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A Nonparametric Test for the Presence of Immunes In Type I Censored Data

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Abstract

Mixture models which allow a component of `immune' or `cured' individuals to be present in a population otherwise subject to death or failure are of great use in toxicological, medical and other contexts. In Type I censoring, a simple nonparametric procedure to test whether there is a strong evidence of `immune' individuals is proposed. This test is shown to be consistent when the observation time is long enough. The usefulness of the test is verified by our simulation studies.

Keywords: **immune; mixture model; nonparametric test.**

1.Introduction

Mixture models which allow a component of `immune' or `cured' individuals to be present in a population otherwise subject to death or failure are very useful in toxicological, medical and other contexts. There has been a lot of interest in the application of such models; see for example Farewell (1982), Larson and Dinse (1985), Kuk and Chen (1992), Ghitany, Maller and Zhou (1994). For Type I censoring, let t_0 be the end of study period which we call the fixed censoring time. Under mixture models, $\overline{F}(t)$, the survival

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function for lifetime of an individual i drawn at random is

$$\overline{F}(t) = P_I + (1-P_I)(1-F_d(t)) \qquad t \in [0, t_0], \tag{1.1}$$

where $0 \le P_I < 1$ denotes the proportion of `immune' individuals, $F_d(t)$ denotes the distribution function of `susceptible' individuals and $t_f = \sup\{t \ge 0 : F_d(t) < 1\}$ is the right extreme.

Given a data set of size of n, let m denote the number of death occurring before t_0. When $m < n$ is observed, an important question is whether there really is an `immune' proportion in the population. In the following section, a simple nonparametric statistic is proposed to test null hypothesis $H_0 : P_I = 0$ against alternative $H_a : P_I > 0$.

2. Testing for the Presence of Immunes

Given $m < n$, let $T_{(i)}(i = 1,...,m)$ denote the i^{th} order statistic of failure time. Under H_0, $m < n$ implies $t_0 < t_f$ and, therefore, for large m, $T_{(m)}$ tends to be close to t_0. Under H_a, however, there would be an interval between $T_{(m)}$ and t_0 when $t_0 - t_f$ is sufficiently large. Hence, intuitively, H_0 should be rejected when $t_0 - T_{(m)}$ is too large.

Let $d_m = t_0 - t_{(m)}$, where $t_{(m)}$ is the observed value of $T_{(m)}$ in a given data set. Consider the p-value corresponding to the realization d_m

$$P_m = P(t_0 - T_{(m)} \ge d_m) \tag{2.1}$$

The idea is to reject H_0 when $\hat{P}_m = P(\hat{t}_0 - T_{(m)} \ge d_m) \le \alpha$, where $\hat{t}_0$ is some substitute of t_0. It is desirable that $\hat{t}_0$ possesses the following properties:

(i) Under H_0, $\hat{t}_0$ should be close to t_0, and

(ii) $E[\hat{t}_0 \mid H_a]$ is a decreasing function of $t_0 - t_f$ and P_I.

With the criteria above, we choose $\hat{t}_0$ as

$$\hat{t}_0 = w_m(3T_{(m)} - 3T_{(m-1)} + T_{(m-2)}) + (1 - w_m)t_0,$$

where $w_m = \left(\frac{n-m}{n}\right)$.

By Schucany, Gray and Owen (1971), it follows directly that give m and under H_0

$$E[\hat{t}_0 \mid H_0] = t_0 - O(w_m m^{-3}),$$

and under H_a

$$E[\hat{t}_0 \mid H_a] = t_0 - \{P_1(t_0 - \min\{t_0, t_f\}) + O(w_m m^{-3})\}.$$

Hence, $\hat{t}_0$ satisfies criterion (i) and (ii). Replacing t_0 in (2.1) with $\hat{t}_0$ leads to

$$\hat{P}_m = P(\hat{t}_0 - T_{(m)} \geq d_m)$$

$$= P(T_{(m)} \leq t_{(m)} + (\hat{t}_0 - t_0)).$$

Now, let

$$\tilde{P}_m = (1 - \frac{\sum_{i=1}^{m} I^i_{[T_{(m)}+(\hat{t}_0 - t_0), t_0]}}{m})^m,$$

where

$$I^i_{[T_{(m)}+(\hat{t}_0 - t_0), t_0]} = \begin{cases} 1, & \text{If } T_i \in [T_{(m)} + (\hat{t}_0 - t_0), t_0] \\ 0, & \text{otherwise.} \end{cases}$$

We estimate $\hat{P}_m$ by $\tilde{P}_m$ and set up the following test :

$$\text{Reject } H_0 \quad \textit{iff} \quad \tilde{P}_m \leq \alpha \tag{2.2}$$

The following theorem investigates the asymptotic properties of test (2.2).

Theorem 1:

Test (2.2) satisfies the following properties:

$$(1)\ \lim_{m\to\infty} P(\tilde{P}_m \le \alpha \mid m, H_0) = 0,$$

$$(2)\ \lim_{m\to\infty} P(\tilde{P}_m \le \alpha \mid m, H_a, t_0 > t_f) = 1.$$

proof:

$$\tilde{P}_m \le \alpha \ \Leftrightarrow\ (1 - \frac{\sum_{i=1}^{m} I^i_{[T_{(m)}+(\hat{t}_0 - t_0), t_0]}}{m})^m \le \alpha,$$

$$\Leftrightarrow\ \sum_{i=1}^{m} I^i_{[T_{(m)}+(\hat{t}_0 - t_0), t_0]} \ge m(1-\alpha^{\frac{1}{m}}),$$

$$\Leftrightarrow\ T_{(m-k_m(\alpha))} > T_{(m)} + (\hat{t}_0 - t_0),$$

where $k_m(\alpha) = [m(1-\alpha^{\frac{1}{m}})]$, the greatest integer less than or equal to $m(1-\alpha^{\frac{1}{m}})$. Since $\lim_{m\to\infty} k_m(\alpha) = 0$ and under H_0 $(\hat{t}_0 - t_0) \xrightarrow{p} 0$, where $\xrightarrow{p}$ denotes convergence in probability,

$$\lim_{m\to\infty} P(T_{(m-k_m(\alpha))} > T_{(m)} + (\hat{t}_0 - t_0) \mid m, H_0)$$

$$= \lim_{m\to\infty} P(T_{(m-k_m(\alpha))} > T_{(m)} \mid m, H_0) = 0$$

Under $t_0 > t_f$, it follows that $(\hat{t}_0 - t_0) \xrightarrow{p} P_1(t_f - t_0) < 0$ and

$$\lim_{m\to\infty} P(T_{(m-k_m(\alpha))} > T_{(m)} + (\hat{t}_0 - t_0) \mid m, H_a, t_0 > t_f)$$

$$= \lim_{m\to\infty} P(T_{(m-k_m(\alpha))} > T_{(m)} + P_1(t_f - t_0) \mid m, H_a, t_0 > t_f)$$

$$= 1.$$

The proof is complete.

3.Simulation Results

In this section, we examine the performance of test (2.2) for truncated Weibull distribution. With the choice of scale parameter values $\lambda = 1.0$ and shape parameter values $\delta = 0.5$, 1.0 and 2.0, it represents a diverse class of distribution in terms of skewness and tailweight. The simulations are performed using the APL programming language. The significance level, α, is set at 0.05, t_f is set at 3.0, and t_0 ranges over 1.0, 2.0, 4.0 and 5.0. P_I is set at 0.0(0.2)0.8. The sample sizes are chosen as 50 and 100 and the replication is 50000 times. Table 1 shows (see Appendix) estimated size and power of the test.

Simulation results indicate in all the cases studied test (2.2) provides acceptable empirical significance levels. The power of the test increases as P_I increases. However, before t_0 exceeds t_f, the power is very small except for large P_I. After t_0 exceeds t_f, the power increases substantially and becomes higher as $t_0 - t_f$ increases. When $n = 50(100)$, and $t_0 = 5.0$, the power of the test is large in all the cases studied except for $P_I = 0.2$.

4.Example

In the experiment reported by Pierce, Stewart and Kopecky (1979), subsequently denoted by PSK, fish are subjected to three levels of zinc concentration and approximate time to death is observed. Half the fish at each concentration level received one week's acclimation to the test aquaria and half received two weeks' acclimation. There are six treatment groups, therefore, and 50 fish are randomly assigned to each group. The experiment runs for 10 days. Table 2 (see Appendix), taken from PSK, shows the daily

mortalities. Farewell (1982) analyzed PSK data assuming mixture models which postulate a fraction of `long-term' surviors, i.e., `immune' individuals.

In PSK data, we further assume that the failures occur uniformly over the 24 hour period. Take for example, the three failures on day 5, we set the failure time at 5.25, 5.5 and 5.75. To justify the use of mixture model by Farewell (1982), test (2.2) is applied to the modified PSK data for testing H_0. The test size is shown on the last row of Table 2. According to the test, there is evidence for the existence of `long-term' survivors for treatment groups with low level of zinc concentration and group with medium level of zinc concentration and two weeks' acclimation. However, the observation time is not long enough to conclude the existence of `long-term' survivors for the rest of treatment groups.

5. Conclusions

In summary, we have introduced a simple nonparametric test for the presence of immune individuals in toxicological or medical data. Although the derivation of test (2.2) is heuristic, the usefulness of the test is justified by Theorem 1 and the simulation results.

Table 1. Estimated size and power from 50000 simulations for truncated Weibull with $t_f = 3.0$ and $\alpha = 0.05$

n	P_I	$t_0 = 1.0$	$t_0 = 2.0$	$t_0 = 4.0$	$t_0 = 5.0$
		$\lambda = 1.0$	$\delta = 0.5$		
50	0.0	0.040(38.4*)	0.008(45.9)	.	.
	0.2	0.086(30.7)	0.053(36.8)	0.198(40.0)	0.407(40.0)
	0.4	0.140(23.0)	0.120(27.6)	0.388(30.0)	0.647(30.0)
	0.6	0.203(15.4)	0.195(18.4)	0.480(20.0)	0.699(20.0)
	0.8	0.299(7.7)	0.300(9.2)	0.524(10.0)	0.743(10.0)
100	0.0	0.035(76.8)	0.006(91.9)	.	.
	0.2	0.078(61.4)	0.046(73.6)	0.355(79.9)	0.669(80.0)
	0.4	0.126(46.0)	0.101(55.1)	0.571(59.9)	0.853(60.0)
	0.6	0.178(30.7)	0.164(36.8)	0.615(40.0)	0.911(40.0)
	0.8	0.251(15.3)	0.251(18.4)	0.693(19.9)	0.962(20.0)
n	P_I	$\lambda = 1.0$	$\delta = 1.0$		
50	0.0	0.062(33.2)	0.009(45.4)	.	.
	0.2	0.102(26.6)	0.055(36.4)	0.236(40.0)	0.458(40.0)
	0.4	0.147(19.9)	0.119(27.3)	0.443(29.9)	0.712(30.0)
	0.6	0.190(13.3)	0.194(18.2)	0.569(19.9)	0.765(20.0)
	0.8	0.255(6.8)	0.286(9.1)	0.634(10.0)	0.805(10.0)
100	0.0	0.059(66.5)	0.008(90.9)	.	.
	0.2	0.098(53.2)	0.049(72.7)	0.364(80.0)	0.679(80.0)
	0.4	0.139(39.9)	0.104(54.6)	0.600(59.9)	0.894(60.0)
	0.6	0.182(26.6)	0.169(36.3)	0.657(40.0)	0.952(40.0)
	0.8	0.230(13.3)	0.248(18.2)	0.694(20.0)	0.964(20.0)
n	P_I	$\lambda = 1.0$	$\delta = 2.0$		
50	0.0	0.068(31.6)	0.003(48.4)	.	.
	0.2	0.103(25.2)	0.070(39.2)	0.508(39.9)	0.687(40.0)
	0.4	0.141(18.9)	0.167(29.4)	0.746(29.9)	0.883(30.0)
	0.6	0.180(12.6)	0.269(19.6)	0.831(19.9)	0.935(20.0)
	0.8	0.231(6.5)	0.370(9.8)	0.864(10.0)	0.948(10.0)
100	0.0	0.068(63.2)	0.001(97.8)	.	.
	0.2	0.103(50.5)	0.056(78.5)	0.513(80.0)	0.716(80.0)
	0.4	0.138(37.9)	0.141(58.8)	0.756(59.9)	0.899(60.0)
	0.6	0.177(25.2)	0.236(39.2)	0.838(39.9)	0.944(40.0)
	0.8	0.220(12.6)	0.333(19.6)	0.873(20.0)	0.958(20.0)

*: Number in parenthesis is the number of death(m).

Table 2. Daily mortality from groups of 50 fish per treatment combination

Day		Acclimation time					
		One week			Two week		
	Zinc	low	med.	high	low	med.	high
1		0	0	0	0	0	0
2		3	3	2	0	1	3
3		12	17	22	13	21	24
4		11	16	15	8	8	10
5		3	5	7	0	5	4
6		0	1	1	0	0	1
7		0	0	2	0	0	0
8		0	1	0	0	0	0
9		0	0	0	0	0	0
10		0	0	0	0	0	0
Total		29	43	49	21	35	42
Test Size		0.00	0.73	0.36	0.00	0.00	0.21

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型一設限下，免疫個體存在與否之無母數檢定

沈葆聖*

在混合模式(mixture model)下，族群由`非免疫'個體和`免疫'個體所組成這些年來，混合模式(mixture models)已廣泛的應用在毒物學和臨床醫學分析上。本文對於型一設現(Type I censoring)資料，提出一無母數檢定用以檢定族群是否存在`免疫'個體，我們證明該檢定為一致性檢定，模擬結果證實其實用性。

關鍵詞：免疫；混合模式；無母數檢定。

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