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MINIMAL SUFFICIENCY AND COMPLETENESS FOR DICHOTOMOUS QUANTAL RESPONSE MODELS

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Minimal sufficiency and completeness are examined for the multistage, multihit and Weibull quantal response models. It is shown that the response counts are minimal sufficient statistics and conditions are presented for completeness for the families of these models. These results provide an example of a complete sufficient statistic for a curved exponential family which is of higher dimension than the parameter space. Uniformly minimum variance unbiased (UMVU) estimators may not exist for the probability of response at a given dose if the response counts are not complete sufficient statistics.

1. Introduction. This paper discusses the properties of minimal sufficiency and completeness for dichotomous quantal response models. Such models have many applications. One application is in the area of *risk assessment* of toxic substances where the experimenter is often interested in estimating the probability of some response (e.g., a tumor), as a function of dose level. Data is often obtained from animal studies that use dose levels sufficiently large to produce a response in a reasonable length of time, with a reasonable sample size. These results are extrapolated from the dose levels in the experiment to the anticipated exposure levels in man. For more information on the topic of risk assessment, we refer the reader to Cornfield (1977), Crump, Hoel, Langley and Peto (1976) and Hogan and Hoel (1989). Statistical procedures often assign a functional form to the probability of response. These functional forms are derived from theories regarding the mechanism of action that leads to a response or can be viewed in the context of generalized linear models [McCullagh and Nelder (1989)]. The Weibull model is a so-called tolerance distribution model. The multistage and multihit models are often referred to as stochastic or mechanistic models. We refer the reader to Hoel (1985), Krewski and Van Ryzin (1981) and Rai and Van Ryzin (1981) for more information on the theories behind these and other models.

Frequently, statistical applications of these models use the method of maximum likelihood for parameter estimation and statistical inferences are obtained by using the asymptotic properties of the maximum likelihood estimator. Maximum likelihood estimation for these procedures has been studied extensively [see Krewski and Van Ryzin (1981), Rai and Van Ryzin (1981) and

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Guess and Crump (1978)]. Various statistical issues in bioassay have been discussed by Haseman (1984).

For the case of the logistic model, sufficiency and completeness are a consequence of the identification of the resulting family of distributions as a full rank exponential family. In this paper, we discuss models that belong to curved exponential families and restrict attention to the multistage, gamma multihit and Weibull dose-response models. Section 2 contains a brief description of the models and the notation that is used. Section 3 discusses minimal sufficiency and shows that the response counts are minimal sufficient. Completeness is discussed in Section 4. Necessary and sufficient conditions are given for completeness of the family generated by the multistage dose-response model. Sufficient conditions for completeness are given for the family generated by the gamma multihit model and the family of distributions generated from the Weibull model is shown to be complete for any set of doses. When the vector of response counts is a complete sufficient statistic, we show that it is possible to have a complete sufficient statistic whose dimension is greater than the dimension of the parameter space. These are believed to be the first such examples for these types of models. A discussion of estimation for these models is contained in Section 5. We show that if the response counts are not complete, then a UMVU estimator may not exist for the probability of response at certain doses.

For simplicity, the material throughout this paper covers the case of a single explanatory variable using dose-response terminology.

2. Dose-response models. Let $0 < d_1 < d_2 < \cdots d_m$ represent the dose levels in a study. Assign N_i subjects to dose level d_i and let n_i be the observed number of responses. The N_i's are fixed numbers. Let $n = (n_1, n_2, \dots, n_m)'$ and $N = (N_1, N_2, \dots, N_m)'$ be the vectors of response counts and numbers of subjects at each dose respectively. Let $p_\theta(d)$ be the probability of response at dose $d > 0$, where θ is a $p \times 1$ $(p \le m)$ vector of parameters that lie in a parameter space Θ. The probability distribution of n is

$$\begin{aligned} P_\theta^M(n) &= \prod_{i=1}^{m} \binom{N_i}{n_i} p_\theta(d_i)^{n_i}[1 - p_\theta(d_i)]^{N_i - n_i} \\ &= \exp\left\{ \sum_{i=1}^{m} \ln\left(\frac{p_\theta(d_i)}{1 - p_\theta(d_i)} \right) n_i + \sum_{i=1}^{m} N_i \ln[1 - p_\theta(d_i)] \right\} \prod_{i=1}^{m} \binom{N_i}{n_i} \qquad (1) \\ &= \exp\left\{ \sum_{i=1}^{m} \eta_i(\theta) T_i(n) - B(\theta) \right\} h(n), \end{aligned}$$

where M denotes a particular dose-response model. The family of distributions $\mathscr{F}_M$ that is generated by dose-response model M is

$$\mathscr{F}_M = \{P_\theta^M(n), \theta \in \Theta\}. \qquad (2)$$

$\mathscr{F}_M$ is, in general, a *curved exponential family* [see Moolgavkar and Venzon (1987)].

EXAMPLE 1. *One-hit model.* The one-hit model [Krewski and Van Ryzin, (1981)] assumes that the probability of response is given by

$$p_\theta(d) = 1 - \exp(-\theta d), \qquad \Theta = \{\theta : \theta > 0\}, \qquad d > 0.$$

Let M_0 denote the one-hit dose-response model and let $\mathscr{F}_{M_0}$ denote the family of distributions generated by M_0. If $m = 1$, $\mathscr{F}_{M_0}$ is a one-parameter exponential family. If $m > 1$, the vector

$$\begin{pmatrix} \eta_1(\theta) \\ \eta_2(\theta) \\ \vdots \\ \eta_m(\theta) \end{pmatrix} = \begin{pmatrix} \ln(e^{\theta d_1} - 1) \\ \ln(e^{\theta d_2} - 1) \\ \vdots \\ \ln(e^{\theta d_m} - 1) \end{pmatrix}$$

forms a curve in $\mathbb{R}^m$ and $\mathscr{F}_{M_0}$ is a curved exponential family.

The dose-response models we study are presented below. Each probability distribution is obtained by substituting a particular form of $p_\theta(d)$ into (1). The models are denoted M_1, M_2 and M_3 and their respective families of distributions, $\mathscr{F}_{M_1}$, $\mathscr{F}_{M_2}$ and $\mathscr{F}_{M_3}$.

(M_1) *The multistage model:*

$$p_\theta(d) = 1 - \exp\left\{ -\sum_{j=1}^{p} \theta_j d^j \right\}, \qquad \Theta = \{\theta : 0 < \theta_1, \theta_2, \ldots, \theta_p < \infty\}, \qquad d > 0.$$

For simplicity, we shall assume that p is a fixed integer and that $p \geq 1$.

(M_2) *The gamma multihit model:*

$$p_\theta(d) = \int_0^{\theta_1 d} \frac{u^{\theta_2 - 1} e^{-u}}{\Gamma(\theta_2)}\, du, \qquad \Theta = \{\theta : 0 < \theta_1, \theta_2 < \infty\}, \qquad d > 0.$$

(M_3) *The Weibull model:*

$$p_\theta(d) = 1 - e^{-e^{(\theta_1 + \theta_2 \ln d)}}, \qquad \Theta = \{\theta : -\infty < \theta_1, \theta_2 < \infty, \theta_2 \neq 0\}, \qquad d > 0.$$

3. Minimal sufficiency. We will show for each model, that the vector n is a minimal sufficient statistic. We begin by describing a condition for minimal sufficiency, and then discuss each model in a different subsection.

LEMMA 1. *Let X be an $m \times m$ matrix with i, jth element*

$$x_{ij} = \ln\left\{ \frac{p_{\theta_j}(d_i)\left[1 - p_{\theta_0}(d_i)\right]}{p_{\theta_0}(d_i)\left[1 - p_{\theta_j}(d_i)\right]} \right\}, \qquad \theta_j = (\theta_{j1}, \theta_{j2}, \ldots, \theta_{jp})', \qquad d_i > 0.$$

If unique vectors $\theta_0, \theta_1, \ldots, \theta_m$ can be chosen such that X is invertible, then n is a minimal sufficient statistic for the family of distributions (2).

PROOF. If X is invertible, the statistic (6) in Lehmann's (1983) Theorem 1.5.3 is equivalent to n. □

The following lemma describes a special case for which X is invertible. The proof follows by induction of m and has been omitted.

LEMMA 2. *Let*

$$p_{\theta_j}(d_i) = 1 - c_i \exp\{-\delta_{j1} d_i\}, \qquad i = 1, \dots, m;\, j = 0, 1, \dots, m, \tag{3}$$

where $d_i > 0$ *and* c_i *is a fixed quantity,* $0 < c_i \leq 1$. *Then, there exists* $\theta_{01}, \theta_{11}, \dots, \theta_{m1}$ *not equal, such that X is invertible.*

3.1. *Multistage model.* Let $\theta_{jk} = \theta_k$, $j = 0, 1, \dots, m$; $k = 2, 3, \dots, p$ for fixed θ_k. Then $p_{\theta_j}(d_i)$ assumes the form of (3) with

$$c_i = \exp\Big\{-\big(\theta_2 d_i^2 + \cdots + \theta_p d_i^p\big)\Big\}.$$

X is invertible by Lemma 2. Therefore, n is minimal sufficient for $\mathscr{F}_{M_1}$ by Lemma 1.

3.2. *Gamma multihit model.* Fix $\theta_{j2} = 1$, $j = 0, 1, \dots, m$. Then $p_{\theta_j}(d_i)$ assumes the form of (3) with $c_i = 1$. Apply Lemmas 1 and 2 to show that n is minimal sufficient for $\mathscr{F}_{M_2}$.

3.3. *Weibull model.* Let $\theta_2 = 1$. Then $p_{\theta_j}(d_i)$ assumes the form of (3) with $c_i = 1$. Therefore, by Lemmas 1 and 2, n is minimal sufficient for $\mathscr{F}_{M_3}$. (Minimal sufficiency of n also follows from the completeness result established later in this paper.)

In the following example, n is minimal sufficient, but is not complete.

EXAMPLE 2. Let $p_\theta(d) = 1 - \exp(-\theta d)$, $\theta > 0$ with $m = 2$, $N_1 = 2$, $N_2 = 1$, $d_1 = 1$ and $d_2 = 2$. The vector of response counts n is not complete. To see this, let $f(n_1, n_2) = \mathscr{I}_{\{0\}}(n_1) - \mathscr{I}_{\{0\}}(n_2)$, where $\mathscr{I}_A(x)$ is the indicator function of the set A, that is,

$$\mathscr{I}_A(x) = \begin{cases} 1, & \text{if } x \in A, \\ 0, & \text{if } x \notin A. \end{cases} \tag{4}$$

Then $Ef(n_1, n_2) = 0$, but $f(n_1, n_2) \neq 0$ with positive probability. Therefore, n is not complete. Note that n is minimal sufficient since the dose-response model is the one-hit. □

4. Completeness. In this section, we discuss completeness for the families $\mathscr{F}_{M_1}$, $\mathscr{F}_{M_2}$ and $\mathscr{F}_{M_3}$. We begin with the multistage model.

4.1. *Multistage model.* Theorem 1 states conditions for completeness for $\mathscr{F}_{M_1}$. The proof is sketched in the Appendix. We also present two corollaries to the theorem.

THEOREM 1. *The family of distributions* $\mathscr{F}_{M_1}$ *is complete with complete sufficient statistic* $T_n = n$ *if and only if*

$$\begin{pmatrix} \sum_{i=1}^{m} d_i a_i \\ \vdots \\ \sum_{i=1}^{m} d_i^p a_i \end{pmatrix} = 0_p \quad \textit{implies } a_i = 0 \tag{5}$$

for $a_i \in \{0, \pm 1, \pm 2, \dots, \pm N_i\}$, $i = 1, 2, \dots, m$.

COROLLARY 1. *The family of distributions* $\mathscr{F}_{M_1}$ *is complete with complete sufficient statistic* $T_n = n$ *if there exists some* k, $k = 1, 2, \dots, p$; *such that*

$$\sum_{i=1}^{m} a_i d_i^k = 0 \quad \textit{implies } a_i = 0 \tag{6}$$

for $a_i \in \{0, \pm 1, \pm 2, \dots, \pm N_i\}$, $i = 1, 2, \dots, m$.

PROOF. Equation (6) implies (5) of Theorem 1. □

COROLLARY 2. $\mathscr{F}_{M_1}$ *is a complete family of distributions with complete sufficient statistic* $T_n = n$, *if* $p = m$.

PROOF. Recall that $d_i > 0$, $i = 1, 2, \dots, m$; by definition of $\mathscr{F}_{M_1}$ and let

$$X = \begin{pmatrix} d_1 & d_2 & \cdots & d_m \\ d_1^2 & d_2^2 & \cdots & d_m^2 \\ \vdots & \vdots & & \vdots \\ d_1^m & d_2^m & \cdots & d_m^m \end{pmatrix}.$$

It is easy to show that X is invertible. Therefore, $Xa = 0_m$ implies $a = 0_m$, where a is an arbitrary $m \times 1$ vector. Since this is condition (5) of Theorem 1, the proof is complete. □

Examples 3 and 4 discuss some two-dose designs where n is complete for $\mathscr{F}_{M_1}$.

EXAMPLE 3. Suppose $m = 2$ and that doses $0 < d_1 < d_2$ are chosen such that d_1/d_2 is an irrational number. Apply Corollary 1 to show that n is complete for the family $\mathscr{F}_{M_1}$. If $a_1 = 0$, then $a_2 = 0$ and conversely. If a_1 and a_2 are nonzero, then $a_1 = -a_2(d_2/d_1)$ is an irrational number which is impossible since $a_1 \in \{0, \pm 1, \pm 2, \dots, \pm N_1\}$.

EXAMPLE 4. Consider the two-dose design obtained by choosing $d_2/d_1 > N_1$. Again, if $a_1 = 0$, then $a_2 = 0$ and conversely. If $a_1 < 0$, then $a_2 > 0$ and

$$a_1 d_1 + a_2 d_2 = d_1\left\{a_1 + a_2\left(\frac{d_2}{d_1}\right)\right\} > d_1(a_1 + a_2 N_1) \geq 0.$$

If $a_1 > 0$, then $a_2 < 0$ and

$$a_1 d_1 + a_2 d_2 = d_1\left\{a_1 + a_2\left(\frac{d_2}{d_1}\right)\right\} < d_1(a_1 - N_1) \leq 0.$$

Therefore, $a_1 d_1 + a_2 d_2 = 0$ only if $a_1 = a_2 = 0$, and n is complete for $\mathscr{F}_{M_1}$ by Corollary 1.

In the next example, a complete sufficient statistic exists for a curved exponential family and its dimension is greater than the dimension of the parameter space.

EXAMPLE 5. For the family of one-hit models with $m = 3$, $N_1 = N_2 = N_3 = 5$, $d_1 = 1$, $d_2 = 1\frac{1}{6}$ and $d_3 = 1\frac{2}{7}$, substitute for a_2 and a_3 in

$$a_1 = -(7a_2/6 + 9a_3/7).$$

The only integer solution is $a_1 = a_2 = a_3 = 0$. Therefore, n is complete by Corollary 1. The dimension of n equals 3 and the dimension of the parameter space equals 1.

4.2. *The multihit model.* The following theorem provides a sufficient condition for completeness of the family of distributions $\mathscr{F}_{M_2}$.

THEOREM 2. *The family of distributions $\mathscr{F}_{M_2}$ is complete with complete sufficient statistic $T_n = n$ provided that*

$$\sum_{i=1}^{m} a_i d_i = 0 \quad \textit{implies } a_i = 0$$

for $a_i \in \{0, \pm 1, \pm 2, \dots, \pm N_i\}$, $i = 1, 2, \dots, m$.

PROOF. Let $\mathscr{F}_{M_2}^*$ be the subfamily of $\mathscr{F}_{M_2}$ consisting of models with $\theta_2 = 1$. Then $\mathscr{F}_{M_2}^*$ is the family of one-hit models. Therefore, n is complete for $\mathscr{F}_{M_2}^*$ by Theorem 1. Since $\mathscr{F}_{M_2}^* \subset \mathscr{F}_{M_2}$ and the one-hit model and gamma multihit model have the same support, a statistic that is complete for $\mathscr{F}_{M_2}^*$ is also complete for $\mathscr{F}_{M_2}$ by Lehmann's (1983) problem 5.27 on page 67 (note: we believe that the additional condition, $\mathscr{P}_0 \subset \mathscr{P}_1$, is required in Lehmann's problem). $\square$

4.3. *The Weibull model.* The following theorem states that n is a complete sufficient statistic for any collection of m doses d_i, $i = 1, 2, \ldots, m$.

THEOREM 3. *The family of distributions $\mathscr{F}_{M_3}$ is complete with complete sufficient statistic $T_n = n$.*

PROOF. Let $\mathscr{F}^*_{M_3}$ be the subfamily of $\mathscr{F}_{M_3}$ consisting of models with θ_2 fixed. $\mathscr{F}^*_{M_3}$ is the family of one-hit models. The vector n is complete for $\mathscr{F}^*_{M_3}$ by Theorem 1 if

$$\sum_{i=1}^{m} a_i d_i^{\theta_2} = 0 \quad \text{implies } a_i = 0$$

for $a_i \in \{0, \pm 1, \pm 2, \ldots, \pm N_i\}$, $i = 1, 2, \ldots, m$. Since θ_2 is fixed but arbitrary, the result must hold for some θ_2. Since $\mathscr{F}^*_{M_3} \subset \mathscr{F}_{M_3}$ and the one-hit and Weibull models have the same support, n is complete for $\mathscr{F}_{M_3}$ by problem 5.27 on page 67 of Lehmann (1983). $\square$

5. Applications to estimation.

Since $E_\theta(n_i/N_i) = p_\theta(d_i)$, the probability of response at each dose has an unbiased estimator. The estimator n_i/N_i is uniformly minimum variance unbiased (UMVU) when n is complete. The following two examples illustrate what happens when n is not complete.

EXAMPLE 2 (Continued). There exist UMVU estimators for some of the $p_\theta(d_i)$'s but not all of them as guaranteed by completeness. To see this, apply Theorem 2.1.1 of Lehmann (1983) to find the totality of functions that possess UMVU estimators. First, characterize the totality of unbiased estimators of zero. (It suffices to restrict attention to estimators with finite variance.) Let Δ be the class of estimators with finite variance and let $\mathscr{U}$ be the class of all unbiased estimators of zero that belong to Δ. Then, for any estimator $U(n) \in \mathscr{U}$, $E_\theta(U) = 0$ for all $\theta > 0$, if and only if

$$U(n) = a\{\mathscr{T}_{\{0\}}(n_1) - \mathscr{T}_{\{0\}}(n_2)\}$$

for an arbitrary finite number a and $\mathscr{T}_A(x)$ given by (4). This can be shown by expanding and collecting terms in the equation $E_\theta(U) = 0$. Any $\delta(n) \in \Delta$ is a UMVU estimator for its expectation, if and only if $E_\theta(\delta U) = 0$ for all $U \in \mathscr{U}$ and all $\theta > 0$. This implies that $\delta(0, 1) = \delta(1, 0) = \delta(2, 0)$. Therefore, for arbitrary finite numbers a, b, c, and d,

$$\delta(n) = a\mathscr{T}_{\{(0,0)\}}(n) + b\mathscr{T}_{\{(0,1),(1,0),(2,0)\}}(n) + c\mathscr{T}_{\{(1,1)\}}(n) + d\mathscr{T}_{\{(2,1)\}}(n).$$

The totality of functions that possess a UMVU estimator is

$$E_\theta(\delta) = (a - 2b + 2c - d)e^{-4\theta} + 2(d - c)e^{-3\theta}$$
$$+ 2(b - c)e^{-2\theta} + 2(c - d)e^{-\theta} + d.$$

Since there does not exist a, b, c and d such that $E_\theta(\delta) = p_\theta(d_1) = 1 - e^{-\theta}$, no UMVU estimator exists for $p_\theta(d_1)$. In fact, the estimator which minimizes the variance is

$$\delta_\theta(n) = \frac{n_1}{2} + \frac{1}{2(1+e^{-\theta})}\left[\mathscr{T}_{\{0\}}(n_1) - \mathscr{T}_{\{0\}}(n_2)\right]$$

which depends on θ and is therefore only locally minimum variance unbiased (LMVU). Hence, the natural estimator $n_1/2$ is not UMVU for $p_\theta(d_1)$ in this case.

There exists a UMVU estimator for $p_\theta(d_2)$ in the previous example. We might expect that it is given by $\delta^*(n) = n_2/N_2 = 1 - \mathscr{T}_{\{0\}}(n_2)$ which would be the UMVU estimator if n were complete. The next example shows that this is not the case.

EXAMPLE 2 (Continued). It is easy to see from the previous example that a UMVU estimator for $p_\theta(d_2) = 1 - e^{-2\theta}$ is

$$\delta^{**}(n) = 1 - \tfrac{1}{2}\left[\mathscr{T}_{\{0\}}(n_1) + \mathscr{T}_{\{0\}}(n_2)\right].$$

This estimator uses information from both doses, and $\operatorname{var}(\delta^{**}) = \frac{1}{2}\operatorname{var}(\theta^*)$. Therefore, we get a more precise estimate for $p_\theta(d_2)$, but lose the ability to estimate $p_\theta(d_1)$ with a UMVU estimator.

APPENDIX

PROOF OF THEOREM 1. *Sufficiency.* Show that $E_\theta\delta(n) = 0$ all $\theta \in \Theta$, implies that $\delta(n) = 0$ a.e. $\mathscr{F}_{M_1}$:

$$E_\theta\delta(n) = \sum_{j_1=0}^{N_1} \cdots \sum_{j_m=0}^{N_m} c(j) \prod_{j=1}^{p} \exp\left\{-\theta_j \sum_{i=1}^{m} d_i^j (N_i - j_i)\right\},$$

where

$$c(j) = \sum_{k_1=j_1}^{N_1} \cdots \sum_{k_m=j_m}^{N_m} \delta(k) \left\{\prod_{i=1}^{m} \binom{N_i}{k_i}\binom{k_i}{j_i}\right\}(-1)^{\Sigma(k_i - j_i)}.$$

By induction, it is not difficult to show that if $E_\theta\delta(n) = 0$ for all $\theta \in \Theta$, then $c(j) = 0$ for all j, and that if $c(j) = 0$ for all j, then $\delta(k) = 0$ for all k.

NECESSITY. Suppose for some $j \neq j^*$; $j_i, j_i^* \in \{0, 1, \ldots, N_i\}$, that

$$\begin{pmatrix} \sum_{i=1}^{m} d_i j_i \\ \vdots \\ \sum_{i=1}^{m} d_i^p j_i \end{pmatrix} = \begin{pmatrix} \sum_{i=1}^{m} d_i j_i^* \\ \vdots \\ \sum_{i=1}^{m} d_i^p j_i^* \end{pmatrix}.$$

Without loss of generality, we can assume that $j_1 - j_1^* > 0$.

Let

$$\delta_1(n) = \frac{\binom{N_1 - (j_1 - j_1^*)}{n_1}\binom{N_2 + j_2}{n_2} \cdots \binom{N_m - j_m}{n_m}}{\prod_{i=1}^m \binom{N_i}{n_i}}$$

and

$$\delta_2(n_2, \dots, n_m) = \frac{\binom{N_2 - j_2^*}{n_2} \cdots \binom{N_m - j_m^*}{n_m}}{\prod_{i=2}^m \binom{N_i}{n_i}}.$$

Then $E_\theta(\delta_1 - \delta_2) = 0$. However, $\delta_1 \neq \delta_2$ since δ_1 is a function of n_1 and δ_2 is not. Therefore, the condition for completeness is violated. □

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