distribution and the t-distribution with n degrees of freedom. Then $|Y|\succ|X|$ $(\mathcal{T})$. In fact, let $N_0, N_1, \cdots, N_n$ be $(n+1)$ mutually independent random variables with the common distribution $N(0, 1)$. By putting $X=N_0$ and $Z^2=\sum N_i^2/n$ the statement follows from Corollary 2.

See Section 4 for further applications.

PROPOSITION 4.
(i) $S(u; 1/X) = S(1-u; X)$.
(ii) $Y \succ X$ ($\mathcal{T}$) iff $1/Y \succ 1/X$ ($\mathcal{T}$).

PROOF. If X has the distribution function $F(x)$, then $1/X$ has the distribution function $1-F(1/x)$ $(=u)$ and the probability density $x^{-2}f(x^{-1})$. From these,

$$S(u; 1/X) = x^{-1}f(x^{-1}) = F^{-1}(1-u)f(F^{-1}(1-u)) = S(1-u; X) .$$

The part (ii) is obvious from (i) and Proposition 2-(i).

This proposition shows that our definition $\mathcal{T}$ compares not only the heaviness of right tail of the distributions on $(0, \infty)$, but also largeness of their probabilities near the origin.

From Proposition 4, it is also clear that $\log X$ has a density function symmetric about a point iff $S(u; X)$ is symmetric about $u=1/2$. The lognormal and the loglogistic distributions discussed in the followings are the examples of this fact.

3. Comparison of tail of distributions

The following six families of distributions are discussed here. All parameters are assumed to be positive unless specified otherwise.

(a) Loglogistic distribution $LL(\beta, \alpha)$. The distribution function is given by

$$F_L(\beta, \alpha, x) = \alpha x^{\beta}/(1+\alpha x^{\beta}) , \tag{5}$$

and used in the logit model. This nomenclature is consistent with the lognormal distribution; that is, a random variable X has the loglogistic distribution, if $\log X$ has the logistic distribution.

(b) Weibull distribution $Wb(\gamma, \alpha)$. The distribution function is given by

$$F_W(\gamma, \alpha, x) = 1 - e^{-\alpha x^{\gamma}} . \tag{6}$$

The model using this is popular in the reliability theory and was discussed for estimation of safe doses in [15].

(c) Gamma distribution $Ga(k, \alpha)$. The distribution function is given by

$$F_G(k, \alpha, x) = \int_0^{\alpha x} t^{k-1}e^{-t}/\Gamma(k)dt . \tag{7}$$

When k is a positive number, this represents the (one target) k-hit model, but k can be generalized to a positive real number.

(d) Exponential-polynomial distribution $EP(n, \alpha_1, \cdots, \alpha_n)$. The distribution function is given by

$$(8) \qquad F_P(n, \alpha_1, \cdots, \alpha_n, x) = 1 - \exp\left(-\sum_{i=1}^{n} (\alpha_i x)^i\right),$$

where n is a positive integer and $\alpha_1, \cdots, \alpha_n$ are nonnegative. The model using this is called the polynomial model which was introduced by Armitage-Doll model [1]. The expression (8) is slightly different from usual expression $1-\exp(-\sum \alpha_i x^i)$ used in [18], and is more convenient in the present discussion. The number m is an integer such that $\alpha_m > 0$, and $\alpha_i = 0$ for $i < m$.

(e) Exponential distribution $E(\alpha)$. The distribution function is given by

$$(9) \qquad F_E(\alpha, x) = 1 - e^{-\alpha x}.$$

The model using this is called the linear model in contrast with the polynomial model, and called the one-hit model in contrast with the multi-hit model.

(f) Lognormal distribution $LN(\tau, \alpha)$. The distribution function is given by

$$(10) \qquad F_N(\tau, \alpha, x) = \Phi(\log \alpha x^\tau),$$

where $\Phi(x)$ denotes the standard normal distribution function. The model using this is the probit model.

Each of these families listed above has a scale parameter α, which is irrelevant for comparing tail as shown in Proposition 2-(i). Thus the parameter α is fixed at 1 for simplicity, unless confusion occurs. Notations for the distributions and the distribution functions will be simplified like $LL(\beta)$ and $F_L(\beta, x)$.

The family E is the intersection of the three families, $Ga(k)$, $Wb(\gamma)$ and $EP(n, \alpha_1, \cdots, \alpha_n)$. When γ is a positive integer, the distribution $Wb(\gamma)$ is included in the family $EP(n, \alpha_1, \cdots, \alpha_n)$.

The probit and logit models are popular. A procedure for estimating safe doses by Mantel and Bryan [13] is based on the probit model. The multi-hit model was introduced by Iversen and Arley [12] and was discussed in [18]. The multistage model has attracted the attention of researchers and was studied in [5], [11]. The model using the Weibull distribution was discussed in [15].

Tails of distributions of these families are compared in Theorem 2 below. The outline of the proof will be presented in Section 7.

DEFINITION 2. The two conditions, Condition A and Condition B are defined as follows:

Condition A: (β, k') satisfies Condition A, iff either $\beta \leq \text{Min}\{k', 1\}$ or

$1 \leqq \beta \leqq \mathrm{Min}\, x^{k'} e^{-x} / \Gamma(k') I(k', x)(1 - I(k', x))$ holds, where $I(k', x) = F_G(k', x)$.
Condition B: A pair of vectors $(n, \alpha_1, \cdots, \alpha_n)$ and $(n', \alpha'_1, \cdots, \alpha'_n)$ satisfies Condition B, iff $n \leqq n'$ and $\alpha'_1/\alpha_1 \leqq \alpha'_2/\alpha_2 \leqq \cdots \leqq \alpha'_n/\alpha_n$, where $a/0$ for any $a > 0$ is considered to be larger than any positive number and $0/0$ is disregarded.

THEOREM 2.
(i) *Sufficient conditions that a distribution has heavier tail than another distribution are summarized in Table* 1. *A distribution of the first column* $\mathcal{L}(\cdot)$ *has heavier tail than another distribution of the head line* $\mathcal{L}(\cdot')$, *if the condition in the corresponding entry is satisfied.*
(ii) *Except for Condition* B, *all conditions are necessary.*

Table 1. Conditions that a distribution of the first column has heavier tail than another of the top line $(\mathcal{T})$ [cf. Theorem 2]. $C = 4/\sqrt{2\pi}$ and m' denotes the integer such that $\alpha'_{m'} > 0$, and $\alpha'_j = 0$ for $j < m'$. Condition B is sufficient, and all the others are necessary and sufficient.

Heavier \ Lighter	$LL(\beta')$	$Wb(\gamma')$	$Ga(k')$	$EP(n', \alpha'_1, \cdots, \alpha'_n)$	E	$LN(\tau')$
$LL(\beta)$	$\beta \leqq \beta'$	$\beta \leqq \gamma'$	Condition A	$\beta \leqq m'$	$\beta \leqq 1$	$\beta \leqq C\tau'$
$Wb(\gamma)$	Empty	$\gamma \leqq \gamma'$	$\gamma \leqq \mathrm{Min}\,\{1, k'\}$	$\gamma \leqq m'$	$\gamma \leqq 1$	Empty
$Ga(k)$	Empty	$\mathrm{Min}\,\{1, k\} \leqq \gamma'$	$k \leqq k'$	$k \leqq m'$	$k \leqq 1$	Empty
$EP(n, \alpha_1, \cdots, \alpha_n)$	Empty	$n \leqq \gamma'$	$n = 1,\ k \geqq 1$	Condition B	$n = 1$	Empty
E	Empty	$1 \leqq \gamma'$	$1 \leqq k'$	All	All	Empty
$LN(\tau)$	Empty	Empty	Empty	Empty	Empty	$\tau \leqq \tau'$

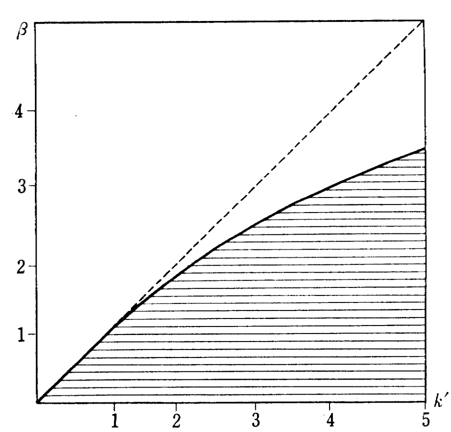

Fig. 1. Condition A: A point (k', β) in the shaded area satisfies Condition A of Theorem 1 and Table 1, a necessary and sufficient condition for $LL(\beta) \succ Ga(k')$ $(\mathcal{T})$.

Remarks.

(i) Condition A is satisfied for $\beta \leqq \Gamma(k')/2(k'-1)^{k'-1}e^{-(k'-1)} \doteqdot \sqrt{\pi(k'-1)/2}$ but not for $\beta = k' > 1$. Figure 1 obtained by numerical computations shows Condition A for $k' \leqq 5$.

(ii) Suppose $n=2$. Then, $EP(n, \alpha_1, \alpha_2) \succ EP(n, \alpha_1', \alpha_2')$ $(\mathcal{T})$ iff $\alpha_1'/\alpha_1 \geqq \alpha_2'/\alpha_2$. But Condition B is not sufficient for $n \geqq 3$. Remark that a pair of vectors $(n, \alpha_1, \cdots, \alpha_n)$ and $(n, \alpha\alpha_1, \cdots, \alpha\alpha_n)$ satisfies Condition B for any $\alpha > 0$.

(iii) van Zwet [22] stated a stronger proposition than that $Ga(k) \succ Ga(k')$ $(\mathcal{T})$ iff $k \leqq k'$.

4. Beta loglogistic distribution

The beta loglogistic distribution, $BL(\lambda_1, \lambda_2, \beta, \alpha)$ has the distribution function

$$F_{BL}(\lambda_1, \lambda_2, \beta, \alpha, x) = \int_0^{\alpha x^\beta/(1+\alpha x^\beta)} B(\lambda_1, \lambda_2)^{-1} t^{\lambda_1 - 1}(1-t)^{\lambda_2 - 1} dt \,, \tag{11}$$

and the density function

$$f_{BL}(\lambda_1, \lambda_2, \beta, \alpha, x) = B(\lambda_1, \lambda_2)^{-1} \beta \alpha^{\lambda_1} x^{\beta\lambda_1 - 1}/(1+\alpha x^\beta)^{\lambda_1+\lambda_2} \,. \tag{12}$$

This is a beta transformation of the loglogistic distribution function $F_{LL}(\beta, \alpha, x)$. It can also be regarded as a power transformation of the beta variable of the second type, i.e. F variable. The family of $BL(\lambda_1, \lambda_2, \beta, \alpha)$ was introduced in [16] and used for fitting dose response curves in [17]. As in the previous section, α is often omitted and assumed to be 1, for simplicity.

The family of $BL(\lambda_1, \lambda_2, \beta, \alpha)$ and its limit distributions (that is, the closure) include all the families of distributions listed in the previous section except for $EP(n, \alpha_1, \cdots, \alpha_n)$. This is shown in the following proposition. The proof is straightforward and is omitted here.

PROPOSITION 5.

(i) [16] $BL(1, 1, \beta) \sim LL(\beta)$,

(ii) [16] $BL(\lambda, \lambda, \sqrt{2/\lambda}\,\tau) \sim LN(\tau)$ $(\lambda \to \infty)$,

(iii) $BL(1, \lambda, \gamma, 1/\gamma) \sim Wb(\gamma)$ $(\lambda \to \infty)$ and

(iv) $BL(k, \lambda, 1, 1/\lambda) \sim Ga(k)$ $(\lambda \to \infty)$,

where the symbol $\sim$ denotes "is equivalent to" and $\sim \cdots (\lambda \to \infty)$ denotes "(the left-hand side) converges in law (to the right-hand side) as λ tends to infinity".

The following proposition shows that among the family of $BL(\lambda_1, \lambda_2, \beta)$ tail orderings are monotone in λ_1, and λ_2 as well as in β.

PROPOSITION 6.
(i) For any $\lambda_1'\geqq\lambda_1$, $\lambda_2'\geqq\lambda_2$ and $\beta'\geqq\beta$ it holds that $BL(\lambda_1, \lambda_2, \beta)\succ BL(\lambda_1', \lambda_2', \beta')$ $(\mathcal{T})$.
(ii) A necessary condition that $BL(\lambda_1, \lambda_2, \beta)\succ BL(\lambda_1', \lambda_2', \beta')$ $(\mathcal{T})$ is that $\lambda_1'\beta'\geqq\lambda_1\beta$ and $\lambda_2'\beta'\geqq\lambda_2\beta$.

PROOF. (i) We have only to prove $BL(\lambda_1, \lambda_2, 1)\succ BL(\lambda_1', \lambda_2', 1)$ $(\mathcal{T})$ because of Proposition 2-(ii). Remark first that $f_{BL}(\lambda_1, \lambda_2, 1, x)$ satisfies the condition of Theorem 1. In fact,

$$-x\frac{d}{dx}\log f_{BL}(\lambda_1, \lambda_2, 1, x)=-(\lambda_1-1)+(\lambda_1+\lambda_2)x/(1+x)\ ,$$

which is nondecreasing, showing that $S(u; f_{BL})$ is concave. Next, let $V(\lambda_1)$, $V(\lambda_2)$ and $V(\mu)$ be independent gamma variables with the standard scale parameters and the shape parameters λ_1, λ_2 and μ respectively, and let $Y(\lambda_1, \lambda_2)$ be a $BL(\lambda_1, \lambda_2, 1)$ variable. Let the symbol $\sim$ denote to have the same distribution.

$$Y(\lambda_1, \lambda_2)\sim\frac{V(\lambda_1)+V(\mu)}{V(\lambda_2)}\cdot\frac{V(\lambda_1)}{V(\lambda_1)+V(\mu)}\sim Y(\lambda_1+\mu, \lambda_2)\cdot Z(\lambda_1, \lambda_1+\mu)$$

and

$$Y(\lambda_1, \lambda_2)\sim\frac{V(\lambda_1)}{V(\lambda_2)+V(\mu)}\cdot\frac{V(\lambda_2)+V(\mu)}{V(\lambda_2)}\sim Y(\lambda_1, \lambda_2+\mu)/Z(\lambda_2, \lambda_2+\mu)$$

where $Z(\lambda_1, \lambda_1+\mu)$ (or $Z(\lambda_2, \lambda_2+\mu)$) is a beta random variable of the first type with the parameters of the arguments and independent of $Y(\lambda_1+\mu, \lambda_2)$ (or $Y(\lambda_1, \lambda_2+\mu)$), since $V(\lambda_i)+V(\mu)$ is independent of $V(\lambda_i)/(V(\lambda_i)+V(\mu))$. Using Corollary 2 of Theorm 1,

$$Y(\lambda_1, \lambda_2)\succ Y(\lambda_1+\mu, \lambda_2)\ (\mathcal{T})\qquad\text{and}\qquad Y(\lambda_1, \lambda_2)\succ Y(\lambda_1, \lambda_2+\mu)\ (\mathcal{T})$$

for any $\lambda_1, \lambda_2, \mu>0$.
(ii) Let Y be a $BL(\lambda_1, \lambda_2, \beta)$ variable. It is known that $1/Y$ has $BL(\lambda_2, \lambda_1, \beta)$. The functions $S(u; \cdot)$ for these variables are, by Taylor's expansion of f_{BL} and its integration,

$$S(u; Y)=\beta\lambda_1u+O(u^{1+1/\lambda_1})$$

and

$$S(1-u; Y)=S(u; 1/Y)=\beta\lambda_2u+O(u^{1+1/\lambda_2})$$

due to Proposition 4-(ii). Applying Proposition 1-(ii), we show the condition (ii) necessary.

COROLLARY 1. *A necessary and sufficient condition that* $BL(\lambda_1, \lambda_2,$

$\beta) \succ BL(\lambda_1', \lambda_2', \beta)$ $(\mathcal{T})$ *is* $\lambda_1' \geqq \lambda_1$ *and* $\lambda_2' \geqq \lambda_2$.

Example 2.

(i) Suppose $\beta \leqq \gamma'$. Then it holds that $BL(1, 1, \beta) \succ BL(1, \lambda, \gamma')$ $(\mathcal{T})$ for any $\lambda \geqq 1$. This implies $LL(\beta) \succ Wb(\gamma')$ $(\mathcal{T})$, since tail ordering is closed with respect to the limit of distributions in law. This was directly shown in Example 1 of Section 2.

(ii) Suppose $\gamma \leqq 1$ and $k' \geqq 1$. Then $Wb(\gamma) \succ Ga(k')$ $(\mathcal{T})$. Conversely, suppose $\gamma' \geqq 1$ and $k \leqq 1$. Then $Ga(k) \succ Wb(\gamma')$ $(\mathcal{T})$.

(iii) Suppose $k' \geqq k$. Then $Ga(k') \succ Ga(k)$ $(\mathcal{T})$. This fact can be shown directly in a similar way to the proof of Proposition 6.

5. Heaviness of tail at the origin

It is well known that the linear model and the probit model derive quite different estimators of safe doses. However, Theorem 2 says that the inequality relation $E \succ LN(\sigma)$ $(\mathcal{T})$ does not hold. This is because our definition $\mathcal{T}$ means larger probability in both right tail and near the origin, as discussed after Proposition 4. Since very low doses are estimated by extrapolation from relatively higher doses in the risk assessment, larger probability only near the origin is essential. So we need another comparison weaker than $\mathcal{T}$.

DEFINITION 3. A distribution function $G(x)$ is said to have heavier tail at the origin than another $F(x)$, iff there is a positive value u_0 such that $G^{-1}(u)/F^{-1}(u)$ is increasing in u $(0<u<u_0)$, which is denoted by $G(x) \succ F(x)$ $(\mathcal{T}_0)$.

Similar results to those for heaviness of tail hold for heaviness of tail at the origin. Next we give two propositions without proofs, since they are obtained by elementary but tedious calculations.

Proposition 6 is replaced by:

PROPOSITION 7.

(i) Sufficient conditions that $BL(\lambda_1, \lambda_2, \beta) \succ BL(\lambda_1', \lambda_2', \beta)$ $(\mathcal{T}_0)$ are that $\lambda_1'\beta' > \lambda_1\beta$ and that $\lambda_1' = \lambda_1$, $\lambda_2' \geqq \lambda_2$ and $\beta' \geqq \beta$.

(ii) A necessary condition that $BL(\lambda_1, \lambda_2, \beta) \succ BL(\lambda_1', \lambda_2', \beta')$ $(\mathcal{T}_0)$ is $\lambda_1'\beta' \geqq \lambda_1\beta$.

PROPOSITION 8. Under the notations in Section 3, limiting behaviors of tail at the origin are evaluated quantitatively as follows:

(i) $\lim_{u\to 0} S(u; LL(\beta))/u = \lim_{x\to 0} f_L(\beta, x)x/F_L(\beta, x) = \beta$,

(ii) $\lim_{u\to 0} S(u; Wb(\gamma))/u = \gamma$,

(iii) $\lim_{u\to 0} S(u; Ga(k))/u = k$,

(iv) $\lim_{u \to 0} S(u; EP(n, \alpha_1, \cdots, \alpha_n))/u = m$,
where m is as defined in Section 3 (d), and
(v) $\lim_{u \to 0} S(u; LN(\tau))/u = \infty$.

To state the theorem corresponding to Theorem 2, the following definition is needed.

DEFINITION 4. A pair of vectors $(n, \alpha_1, \cdots, \alpha_n)$ and $(n', \alpha'_1, \cdots, \alpha'_n)$ satisfies Condition C, iff one of the following three holds:
(i) $m < m'$, where m is as defined in Section 3 (d),
(ii) $m = m'$ and there exists an integer l such that $\alpha'_m/\alpha_m = \cdots = \alpha'_{l-1}/\alpha_{l-1} < \alpha'_l/\alpha_l$,
(iii) $m = m'$, $n = n'$ and $\alpha'_m/\alpha_m = \alpha'_2/\alpha_2 = \cdots = \alpha'_n/\alpha_n$.

THEOREM 3. *Necessary and sufficient conditions that a distribution listed in Section 3 has heavier tail at the origin than another distribution are summarized in Table 2. In other words, $\mathcal{L}(\cdot) \succ \mathcal{L}(\cdot')$ $(\mathcal{T}_0)$, iff the parameters satisfy the condition in the corresponding entry.*

Table 2. Conditions that a distribution of the first column has heavier tail at the origin than another of the top line $(\mathcal{T}_0)$ [cf. Theorem 3]. All conditions are necessary and sufficient.

Heavier \ Lighter	$LL(\beta')$	$Wb(\gamma')$	$Ga(k')$	$EP(n', \alpha'_1, \cdots, \alpha'_n)$	E	$LN(\tau')$
$LL(\beta)$	$\beta \leqq \beta'$	$\beta \leqq \gamma'$	$\beta < k'$ $\beta = k' \leqq 1$	$\beta \leqq m'$	$\beta \leqq 1$	All
$Wb(\gamma)$	$\gamma < \beta'$	$\gamma \leqq \gamma'$	$\gamma < k'$ $\gamma = k' < 1$	$\gamma \leqq m'$	$\gamma \leqq 1$	All
$Ga(k)$	$k < \beta'$	$k < \gamma'$ $k = \gamma' > 1$	$k \leqq k'$	$k \leqq m'$	$k \leqq 1$	All
$EP(n, \alpha_1, \cdots, \alpha_n)$	$m < \beta'$	$m < \gamma'$ $m = n \leqq \gamma'$	$m < k'$ $m = n \leqq k'$	Condition C	$n = 1$	All
E	$1 < \beta'$	$1 \leqq \gamma'$	$1 \leqq k'$	All	All	All
$LN(\tau)$	Empty	Empty	Empty	Empty	Empty	$\tau \leqq \tau'$

6. Discussions and remarks

(A) The Probit Model and the Linear Model

These two models are fundamental for estimation of safe doses. As for heaviness of tail, the lognormal and the exponential distributions are quite different. The exponential distribution has much heavier tail at the origin than the lognormal distribution does, as shown in Table 2. This fact was pointed out numerically by several authors, for example [4].

The exponential, however, does not have heavier tail than the lognormal, and the lognormal distribution does not have monotone increasing hazard rate. See Barlow et al. [2] and Gehan [10]. In fact, the hazard rate of the lognormal is increasing near the origin but decreasing at the right tail, and the distribution is regarded inappropriate as a life length distribution having a heavier right tail.

The notion of heaviness of tail at the origin and Proposition 4 make clear how these distributions are different.

(B) Mantel-Bryan Procedure

A method to estimate safe doses was devised and extended by Mantel, Bryan, and others in [13], [14]. They assumed $\Phi(\log x+\alpha)$ as a dose response curve, and claimed that this assumption was conservative. Since τ in the probit model is usually greater than 1, their assertion is reasonable so far as the probit model is valid. A smaller value of τ implies heavier tail of the distribution, which means conservatism in extrapolation from higher doses to lower doses.

However, as shown in Theorem 3, the lognormal distribution has lighter tail than the other distributions discussed here. Thus the Mantel-Bryan method is not necessarily conservative.

(C) Model Fitting and Tail of Distribution

When a candidate model is fitted to experimental data, goodness of fit depends mainly on the center of the distribution rather than its tails. On the other hand, an estimated safe dose obtained by extrapolation depends heavily on tail at the origin of the distribution. This situation is supported by the well known difference between the probit and the logit models. Both models are usually well fitted to bioassay data, and derive close estimators of the ED_{50}, but the tail probability is extremely different as seen in [4].

The parameter k in the gamma distribution, for example, corresponds to heaviness of tail at the origin as shown in Theorem 3. The parameter represents at the same time the variance of $\log X$ of a $Ga(k)$ variable X.

(D) Heterogeneous Population

The gap between a heterogeneous population like human beings and a homogeneous population like experimental animals is frequently discussed. It is considered that a heterogeneous population consists of several homogeneous populations. Roughly speaking, a dose response curve corresponding to a homogeneous population has lighter tail than that corresponding to a heterogeneous population. Theorem 1 supports this under a weak condition.

7. Outline of the proof of Theorem 2

Theorem 2 consists of many statements. Some of them can be proved using Propositions 2-(ii) and 6 and Theorem 1. Proof of four pairs of statements, for which conditions are a bit complicated, are given below.

The remainder can be proven after straightforward but tedious calculations, like the following proofs in this section. Proposition 1-(ii) is useful in these proofs. The affirmative statements are shown analytically. The study of behaviors of $f(F^{-1}(u))F^{-1}(u)/g(G^{-1}(u))G^{-1}(u)$ at neighborhoods of $u=0$ and $u=1$ proves the negative statements. The negative statements near 0 are obtained in Theorem 3.

(a) Proof of statements between $LL(\beta)$ and $Ga(k)$. Let $x(u)=F_L^{-1}(\beta, u)$ and $y(u)=F_G^{-1}(k, u)$, where $F_L(\beta, x)$ and $F_G(k, x)$ are given in (5) and (7). Then it holds that

$$\int_0^{y(u)} t^{k-1}e^{-t}/\Gamma(k)dt=u \ . \tag{13}$$

By differentiating both sides, it follows that

$$(y(u)^{k-1}e^{-y(u)}/\Gamma(k))y'(u)=1 \ ,$$

that is,

$$y(u)/y'(u)=y(u)^k e^{-y(u)}/\Gamma(k) \ . \tag{14}$$

Similarly,

$$x(u)/x'(u)=\beta u(1-u) \ . \tag{15}$$

By Proposition 1-(ii), $LL(\beta)\succ Ga(k)$ $(\mathcal{T})$ is equivalent to

$$\beta u(1-u)\leqq y(u)^k e^{-y(u)}/\Gamma(k) \qquad \text{for } 1>u>0 \ ,$$

which is replaced by

$$\beta\leqq \operatorname*{Min}_x \frac{x^k e^{-x}/\Gamma(k)}{I(k, x)(1-I(k, x))} \tag{16}$$

where $I(k, x)=F_G(k, x)$. Figure 1 is obtained numerically from (16).

Conversely, it follows from (15) that

$$\lim_{u\to 1}\{x(u)/(x'(u)(1-u))\}=\beta \ .$$

On the other hand, it holds that

$$\lim_{u\to 1}\{y(u)/(y'(u)(1-u))\}=\lim_{x\to\infty}\left\{1\Big/\int_1^\infty t^{k-1}e^{x(1-t)}dt\right\}=\infty \ .$$

This means that it does not hold for any k and β that $LL(\beta)\prec Ga(k)$ $(\mathcal{T})$.

(b) Proof of statements between $LL(\beta)$ and $LN(\tau)$. Let $x(u)$ be defined as in (a) and $y(u)$ be $F_N^{-1}(\tau, u)$. Then

$$y(u)/y'(u)=\tau \exp\{-(1/2)(\tau \log y(u))^2\}/\sqrt{2\pi}\ .$$

Thus $LL(\beta)\succ LN(\tau)$ $(\mathcal{T})$ is equivalent to

$$\beta u(1-u)\leqq \tau \exp\{-(1/2)(\tau \log y(u))^2\}/\sqrt{2\pi} \qquad \text{for } 1>u>0\ ,$$

that is,

$$\begin{aligned}(17)\qquad \beta/\tau &\leqq \operatorname*{Min}_u \exp\{-(1/2)(\tau \log y(u))^2\}/\sqrt{2\pi}\,u(1-u)\\ &=\operatorname*{Min}_x \exp\{-(1/2)x^2\}/\sqrt{2\pi}\,\Phi(x)(1-\Phi(x))\\ &=1/\sqrt{2\pi}\,\Phi(0)(1-\Phi(0))\\ &=4/\sqrt{2\pi}\ .\end{aligned}$$

Conversely, since

$$\lim_{x\to\infty} \exp\{-(1/2)x^2\}/\sqrt{2\pi}\,\Phi(x)(1-\Phi(x))=\infty\ ,$$

it does not hold for any β and τ that $LL(\beta)\prec LN(\tau)$ $(\mathcal{T})$.

(c) Proof of statements between $Wb(\gamma)$ and $Ga(k)$. Let $y(u)$ be defined as in (a) and $x(u)$ be defined by

$$x(u)=F_W^{-1}(\gamma, u)=(-\log(1-u))^{1/\gamma}\ .$$

Then it holds that

$$x(u)/x'(u)=\gamma(1-u)(-\log(1-u))\ .$$

Suppose that $Wb(\gamma)\succ Ga(k)$ $(\mathcal{T})$. Proposition 1-(ii) implies that for $1>u>0$

$$\gamma(1-u)(-\log(1-u))\leqq y(u)^k e^{-y(u)}/\Gamma(k)\ ,$$

or, that for any $x>0$

$$\gamma(1-I(k, x))(-\log(1-I(k, x)))-x^k e^{-x}/\Gamma(k)\leqq 0\ .$$

Some calculations lead to

$$\lim_{u\to 0} \gamma(1-u)(-\log(1-u))/u=\gamma$$

$$\lim_{u\to 0} y(u)^k e^{-y(u)}/\Gamma(k)u=k\ ,$$

and

$$\lim_{x\to\infty} (1-I(k, x))(-\log(1-I(k, x)))/x^k e^{-x}/\Gamma(k)=1\ .$$

Thus a necessary condition that $Wb(\gamma)\succ Ga(k)$ $(\mathcal{T})$ is $\gamma\leqq \mathrm{Min}(k, 1)$.

Next we show the above condition is sufficient. Suppose that $k>$

1, since the part of $k \leqq 1$ is easily derived from Proposition 4. Let $\phi(x)$ be the left-hand side of (18). Then

$$\phi'(x)=\gamma(-\log(1-I(k, x))+1)x^{k-1}e^{-x}/\Gamma(k)-(k-x)x^{k-1}e^{-x}/\Gamma(k) .$$

$\phi'(x)=0$ is equivalent to

$$-\log(1-I(k, x))=-1+(k-x)/\gamma .$$

Since $-\log(1-I(k, x))$, $k \geqq 1$, is starshaped, that is, $-\log(1-I(k, x))/x$ is increasing in x, $\phi'(x)$ changes its sign once from minus to plus. The function $\phi(x)$ is shown to be negative for any x, since $\phi(x)$ is continuous and $\lim_{x\to 0}\phi(x)$ and $\lim_{x\to\infty}\phi(x)$ are not positive under the condition.

(d) Proof of statements within $EP(n, \alpha_1, \cdots, \alpha_n)$. Let $x(u)=F_P^{-1}(n, \alpha_1, \cdots, \alpha_n, u)$ and $y(u)=F_P^{-1}(n', \beta_1, \cdots, \beta_{n'}, u)$. Since

$$x(u)/x'(u)=\exp\{-\sum(\alpha_i x_i)^i\}\sum i(\alpha_i x_i)^i=(1-u)\sum i(\alpha_i x_i)^i ,$$

$EP(n, \alpha_1, \cdots, \alpha_n) \succ EP(n', \beta_1, \cdots, \beta_{n'})$ $(\mathcal{T})$ is equivalent to

$$\sum i(\alpha_i x(u))^i \leqq \sum i(\beta_i y(u))^i \qquad \text{for } 1>u>0 . \tag{19}$$

Now, suppose that $\{\beta_i/\alpha_i\}$ is an increasing sequence. For any value of u, there exists an integer l such that

$$\beta_1/\alpha_1 \leqq \cdots \leqq \beta_l/\alpha_l \leqq x(u)/y(u) \leqq \cdots \leqq \beta_k/\alpha_k .$$

For $i \geqq l+1$ it holds that

$$(\beta_i y(u)/\alpha_i x(u))^i \geqq 1 . \tag{20}$$

On the other hand, for $i \leqq l$ it holds that

$$(\beta_i y(u)/\alpha_i x(u))^i \leqq 1 . \tag{21}$$

Definitions of $x(u)$ and $y(u)$, (20) and (21) imply (19).

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