INCORPORATING HISTORICAL CONTROL INFORMATION IN BIOASSAY TESTING ACCOUNTING FOR SURVIVAL DIFFERENCES

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GARY THOMAS BROOKS. Incorporating Historical Control Information in Bioassay Testing Accounting for Survival Differences (Under the direction of DR. LAWRENCE KUPPER and DR. DAVID G. HOEL.)

In determining whether or not substance are carcinogenic one of the most useful tests is life-time rodent carcinogenesis bioassay of the National Cancer Institute. From repeated testing a large database of historical control information is now available. Appropriate statistical methodology are developed and evaluated to utilize this control data.

A conditional-exact test with an approximation as well as an asymptotic test are derived that incorporate the historical control data while accounting for differences in survival between dose groups. The procedures are locally most powerful tests applicable without the need for determination of tumor type as lethal or incidental.

Simulations are used to access the normality of the statistics and the Type I errors of the tests. Examples are used to compare the tests to those without both or either control data and time included, as well as the effect of grouping in time. The tests' robustness against the variability in the parameter estimates used is evaluated with recommendations for use.

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1.1 Introduction

Every day more and more substances are suspected of being carcinogenic. The problem is how to determine if they are without actually placing man in danger. From a regulatory point of view one of the most useful tests to date is the life-time rodent carcinogenesis bioassay of The National Cancer Institute (NCI). A positive result on this test is usually the strongest evidence of a similar effect in man. The savings in time and money afforded by the test increases the need to develop an analysis which will produce unbiased conclusions while powerful enough to be sensitive to small increases in the probability of incidence.

The NCI and National Toxicology Program (NTP) now have available the results from nearly 300 reports from laboratory animal carcinogenicity studies each of which included a control group regardless of the chemical tested. Most of the studies were two years in length involving both sexes of the Fischer 344 rats and B6C3F1 mice. From each of these detailed histopathology data were obtained for each individual animal, computerized and stored on the Carcinogenesis Bioassay Data System (CBDS). Haseman (1984) presents some of the problems encountered in the utilization of this historical control data, one of these was the need to develop appropriate statistical methodology to utilize the control data.

Standard practice to date has been to compare treated and control groups using only the current experiment and generally only those animals which survive to the full term.

Of the 170 studies Haseman presents, the average survival rate to full term was 72% ranging from 44-88%. Any statistical procedure that only considers full term data would therefore expect to disregard one-fourth of the current information.

Although the concurrent control group should be considered the most appropriate when testing (Gart, 1979), there are times when the historical control data can be of use. Three very useful times are: 1) as a measure of quality control, 2) when the background rate is low, 3) when the significance is marginal when compared to only the concurrent controls.

The purpose of this research then is the development and evaluation of testing procedures that will make use of existing historical control data while allowing for the inclusion of less than full-term observations.

1.2 Review of Some Current Testing Procedures

The statistical procedures usually used by the NCI and others for the evaluations of tumor incidence data are Fisher's exact test for pairwise comparisons and the Cochran-Armitage (C-A) Test for dose-response trends; Cochran (1954), Armitage (1955). The C-A statistic is distributed asymptotically as a chi-square random variable with the one degree of freedom under the null hypothesis of no differences in the probability of developing a response between all groups. Cox (1958) showed it to be uniformly most powerful unbiased against logistic alternatives, and Tarone and Gart (1080) that it is asymptotically locally optimal against any alternative which can be expressed as a smooth function of dose. Being a test of a non-zero slope, in the case with equal sample sizes and two dose groups, the first dose being half of the second, the statistic tends to downplay the observations in the first dose group. The C-A test considers only full term observations and utilizes only the concurrent control group.

1.2.1 Parametric Tests Incorporating Time

Peto (1980) points out that after controlling for experimental biases, three possible reasons exist for differences in tumor yields in treatment and control

groups: 1) differences in survival affecting the length of time at risk of developing the response, 2) difference due to chance alone, 3) an effect due to treatments. Any good testing procedure must correct for #1 while determining between #2 and #3. This need to take into account differences in intercurrent mortality in the analysis of tumor incidence data has led to development of many different methods.

Included among the parametric models is the use of a Weibull distribution for analyzing the time-to-tumor data proposed by Pike (1966) and later by Peto and Lee (1973). Under the assumption that a determination can be made between fatal and incidental tumors, Kodell and Nelson (1980) fit independent Weibulls to time to onset of tumor and time to death after onset.

Turnbull and Mitchell (1978) divide the entire time into intervals. Making assumptions on withdrawals they obtain iterative maximum likelihood estimations of the $K=2^I$ prevalences for each interval, where each state is a possible combination of "presence" or "absence" of the I diseases of interest. With "group" and the I diseases as main effects the log prevalences are modeled in a complete factorial design, testing the group by disease interactions of interest. The possibly large number of empty cells and interval dependence are problems which should be examined further. In a follow-up paper (Mitchell and Turnbull, 1979) they remove the assumption that lethalities depend only on illness state and not group membership. If the odds ratio can be assumed constant over time, they recommend use of the Mantel-Haenszel test; when the disease of interest is non-lethal and its prevalence a non-decreasing function of time, then the restricted prevalence estimates can be found using procedures given by Ayer et al. (1955). For fatal and possibly fatal diseases a complete factorial model is fit to both the prevalences and lethalities, testing parameters using outlined procedures.

When the response of interest is the prevalence of non-lethal tumors detectable only at death, Dinse and Lagakos (1983) use a logistic regression that allows them to take into account covariables (e.g., weight, litter effects) which could be confounding factors.

Since a later chapter will expand this test to take into account historical control information, the model will be presented here.

Notation:

T - denotes age at death

Y - presence (=1) or absence (=0) of tumor at death

X - treatment indicator (0/1 with only two groups: control/trt)

Z - p-vector of covariables

Modeling the probability of a tumor given T, X, and Z by

$$\Pr\{Y=1 \mid t,x,z\} = \frac{\exp\{\alpha x w(t) + \beta z + \delta(t)\}}{1 + \exp\{\alpha x w(t) + \beta z + \delta(t)\}}$$

yields prevalence odds $\Theta(x, z, t) = \frac{\Pr\{Y=1 \mid t,x,z\}}{\Pr\{Y=0 \mid t,x,z\}} = \exp\{\alpha x w(t) + \beta z + \delta(t)\}$

and treatment odds $\frac{\Theta(1,z,t)}{\Theta(0,z,t)} = \exp\{\alpha w(t)\}$

for one treatment group. Here $w(t)$ is a prespecified function of time weighting the treatment effect and $\delta(t)$ specified by an unknown set of parameters. The hypothesis of no treatment effect is then given by $\alpha=0$. Letting $t_1 < t_2 < \ldots < t_J$

denote the J distinct times of death, $w_j=w(t_j)$ and $\delta_j=\delta(t_j)$, then likelihood-based computer programs can be used to estimate the parameters (α, $\beta_1,\ldots,\beta_p$, $\delta_1,\ldots,\delta_J$). Using these in the score evaluated at $\alpha=0$ yields:

$$u = \sum_{j=1}^{J} W_j \ (n_j - E_j(Z)) \quad \text{where } E_j(Z) = \Sigma_i x_i \ \frac{\exp\{\hat{\beta} Z_i + \hat{\delta}_j\}}{1 + \exp\{\hat{\beta} Z_i + \hat{\delta}_j\}}$$

i being summed over all those that died at time t_j and n_j the observed number of tumors in the treatment group at t_j. Estimating the variance by $\hat{v}$, the reciprocal of the (1,1)-element of the inverse of the observed information matrix evaluated at $\alpha=0$, the statistic:

$$Q = u^2/\hat{v},$$

which is approximately chi-squared with 1 df.

In the case of more than one treatment group the X variable can equal dose. The resulting statistic is the same with n_j equaling $\Sigma\ x_i Y_i$, the weighted (by dose) number of treatment tumors at t_j. The statistic $u/\hat{v}^{1/2}$ provides a trend test that adjusts for covariates, and reduces to a conventional trend test setting $\beta = 0$ with one δ_j constant for each time interval.

Dinse and Lagakos point out that the weight function w(t) can be chosen to give power against a particular shape. In practice the most natural choice is w(t)=1. They also found approximating $\delta(t)$ by a linear or quadratic polynomial to suffice. When many serial sacrifices are present an additional term can be included in the exponential to account for mode of death (natural-sacrificial).

1.2.2 Non-parametric Tests Incorporating Time

If in the development leading to the above we let w(t)=1 and disregard the covariables (β=0) then the ML (maximum likelihood) estimate of $\delta_j = \ln\{(m_j + n_j) \mid (M_j - m_j + N_j - n_j)\}$ where m_j=number controls with tumors, M_j=number controls at risk, n_j=number tumors in treatment group, N_j=number at risk treatment group.

The score function is then the same as in the Hoel-Walberg (1972) test with the variance differing only by a finite population correction term, assuming that the intervals chosen for the Hoel-Walberg analysis contain only one distinct time of death. It is the effect of using "arbitrarily" chosen intervals that is the weakness of the test, which is eliminated by the Q statistic at the expense of assuming a parametric model.

The paper by Hoel and Walberg has been the basis for most of the analysis used to account for survival differences. The Hoel-Walberg statistic combines results across each interval for which a tumor was observed. The procedure requires that cause of death be determined with the type of analysis dependent on whether the tumor causes death or is incidental to death. They give an example to show that applying the wrong type of analysis can lead to different conclusions.

In the case of lethal tumors, they present interval techniques under the additional assumption that the tumor causing death is reasonably independent of other causes of death, pointing out that a Kaplan-Meier (1958) representation is preferable to grouping. When only one treatment group is used, testing is accomplished using Breslow's (1970) test. Since Breslow's test does not readily accomodate ties, this method should not be used with serial sacrifice data. For more than one treatment group the test is useful for detecting differences rather than a trend, so unless modified, the procedure applies to pairwise comparisons.

When the tumor is non-lethal, observable only after death, then the concern is with a difference in prevalence as a function of time. For this case Hoel and Walberg present an interval procedure with a Mantel-Haenszel type test and a "runs" method to display the data, noting for the runs method "no satisfactory statistical test is available." When the tumor may be lethal, ad hoc

adjustments are recommended but here again without a test. The latter two cases also need the assumption of equal force of mortality for animals with and without tumors, which may be too stringent in many cases.

The most complete presentation of procedures to be used is by Peto et al. (1980) given in a form understandable by both researchers and statisticians. Here again it is needed to know whether the tumor directly or indirectly contributed to the death or whether it was incidental to death. After discussing the need for determination of cause of death in any survival-adjusted analysis, they show its feasibility by presenting an example with over 4500 tumors in which 94% of all tumors could be classified as either "definitely incidental" or "definitely fatal." Haseman (1984) points out that although some pathologists remain skeptical as to the accuracy of cause of death determination, the NTP as part of its new modified pathology protocols, requests that an attempt at determination be made for each observed tumor. Requesting the information now will guarantee a sufficient data base to evaluate the feasibility of utilizing "cause of death" determination in future years.

For tumors observed in a fatal context, Peto et al (1980) employ life table methods (similar to Cox (1972), Tarone (1975)) to evaluate tumor incidence. Forming a contingency table at each time point for which a tumor is observed, the results are combined by Mantel-Haenszel (1959, 1966) methods, along with those tumors observed incidentally at the end of the study, for an overall p-value.

For non-fatal tumors, Peto's "Incidental Tumor Test" is essentially the Hoel-Walberg (1972) method. Comparing proportions in selected time intervals, Mantel-Haenszel methods are again employed to combine across time. Again this has the problem of subjective determination of the time intervals, along with reduced power for studies with severely reduced survival in dosed groups.

In an attempt to lessen pathologists' objections to declaring a tumor to be incidental or not, Poon and Hoel (1984) have developed an approach to estimate the survival functions, risk due to a particular type of tumor and risk due to all other competing causes, incorporating the pathologist's degree of confidence in each specific diagnosis. Although not developed to the point of significance testing the method may eliminate some pathologists' objections. It presently allows only one death per time but can be easily expanded to accommodate multiple deaths.

Dinse and Lagakos (1982), also interested in estimating survival functions from incomplete observations, develop nonparametric estimators for the time until disease onset and time until death after onset. The method allows a tumor to cause or not cause death but the determination must be made. No attempt is made to see how robust the estimates are to misclassification.

For lethal tumors and one dose group, Gaylor and Hoel (1981) present a nonparametric procedure due to Kaplan and Meier (1958) for estimating the net probabilities of a tumor as a function of time for censored data. Assuming independence of causes of death, tumor and other, the analysis adjusts for competing causes, testing being done using Breslow's (1970) test. A Cox (1972) test is applied to life tables to detect a trend when more than one dose is used.

With only one dose group and non-lethal tumors, they recommend the interval technique of Peto (1974). Adding observed and expected numbers of tumors across time intervals from treated and control groups, an approximate one degree of freedom chi-square test is used. The example to be presented shows the lack of sensitivity of the test to differences in time related risks.

A concern then is when the compound tested causes an earlier occurrence of the tumor. Consider the example given in Table 1. The statistic value is zero

implying no overall difference, whereas one would suspect that tumors develop quicker in the treated group. The proportion is approximately .5 in all three time periods for the treated group, whereas the control group does not appear to be at risk until the third period.

Table 1. Illustrative Data of Incidental Tumors Among Dying Animals

Observed (Expected)/Number Examined

Group	Period 1	Period 2	Period 3	Totals
Control	0(1.0)/4	0(1.0)/4	50(48)/100	50(50)/108
Treated	2(1.0)/4	2(1.0)/4	46(48)/100	50(50)/108

This type problem seems to exist for all the procedures that consider time as a grouping variable rather than a quantitative variable.

1.3 Tests Incorporating Historical Control Data

Haseman (1984) points out that the simplest strategy for utilizing historical control data is to examine the range and determine if the interval contains the observed incidence of interest. Since the range is sample-size-dependent and tends to broaden as more studies are completed, the fewer historical studies included the more likely a current significant result will be obtained, intuitively, a more appropriate procedure is called for in formal testing. Tarone, Chu and Ward (1981) found that for many tumor types the historical control tumor rates are more variable than would be expected if they followed a binomial distribution. In these cases more is required than merely pooling all the control data for a common rate. Three procedures have recently been developed to account for this "extra-binomial variability."

Dempster, Murray and Weeks (1983) use a Bayesian approach. To account for time in their model they point out that the analysis is appropriate only when

the survival experience of all the groups are identical or when there is no time trend in the prevalence function for tumors. Several assumptions are made in the analysis:

1. The logits of the historical control proportions are iid $N(\mu, \sigma^2)$.
2. All observed counts conditioned on the probability of response for that group are binomially distributed.
3. In the current experiment the treatment effect is linear with slope β on the logit scale
4. The unknown parameters μ, $\ln\sigma$ and β are given uniform prior distributions.

The procedure performs repeated analysis across a range of σ values, integrating over σ in the final step. Conditioning on σ, a marginal density for β is obtained integrating out the remaining parameters from the joint likelihood. Since this is analytically intractable a Taylor series expansion around the maximum likelihood estimates is used yielding an approximately normal marginal for β. Weighting by a prior density σ is integrated out and the test is of the significance of the treatment slope β, assuming normality. The authors admit that the analysis "applicability depends on the adequacy of the multivariate normal approximations." From Monte Carlo simulations presented they conclude that "for the data set studied, the approximate analysis produced sufficient accuracy " The question of the effect of other data sets on the approximations needs to be studied before the analysis is considered ready for use.

A second method, due to Tarone (1982), modifies the Cochran-Armitage (1954, 1955) statistic for dose-response to accommodate historical control information. Cox (1958) showed the C-A statistic to be uniformly most powerful unbiased against logistic alternatives, Tarone and Gart (1980) that it is asymptotically

locally optimal against alternatives which can be expressed as smooth, increasing functions of dose

Tarone assumes the observed control tumor counts follow a binomial distribution with parameter p, but that p varies according to a Beta (α ,β) distribution. A logistic model is used for p:

$$p = \exp(a) / \{1 + \exp(a)\}$$

and the probability of a tumor corresponding to dose d_i:

$$p_i = \exp(a+bd_i) / \{1+\exp(a+bd_i)\}$$

A score statistic for testing H_0:b=0 is derived from the likelihood:

$$\tilde{X}^2 = \{\sum_{i=1}^{r} X_i d_i - \tilde{p}\, \Sigma N_i d_i\}^2 / [\tilde{p}\tilde{q}\, \{\sum_{i=1}^{r} N_i d_i^2 - (\sum_{i=1}^{r} N_i d_i)^2 / \tilde{N}\}]$$

where X_i is the number of tumors in the ith dose group out of N_i subjects, $\tilde{N} = N. + \alpha + \beta$, $\tilde{p} = (X.+\alpha)/\tilde{N}$, $\tilde{q} = 1-\tilde{p}$. X^2 is asympototically a chi-square with 1 degree of freedom if the consistent estimators $\hat{\alpha}$ and $\hat{\beta}$ are used. Tarone notes that the validity of the chi-square approximation has not been checked when $\hat{\alpha}$ and $\hat{\beta}$ are estimated from a few samples.

Dempster (1983), comparing his test to that of Tarone, claims that for tumor sites with moderate to high spontaneous rates both tests should give similar results, but for a low background rate the two methods may give divergent results.

Tarone also notes that, for some tumors, the historical control rates may be less variable then expected from a binomial distribution; then α and β may exceed the total number of controls M. In this case he recommends the total number observed control tumors Y. be substituted for α and M.-Y. for β.

The third method, Hoel (1983), also assumes an underlying beta-binomial model but uses an exact-conditional test rather than an asymptotic one. Considering only one dose group, a likelihood ratio test, with critical region

the tail of a beta-binomial, is developed conditioned on the observed number of control tumors. Upon examination of examples he points out that a considerable increase in power is found with the low spontaneous rates (e.g., Pr {response} = .01) compared to not including the historical control information, but the savings is not as striking for higher rates (e.g., .20). He also recommends use of the beta prior for quality control. When the control response is not statistically compatible with the historical data then the assay may be declared suspect. In summary he notes that the sensitivity of the test procedure to the variability of the prior estiamtes should be examined.

Yanagawa (1983) and others at the National Institute of Environmental Health Sciences have expanded Hoel's one dose exact test to accomodate multiple dose groups, testing for a trend in proportions. The procedure is a locally most powerful test incorporating historical control information using a beta prior distribution, and is a generalization of the dose-response probability model of Tarone and Hoel.

Yanagawa as an alternative to conditioning on the observed number of control tumors considered conditioning on the observed number being in an interval determined by the prior distribution. Although giving similar results the preference is to condition on the observed response. Asymptotic tests were also developed and compared along with the Cochran-Armitage statistic. He found for low spontaneous rates (e.g., .01) the probabilities followed the pattern: C-A Test >> conditional Tests >> Asymptotic Tests (except one).

For higher rates (e.g., .2) the asymptotic and conditional tests were similar and a higher observed control response favored the C-A test.

The concluding recommendations were:

1. A conditional exact test is to be preferred over an asymptotic test.
2. For larger spontaneous rates the advantages gained by incorporating historical information may be less than the assumptions needed.
3. Even in case 2 the historical data should be used for quality control.
4. The effect of prior variability should be examined.

1.4 Outline of Subsequent Chapters

Haseman (1984) notes that a possible area of future research would be the extension of the Tarone and Hoel procedures to adjust for survival differences. Chapter 2 presents the development of such as extension with one additional piece of information being required.

The additional information assumed to be available, at least at some future date, is that the probability of response under the null hypothesis of no treatment effect can be modeled as a function of time prior to full-term. Work has already begun in this area by some as previously mentioned and by others such as Portier (1983); or as pointed out by Krewski and Brown (1981), serial sacrifice experiments may be used to obtain information on time-to-tumor development in cases where this is not directly observable. With this additional assumption testing can be accomplished without determination of cause of death.

In Chapter 3 an approximate asymptotic equivalence for the exact test is developed. Later chapters will compare the exact and asymptotic tests applied to examples from the National Toxicology Program with results from the Tarone and the Cochran-Armitage tests. The effects of variability of prior estimates and recommended procedures from a paper by Yanagawa, Hoel, and Brooks (1984) are given. As an example of how to include historical information into tests

already accounting for time the Dinse and Lagakos' (1983) procedure is used. Here again an approximate test is presented rather than the exact, whose calculations render it almost unusable. And finally a summary and possible future direction is given.

Chapter 2 TEST DEVELOPMENT

2.1 Introduction

The test to be developed here although appropriate in other cases was designed with the bioassay testing of the NCI and NTP in mind. The majority of these investigations are two-year feeding or gavage studies involving male and female Fischer 344 rats and $B6C3F_1$ mice. It is from these that the majority of historical control information is currently available.

Most of them consist of a control group and two dose groups, each containing 50 animals. On the average, over twenty percent of the control group has not survived full-term, with possibly higher fatality in the dosed groups. The purpose of this test is an extension of the Hoel test to recoup this lost information. A feature of the test is that it does not require cause of death determination to be made on each animal, but at the cost of assuming prevalence rates can be determined. The test detects an increasing probability of response with increasing dose. The effect of high dose lowering the probability compared to middle doses on the test has not at present been examined.

2.2 Notation

Let:

$d_1, \ldots, d_r$ be the r doses, $d_0=0$

k_j the number of distinct times of death in the jth dose group $j=0,\ldots r$.

$t_{j1}, \ldots, t_{jk_j}$ the k_j distinct times of death in the jth dose group $j=0,\ldots, r$.

n_{ji} the number of deaths in the jth dose group at time t_{ji} $i=1,\ldots,k_j$ $j=0,\ldots, r$

x_{ji} the number of observed responses j^{th} dose group at time t_{ji} $j=0,\ldots, r$

$i=1,\ldots, k_j$ $0 \leq X_{ji} \leq n_{ji}$

$x_j = (x_{ji}, \ldots, x_{jk_j})$

T^* the time for which historical control information is available (i.e., the length of historical studies, usually 18 or 24 months).

<u>Note</u> A dot as a subscript denotes the sum over all values of that subscript.

$H(a)$ probability of response in the control group at time T^*.

Assume

$H(a+\xi d_j)$ = probability of response in the jth dose group at time T^* (the logistic and one-hit models are used here), strictly increasing and twice differentiable.

$G(T,H(a+\xi d_j)$ = probability of response in the jth dose group at time T. The only point of interest is for $\xi=0$ and $G(.,.)$ is such that:

1) $G(T,H(.)) = k(T)\ H(.) \quad T \leq T^*$

2) $G(T^*, H(.)) = H(.)$

2.3 Conditional Density

The test will condition on the observed control responses and will consider as fixed the times and numbers of deaths in all dose groups. Two additional distributional assumptions are that:

1) conditional on the probability of response

$x_{ji} \sim \text{binomial}\ (n_{ji}, G(t_{ji}, H(a+\xi d_j)))$

2) $H(a) \sim \text{Beta}\ (\alpha, \beta)$ and let

$A = \{a: H(a) \text{ is defined and is appropriate}\}$

Then a has density function $f_a(a) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} H(a)^{\alpha-1} (1-H(a))^{\beta-1} H'(a)$

For given $H(\cdot)$ and $G(\cdot,\cdot)$ X_{oi} given a is binomial

$$f_{x_{oi}|a}(x_{oi}) = \binom{n_{oi}}{x_{oi}} G(t_{oi}, H(a))^{x_{oi}} (1-G(t_{oi}, H(a))^{n_{oi}-x_{oi}}$$

Given a the x_{oi}'s are independent so

$$f_{x_o \mid a}(x_o) = \prod_{i=1}^{k_o} f_{x_{oi} \mid a}$$

implying that $f_{x_o}(x_o) = \int_A \prod_{i=1}^{k_o} f_{x_{oi} \mid a} \, f_a(a) \, da$

Likewise for $X = (X_o, \ldots, X_r)$

$$f(x) = \int_A \prod_{j=1}^{r} \prod_{i=1}^{k_j} \binom{n_{ji}}{x_{ji}} G(t_{ji}, H(a+\xi d_j))^{x_{ji}} \, (1-G(t_{ji}, H(a+\xi d_j))^{n_{ji}-x_{ji}} \quad .$$

$$\prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} G(t_{oi}, H(a))^{x_{oi}} \, (1-G(t_{oi}, H(a))^{n_{oi}-x_{oi}}$$

$$\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} H(a)^{\alpha-1} \, (1-H(a))^{\beta-1} \, H'(a) \, da$$

Let $c_{ji} = k(t_{ji})$ then $G(t_{ji}, H(a)) = c_{ji} \, H(a)$

$j=0, \ldots, r \quad i=1, \ldots, k_j$

Then $f_{x_o}(x_o) = \int_A \prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} G(T_{oi}, H(a))^{x_{oi}} \, (1-G(t_{oi}, H(a))^{n_{oi}-x_{oi}}$

$$\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \quad H(a)^{\alpha-1} \, (1-H(a))^{\beta-1} \, H'(a) \, da$$

$$= \int_A \prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} C_{oi}^{x_{oi}} H(a)^{x_{oi}} f(a) (1-C_{oi}H(a))^{n_{oi}-x_{oi}} da$$

$$= \prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} C_{oi}^{x_{oi}} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \int_A H(a)^{\alpha+x_{o.}-1} \prod_{i=1}^{k_o} (1-C_{oi}H(a))^{n_{oi}-x_{oi}} (1-H(a))^{\beta-1} H'(a) da$$

Let $C_1 = \prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} C_{oi}^{x_{oi}} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}$

$$= C_1 \int_0^1 H^{\alpha+x_{o.}-1} \prod_{i=1}^{k_o-1} \left[\sum_{k=0}^{n_{oi}-x_{oi}} \binom{n_{oi}-x_{oi}}{k} (-C_{oi})^k H^k \right] (1-H)^{\beta+n_{ok_o}-x_{ok_o}-1} dH$$

Letting $a_{ji} = n_{ji}-X_{ji}$ and $\beta^* = \beta+n_{ok_o}-X_{ok_o}$

$$= C_1 \int_0^1 \sum_{j_{01}=0}^{a_{01}} \sum_{j_{02}=0}^{a_{02}} \sum_{j_{ok_o-1}=0}^{a_{ok_o-1}} \binom{a_{oi}}{j_{oi}} (-C_{01})^{j_{01}} \cdots \binom{a_{ok_o-1}}{j_{ok_o-1}} (-C_{ok_o-1})^{j_{ok_o-1}} \cdot$$

$$H^{j_{01}+j_{02}+\ldots+j_{ok_o-1}+x_{o.}+\alpha-1} (1-H)^{\beta^*-1} dH$$

$$= C_1 \sum_{j_{01}=0}^{a_{01}} \cdots \sum \binom{a_{01}}{j_{01}} \cdots (-C_{ok_o-1})^{j_{ok_o-1}} \int_0^1 H^{j_{01}+\ldots+x_{o.}+\alpha-1} (1-H)^{\beta^*-1} dH$$

$$\int_0^1 H^{j_{oi}+\ldots+j_{ok_o-1}+X_o+\alpha-1} (1-H)^{\beta^*-1} dH = \frac{\Gamma(j_{oi}+\ldots+X_{o.}+\alpha)\Gamma(\beta^*)}{\Gamma(j_{oi}+\ldots+X_{o.}+\alpha+\beta^*)}$$

and

$$f_{x_o}(x_o) = \prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} C_{oi}^{x_{oi}} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \sum_{j_{01}=0}^{a_{oi}} \cdots \sum_{j_{ok_o-1}=0}^{a_{ok_o-1}} \binom{a_{oi}}{j_{oi}} \cdots (-C_{ok_o-1})^{j_{ok_o-1}}$$

$$\frac{\Gamma(j_{oi}+\ldots+X_{o.}+\alpha)\Gamma(\beta^*)}{\Gamma(j_{oi}+\ldots+X_{o.}+\alpha+\beta^*)}$$

Making the c_{ji} substitution into f yields:

$$f_x = \int_A \prod_{j=1}^{r} \prod_{i=1}^{k_j} \binom{n_{ji}}{x_{ji}} C_{ji}^{x_{ji}} H(a+\xi d_j)^{x_{ji}} (1-C_{ji} H(a+\xi d_j))^{n_{ji}-x_{ji}}$$

$$\prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} C_{oi}^{x_{oi}} H(a)^{x_{oi}} (1-C_{oi}H(a))^{n_{oi}-x_{oi}}$$

$$\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} H(a)^{\alpha-1}(1-H(a))^{\beta-1}H'(a) \quad da$$

$$= C_1 \prod_{j=1}^{r} \prod_{i=1}^{k_j} \binom{n_{ji}}{x_{ji}} C_{ji}^{x_{ji}} \int_A \prod_{j=1}^{r} \prod_{i=1}^{k_j} H(a+\xi d_j)^{x_{ji}} (1-C_{ji}H(a+\xi d_j)^{n_{ji}-x_{ji}}$$

$$\prod_{i=1}^{k_o} (1-C_{oi}H(a))^{n_{oi}-x_{oi}} H(a)^{\alpha+x_o-1} (1-H(a))^{\beta-1} H'(a) \quad da$$

Then the distribution of X conditioned on X_o is fx/f_{xo}.

$$f_{x \mid x_o}(x \mid x_o) = \frac{C_1 \prod_{j=1}^{r} \prod_{i=1}^{k_j} \binom{n_{ji}}{x_{ji}} C_{ji}^{x_{ji}}}{C_1 \sum_{j_{01}=0}^{a_{01}} \cdots \sum_{j_{ok_o}=0}^{a_{ok_o-1}} \binom{a_{01}}{j_{01}} \cdots (-C_{ok_o-1})^{j_{ok_o-1}} \frac{\Gamma(j_{01}+\ldots+j_{ok_o-1}+X_{o.}+\alpha)\Gamma(\beta^*)}{\Gamma(j_{01}+\ldots+j_{ok_o-1}+X_{o.}+\alpha+\beta^*)}}$$

$$\int_A \prod_{j=1}^{r} \prod_{i=1}^{k_j} H(a+\xi d_j)^{x_{ji}} (1-C_{ji}H(a+\xi d_j))^{n_{ji}-x_{ji}} \prod_{i=1}^{k_o} (1-C_{oi}H(a))^{n_{oi}-x_{oi}}$$

$$H(a)^{\alpha+X_{o.}-1} (1-H(a))^{\beta-1} H'(a)\, da$$

Let c_2 = the constant above.

The test of no trend effect is equivalent to a null hypothesis $H_o:\xi=0$ vs $H_1:\xi>0$.

Under H_o the conditional density reduces to

$$f_{x \mid x_o, H_o} = C_2 \int_A \prod_{j=0}^{r} \prod_{i=1}^{k_j-1} (1-C_{ji}H(a))^{n_{ji}-x_{ji}} H(a)^{\alpha+X_{..}-1} (1-H(a))^{\beta_.-1} H'(a)\, da$$

where $\beta_. = \beta + \sum_{j=0}^{r} n_{jk_j} - x_{jk_j}$

$$= C_2 \int_A \sum_{j_{01}=0}^{a_{01}} \cdots \sum_{j_{ok_o-1}=0}^{a_{ok_o-1}} \cdots \sum_{j_{rk_r-1}=0}^{a_{rk_r-1}} \binom{a_{01}}{j_{01}} (-C_{01})^{j_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}}$$

$$H(a)^{j_{01}+\ldots+j_{rk_r-1}+X_{..}+\alpha-1} (1-H(a))^{\beta_.-1} H'(a)\, da$$

$$=C_2 \sum_{j_{01}=0}^{a_{01}} \cdots \sum_{j_{rk_r-1}=0}^{a_{rk_r-1}} \binom{a_{01}}{j_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}} \int_0^1 H^{j_{01}+\ldots+X..+\alpha-1} (1-H)^{\beta.-1} dH$$

$$=C_2 \sum_{j_{01}=0}^{a_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}} \frac{\Gamma(j_{01}+\ldots+j_{rk_r-1}+X..+\alpha)\Gamma(\beta.)}{\Gamma(j_{01}+\ldots+X..+\alpha+\beta.)}$$

Although rather prohibitive it can be easily programmed on any computer with the facility to accurately handle very large and very small numbers, as a result of the gamma functions.

2.4 Test Statistic

The desired test is a locally most powerful unbiased test of H_0: $\xi = 0$ vs H_1: $\xi > 0$. Since the only point of interest in the null hypothesis is $\xi = 0$ the appropriate test statistic is the total efficient score as shown by Cox and Hinkley (1979) and others.

The statistic u:

$$u = \frac{\partial}{\partial \xi} [\ln \text{lik}(\xi \mid X)]_{H_0} = \{(\text{lik}(\xi \mid X))^{-1} \frac{\partial}{\partial \xi} [\text{lik}(\xi \mid X)]\} \mid_{H_0}$$

with $\text{lik}(\xi \mid X) = f_{X \mid X_0, \xi}$

$$\text{lik}(\xi \mid X) \mid_{H_0} = C_2 \sum_{j_{01}=0}^{a_{01}} \sum_{j_{rk_r-1}=0}^{a_{rk_r-1}} \binom{a_{01}}{j_{01}} (-C_{rk_r-1})^{j_{rk_r-1}} \frac{\Gamma(j_{01}+\ldots+j_{rk_r-1}+X..+\alpha)\Gamma(\beta.)}{\Gamma(j_{01}+\ldots+X..+\alpha+\beta.)}$$

let $\text{lik}\,(\xi \mid X)\,|_{H_o} = C_2 \cdot C_3$

$$\frac{\partial}{\partial\xi}[\text{lik}(\xi \mid X)] = C_2 \frac{\partial}{\partial\xi} [\int_A \prod_{j=1}^{r} \prod_{i=1}^{k_j} H(a+\xi d_j)^{x_{ji}} (1-C_{ji}H(a+\xi d_j)^{n_{ji}-x_{ji}} \quad .$$

$$\prod_{i=1}^{k_o} (1-C_{oi}H(a))^{n_{oi}-x_{oi}} \; H(a)^{X_{o.}+\alpha-1} \; (1-H(a))^{\beta-1} \; H'(a)\; da]$$

Assuming sufficient regularity to allow the order of integration and differentiation to be changed yields:

$$= C_2 \int_A \prod_{i=1}^{k_o} (1-C_{oi}H(a))^{n_{oi}-x_{oi}} \; H(a)^{\alpha+X_{o.}-1} \; (1-H(a))^{\beta-1} \; H'(a) \quad .$$

$$\frac{\partial}{\partial\xi} [\prod_{j=1}^{r} \prod_{i=1}^{k_j} H(a+\xi d_j)^{x_{ji}} (1-C_{ji}H(a+d_j))^{n_{ji}-x_{ji}}] \; da$$

$$= \sum_{j=1}^{r} \sum_{i=1}^{k_j} \{x_{ji} d_j H(a+\xi d_j)^{x_{ji}-1} \prod_{\substack{l=1 \\ (l,m) \neq (j,i)}}^{r} \prod_{m=1}^{k_l} H(a+\xi d_l)^{x_{lm}} \quad .$$

$$\prod_{l=1}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a+\xi d_l))^{n_{lm}-x_{lm}} \; H'(a+\xi d_j)\}$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_r} \{C_{ji} d_j (n_{ji}-x_{ji}) \; (1-C_{ji}H(a+\xi d_j))^{n_{ji}-x_{ji}-1} \quad .$$

$$\prod_{\substack{l=1 \\ (l,m)\neq(j,i)}}^{r} \prod_{m=1}^{k_l} (1-C_{lm}\, H(a+\xi d_l))^{n_{lm}-x_{lm}} \prod_{l=1}^{r} H(a+\xi d_l)^{x_l} \cdot H'(a+\xi d_j)\}$$

Evaluating at $H_o:\xi=0$

$$= \sum_{j=1}^{r} \sum_{i=1}^{k_j} \{x_{ji} d_j H(a)^{x_{ji}-1} \prod_{\substack{l=1 \\ (l,m)\neq(j,i)}}^{r} \prod_{m=1}^{k_l} H(a)^{x_{lm}} \prod_{l=1}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{n_{lm}-x_{lm}} H'(a)\}$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} \{C_{ji} d_j (n_{ji}-x_{ji})\, (1-C_{ji}H(a))^{n_{ji}-x_{ji}-1} \prod_{\substack{l=1 \\ (l,m)\neq(j,i)}}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{n_{lm}-x_{lm}}$$

$$\prod_{l=1}^{r} \prod_{m=1}^{k_l} H(a)^{x_{lm}} H'(a)\}$$

Define $x^1..= x..-x_{o.}$ and

$$b_{lm} = \left\{ \begin{array}{lll} \max\{n_{lm}-x_{lm}-1,0\} & \text{for } l=j\neq 0\ m=i & l=0,\ldots r \\ n_{lm}-x_{lm} & \text{otherwise} & m=1,\ldots,k_l \end{array} \right]$$

then

$$= \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j (n_{ji}-x_{ji})\, H(a)^{x^1..-1} (1-H(a))^{\sum_{l=1}^{r} a_{lk_l}} \prod_{l=1}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm}H(a))^{a_{lm}} H'(a)$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} C_{ji} d_j (n_{ji}-x_{ji})\, H(a)^{x^1..} (1-H(a))^{\sum_{l=1}^{r} b_{lk_l}} \prod_{l=1}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{b_{lm}} H'(a)$$

Finally the statistic $u.(\xi=0)$ is

$$u = \frac{1}{C_3} \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm}H(a))^{a_{lm}} H(a)^{x_{..}+\alpha-2}$$

$$(1-H(a))^{\sum_{l=0}^{r} a_{lk_l}+\beta-1} (H'(a))^2 \, da$$

$$- \frac{1}{C_3} \sum_{j=1}^{r} \sum_{i=1}^{k_j} C_{ji} d_j (n_{ji}-x_{ji}) \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm}H(a))^{b_{lm}} H(a)^{x_{..}+\alpha-1}$$

$$(1-H(a))^{\sum_{l=0}^{r} b_{lk_l}+\beta-1} (H'(a))^2 \, da$$

For most useful choices of H( ) the integral can be evaluated, also in application usually two doses are used and the distinct times of death few (the possibility of grouping will be examined later). Two choices of H( ) will be used here, the logistic (Tarone) and the exponential or one-hit (Hoel).

2.4.1 Logistic Model

Let $H(a)$ = logistic = $e^a/(1-e^a)$ then the derivative

$H'(a) = e^a/(1+e^a)^2 = H(a)\,[1-H(a)]$

$$\text{then } C_3 U_L = \sum_{j=1}^{r} \sum_{i=1}^{k_j} d_j x_{ji} \prod_{l=0}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm}H(a))^{a_{lm}} H(a)^{x_{..}+\alpha-2} (1-H(a))^{\beta_{.}-1}$$

$$H(a)\,(1-H(a))\,H'(a)\,da$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j (n_{ji} - x_{ji}) \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l - 1} (1 - C_{lm} H(a))^{b_{lm}} H(a)^{x_{..} + \alpha - 1} (1 - H(a))^{\sum_{l=0}^{r} b_{lk_l} + \beta - 1}$$

$$H(a)\ (1 - H(a))\ H'(a)\ da$$

$$= \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \int_0^1 \prod_{l=0}^{r} \prod_{m=1}^{k_l - 1} (1 - C_{lm} H)^{a_{lm}} H^{\alpha + x_{..} - 1} (1 - H)^{(\beta_{.} + 1) - 1}\ dH$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j (n_{ji} - x_{ji}) \int_0^1 \prod_{l=0}^{r} \prod_{m=1}^{k_l - 1} (1 - C_{lm} H)^{b_{lm}} H^{(\alpha + x_{..} + 1) - 1} (1 - H)^{\sum_{l=0}^{r} b_{lk_l} + \beta + 1 - 1}\ dH$$

Let $\beta^*_{ji} = \sum_{l=0}^{r} b_{lk_l} + \beta + 1$; A_{ji} = first integral, B_{ji} = 2nd

$$\text{Then } A_{ji} = \sum_{j_{01}=0}^{a_{01}} \cdots \sum_{j_{ok_o - 1}=0}^{a_{ok_o - 1}} \cdots \sum_{j_{rk_r - 1}=0}^{a_{rk_r - 1}} \binom{a_{01}}{j_{01}} (-C_{01})^{j_{01}} \cdots (-C_{rk_r - 1})^{j_{rk_r - 1}} \quad .$$

$$\cdot \int_0^1 H^{(j_{01} + \ldots + j_{rk_r - 1} + x_{..} + \alpha) - 1} (1 - H)^{(\beta_{.} + 1) - 1} dH \quad .$$

$$= \sum_{j_{01}=0}^{a_{01}} \cdots (-C_{rk_r - 1})^{j_{rk_r - 1}} \frac{\Gamma(j_{01} + \ldots + j_{rk_r - 1} + \alpha + x_{..}) \Gamma(\beta_{.} + 1)}{\Gamma(j_{01} + \ldots + \alpha + x_{..} + \beta_{.} + 1)}$$

$$B_{ji} = \sum_{j_{01}=0}^{b_{01}} \sum_{j_{ok_o-1}=0}^{b_{ok_o-1}} \sum_{j_{rk_r-1}=0}^{b_{rk_r-1}} \binom{b_{01}}{j_{01}} (-C_{01})^{j_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}}$$

$$\int_0^1 H^{(j_{01}+\ldots+j_{rk_r-1}+x..+\alpha+1)-1} (1-H)^{\beta^*_{ji}-1} dH$$

$$= \sum_{j_{01}=0}^{b_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}} \frac{\Gamma(j_{01}+\ldots+x..+\alpha+1)\Gamma(\beta^*_{ji})}{\Gamma(j_{01}+\ldots+x..+\alpha+1+\beta^*_{ji})}$$

Finally $U_L = \frac{1}{C_3} \{ \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j A_{ji} - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j (n_{ji}-x_{ji}) B_{ji} \}$

where A_{ji} and B_{ji} are as above and both depend on j and i.

The computations are speeded up by a relationship between x's with only one change in the number of tumors at full-term. Since the majority of deaths do occur at the terminal sacrifice this greatly reduces the computation time. A computer program to compute this and the one-hit model, to be presented next, is available from the author upon request.

2.4.2 One-Hit Model

Let $H(a)$ = one-hit = $1-e^{-a}$ then the derivative is $H'(a) = e^{-a} = 1-(1-e^{-a}) = 1-H(a)$

$$\text{Then } C_3U_1 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm}H(a))^{a_{lm}} H(a)^{x_{..}+\alpha-2} (1-H(a))^{\beta_{.}} \cdot H'(a)da$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_j (n_{ji}-x_{ji}) \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm}H(a))^{b_{lm}} H(a)^{x_{..}+\alpha-1} (1-H(a))^{\beta^*_{ji}-2}$$

$$(1-H(a))\, H'(a)da$$

$$= \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j \int_0^1 \prod_{l=0}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm}H)^{a_{lm}} H^{x_{..}+\alpha-2} (1-H)^{\beta_{.}+1-1} dH$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_j(n_{ji}-x_{ji}) \int_0^1 \prod_{l=0}^{r} \prod_{m=1}^{k_l-1} (1-C_{lm})^{b_{lm}} H^{x_{..}+\alpha-1} (1-H)^{\beta^*_{ji}-1} dH$$

let A_{ji} = the first integral and B_{ji} = the second.

$$A_{ji} = \sum_{j_{01}=0}^{a_{01}} \sum_{j_{rk_r-1}=0}^{a_{rk_r-1}} \binom{a_{01}}{j_{01}} (-C_{01})^{j_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}} \int_0^1 H^{j_{01}+\ldots+j_{rk_r-1}+x_{..}+\alpha-2}$$

$$(1-H)^{(\beta_{.}+1)-1}\, dH$$

$$= \sum_{j_{01}=0}^{a_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}} \frac{\Gamma(j_{01}+\ldots+j_{rk_r-1}x..+\alpha-1)\Gamma(\beta.+1)}{\Gamma(j_{01}+\ldots+x..+\alpha+\beta.)}$$

$$B_{ji} = \sum_{j_{01}-1=0}^{b_{01}} \cdots \sum_{j_{ok_o}-1=0}^{b_{ok_o}-1} \cdots \sum_{j_{rk_r}-1=0}^{b_{rk_r}-1} \binom{b_{01}}{j_{01}} (-C_{01})^{j_{01}} \ldots (-C_{rk_r-1})^{j_{rk_r-1}}$$

$$\int_0^1 H^{j_{01}+\ldots+\alpha-1} (1-H)^{\beta^*_{ji}-1} \, dH$$

$$= \sum_{j_{01}=0}^{b_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}} \frac{\Gamma(j_{01}+\ldots+j_{rk_r-1}+x..+\alpha)\Gamma(\beta^*_{ji})}{\Gamma(j_{01}+\ldots+j_{rk_r-1}+x..+\alpha+\beta^*_{ji})}$$

Then $U_1 = \frac{1}{C_3} \{ \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j A_{ji} - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j (n_{ji} - x_{ji}) B_{ji} \}$

For both models if we let U_{obs} be the observed value of the statistic, the significance probability is then obtained from:

$p = \Sigma f (X \mid X_{o,\ obs}, Ho)$ with $X_{o,\ obs}$ the observed control responses

$X \mid X_{o,\ obs}: U_x \geq U_{obs}$

Note the two models give the same form of the statistic. In fact they differ only in the ratios of the gamma functions. Using $\Gamma_{L,\ i}$ and $\Gamma_{H,\ i}$ $i=1,2$ for the ratios:

$$\Gamma_{L,\,1} = \frac{(j_{01}+\ldots+x_{..}+\alpha-1)}{(j_{01}+\ldots+x_{..}+\alpha+\beta_{.})} \Gamma_{H,\,1}$$

and

$$\Gamma_{L,\,2} = \frac{(j_{01}+\ldots+x_{..}+\alpha)}{(j_{01}+\ldots+x_{..}+\alpha+\beta^{*}_{ji})} \Gamma_{H,\,2}$$

It is freely admitted here that the statistics are too cumbersome to use only a single time. But if the test is to be applied to a few data sets then the savings in recovered information from early deaths justifies the programming efforts.

2.4.3 Linear Model

In some cases the form of $H(\cdot)$ may not be agreed upon. Then as a first approximation $H(\cdot)$ may be assumed to be linear: $H(a+\xi d_j) = a + \xi d_j$.

The resulting statistic is in the same form as the previous two, in fact, it is identical to the one-hit with $(\beta_{.}+1)$ replaced by $\beta_{.}$ and β^{*}_{ji} by $(\beta^{*}_{ji}-1)$. So again the test will give very similar results for different choices of $H(\cdot)$ lessening the worry about the appropriate choice.

Chapter 3 AN ASYMPTOTIC RESULT AND TWO APPROXIMATE ASYMPTOTIC TESTS

3.1 Introduction

The complexity of computations renders the exact test of Chapter 2, almost useless for the one time user. The score-statistic and an estimate of its variance are presented for unspecified $H(\cdot)$ but again the computations are not simple enough to be very useful. Two approximations to the normalized score-statistic are given, one that could be done by hand and a simple statistic that is in most cases very close to the exact p-value. The derivation of the variance of the score statistic and its asymptotic distribution can be found in many texts for example the one previously referenced by Cox and Hinkley (1979).

3.2 An Exact Asymptotic Statistic

The score statistic $\mu.(\varepsilon)$ is $\frac{\partial}{\partial\varepsilon}$ log lik $(\varepsilon;x)$ where lik $(\varepsilon;x) = f$ the density, so $u. = f'/f$ and is evaluated at the null hypothesis $\varepsilon=0$.

Recall

$$f = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{j=0}^{r} \prod_{j=0}^{k_j} \binom{n_{ji}}{x_{ji}} (C_{ji})^{x_{ji}} \int_A \prod_{j=1}^{r} \prod_{i=1}^{k_j} H(a+\varepsilon d_j)^{x_{ji}} (1-c_{ji}H(a+\varepsilon d_j))^{n_{ji}-x_{ji}}$$

$$\prod_{i=1}^{k_o} (1-C_{ji}H(a))^{n_{oi}-x_{oi}} \; H(a)^{x_{o.}+\alpha-1} (1-H(a))^{\beta-1} \; H'(a)\, da$$

$$f\big|_{H_o} = C. \int_0^1 \prod_{j=1}^{o} \prod_{i=1}^{k_j} (1-C_{ji}H)^{n_{ji}-x_{ji}} H^{x..+\alpha-1} (1-H)^{\beta-1} \, dH$$

$$= C. \sum_{j_{01}=0}^{a_{01}} \cdots \sum_{j_{ok_o-1}=0}^{a_{ok_o-1}} \cdots \sum_{j_{rk_r-1}=0}^{a_{rk_r-1}} \binom{a_{01}}{j_{01}} (-C_{01})^{j_{01}} \cdots (-C_{rk_r-1})^{j_{rk_r-1}} \frac{\Gamma(j+x..+\alpha)\Gamma(\beta.)}{\Gamma(j+x..+\alpha+\beta.)}$$

where j = sum of all j_{ab}'s and $\beta. = \sum_{l=0}^{r} n_{lk_o} - x_{lk_o} + \beta$

$f' = \frac{\partial}{\partial\varepsilon} f$ and under regularity the order of integration and differentiation can be changed yielding.

$$f' = C. \int_A \frac{\partial}{\partial\varepsilon} \left\{ \prod_{j=1}^{r} \prod_{i=1}^{k_j} H(a+\varepsilon d_j)^{x_{ji}} (1-C_{ji}H(a+\varepsilon d_j))^{n_{ji}-x_{ji}} \right\} .$$

$$. \prod_{i=1}^{k_o} (1-C_{ji}H(a))^{n_{ji}-x_{ji}} . H(a)^{x_{0.}+\alpha-1} (1-H(a))^{\beta-1} H'(a) \quad da$$

Then $\frac{\partial}{\partial\varepsilon} \{ \ \} = \sum_{j=1}^{r} \sum_{i=1}^{k_j} \frac{x_{ji} d_j H'(a+\varepsilon d_j)}{H(a+\varepsilon d_j)} \pi_o - \frac{c_{ji} d_j (n_{ji}-x_{ji}) H'(a+\varepsilon d_j)}{1-c_{ji}H(a+\varepsilon d_j)} \pi_o$

where $\pi_o = \{ \ \}$

and $f'_{H_o} = C. \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{a_{lm}} H(a)^{\alpha+x..-2} (1-H(a))^{\beta-1} (H'(a))^2 da$

$$- C. \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \int_A (1-C_{ji}H(a))^{-1} \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{a_{lm}} H(a)^{\alpha+x..-1}$$

$$(1-H(a))^{\beta-1} (H'(a))^2 \, da = C. \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{a_{lm}} H(a)^{\alpha+x..-1} (1-H(a))^{\beta-1} H'(a) .$$

$$[\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \frac{H'(a)}{H(a)} - c_{ji} d_j a_{ji} \frac{H'(a)}{1-c_{ji}H(a)}] \, da$$

$f'' = \frac{\partial^2}{\partial \varepsilon^2} f$ and again under regularity

$$f'' = C. \int_A \frac{\partial^2}{\partial \varepsilon^2} \{ \prod_{j=1}^{r} \prod_{i=1}^{k_j} H(a+\varepsilon d_j)^{x_{ji}} (1-C_{ji}H(a+\varepsilon d_j))^{a_{ji}} \} \prod_{i=1}^{k_o} (1-C_{ji}H(a))^{a_{oi}} H(a)^{x_{o.}+\alpha-1}$$

$$(1-H(a))^{\beta-1} H'(a) \, da$$

Then $$\frac{\partial^2}{\partial \varepsilon^2} \{ \} = \pi_o \, [\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \frac{H'(a+\varepsilon d_j)}{H(a+\varepsilon d_j)} - c_{ji} d_j a_{ji} \frac{H'(a+\varepsilon d_j)}{1-c_{ji} H(a+\varepsilon d_j)}]^2 +$$

$$\pi_o \, [\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j^2 \frac{H'(a+\varepsilon d_j) H(a+\varepsilon d_j) - (H'(a+\varepsilon d_j))^2}{(H(a+\varepsilon d_j))^2} - c_{ji} d_j^2 a_{ji} \cdot$$

$$\frac{H'(a+\varepsilon d_j) (1-c_{ji}H(a+\varepsilon d_j) + c_{ji}(H'(a+\varepsilon d_j))^2}{(1-c_{ji}H(a+\varepsilon d_j))^2}]$$

and $$f'|_{H_o} = C. \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{a_{lm}} H(a)^{\alpha+x..-1} (1-H(a))^{\beta-1} H'(a)$$

$$[. \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \frac{H'(a)}{H(a)} - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \frac{H'(a)}{1-c_{ji}H(a)}]^2$$

$$+ \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \frac{H''(a)\, H(a) - (H'(a))^2}{H^2(a)} - c_{ji} d_j^2 a_{ji} \frac{H''(a)\,(1-c_{ji}H(a)) + c_{ji}(H'(a))^2}{(1-c_{ji}H(a))^2}\, da$$

The statistic $z = u(\cdot)/(i(\cdot))^{1/2}$ has as a limiting distribution the standard normal distribution. The variance of the score being estimated by

$$i(\cdot) = -\frac{\partial^2}{\partial\varepsilon^2} \ln \text{lik}\,(\varepsilon \mid x)\,\Big|_{H_0} = -\frac{\partial}{\partial\varepsilon}\frac{f'}{f} = -\frac{f''f - (f')^2}{f^2}$$

and $z = f'/f \,/\, (-f''f + f'^2)^{1/2} / f = f' / [(f')^2 - f''f]^{1/2}\Big|_{H_0}$

The statistic is computable for specific choices of $H(\cdot)$. Again though the computations are too great and the savings over the exact test not great enough to be completed here for specific $H(\cdot)$.

3.3 A First Approximation

Assuming the logistic model for the dose probabilities, $H(a) = e^a/(1+e^a)$, and substituting $H'(a) = H(a)[1-H(a)]$ and $H''(a) = H(a)\,(1-H(a))(1-2H(a))$ into f' and f'' yields:

$$f'\Big|_{H_0} = C. \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-c_{lm}H(a))^{a_{lm}}\, H(a)^{\alpha+x..-1}\, (1-H(a))^{\beta-1}\, H'(a)\ .$$

$$\left[\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \frac{H(a)(1-H(a))}{H(a)} - c_{ji} d_j a_{ji} \frac{H(a)\,(1-H(a))}{(1-c_{ji}H(a))}\right] da$$

For small background response rates, most of the density will be accounted for by small values of H(a). In this case $1-H(a) \approx 1-c_{ji}\,H(a)$ yielding if we let

$$W_1 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \text{ and } W_2 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji}$$

$$f'\Big|_{H_o} = C. \int_0^1 \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H)^{a_{lm}} H^{\alpha+x..-1} (1-H)^{\beta-1} \left[(1-H)\, W_1 - HW_2\right] dH$$

$$= C. \sum_{j_{01}=0}^{a_{01}} \cdots \sum_{j_{rk_r}=0}^{a_{rk_r}} \binom{a_{01}}{j_{01}} (-C_{01})^{j_{01}} \cdots (-C_{rk_r})^{j_{rk_r}} \frac{\Gamma(\alpha+x..+j)\,\Gamma(\beta)}{\Gamma(\alpha+x..+j+\beta)} \cdot$$

$$\left[\frac{\beta W_1}{\alpha+x..+j+\beta} - \frac{(\alpha+x..+j)\, w_2}{\alpha+x..+j+\beta}\right]$$

Let $W_3 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j^2$ and $W_4 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^2 (n_{ji}-x_{ji})$ Then

$$f''\Big|_{H_o} = C. \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_j} (1-C_{lm}\, H(a))^{a_{lm}} H(a)^{\alpha+x..-1} (1-H(a))^{\beta-1} H'(a) \quad .$$

$$\left\{\left[\frac{H(a)\,(1-H(a))}{H(a)} W_1 - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \frac{H(a)(1-H(a))}{(1-c_{ji}H(a))}\right]^2 + \sum_{j=1}^{r} \sum_{i=1}^{k_j} d_j^2 \right. \quad .$$

$$[\ x_{ji}(1-H(a))\ (1-2H(a)) - x_{ji}(1-H(a))^2 - \frac{c_{ji}a_{ji}H(a)(1-H(a))(1-2H(a))}{(1-c_{ji}H(a))}$$

$$- \frac{c_{ji}a_{ji}H^2(a)(1-H(a))^2}{(1-c_{ji}H(a))^2}\ ]\}\ da$$

Again substituting $1-H(a)$ for $1-c_{ji}H(a)$ yields:

$$[\ ]^2 \approx (1-H(a))^2 W_1{}^2 - 2\ H(a)\ (1-H(a)\ W_1W_2 + H^2(a)W_2{}^2$$

and $\Sigma\ \Sigma\ d_j{}^2\ [\ ] = \sum_{j=1}^{r} \sum_{i=1}^{k_j} d_j{}^2\ \frac{(1-H(a))}{H(a)\ (1-c_{ji}H(a))^2}\ [x_{ji}(1-2H(a))(1-c_{ji}H(a))^2\ H(a)$

$$- x_{ji}H(a)\ (1-H(a))\ (1-c_{ji}H(a))^2 - c_{ji}a_{ji}\ (1-2H(a))\ H(a)^2\ (1-c_{ji}H(a))$$

$$- c_{ji}{}^2a_{ji}\ H^3(a)\ (1-H(a))]$$

$$[\ ] = x_{ji}H(a)\ (1-c_{ji}H(a))^2\ (1-2H(a) - (1-H(a)))$$

$$- c_{ji}a_{ji}H^2(a)\ [(1-2H(a))\ (1-c_{ji}H(a)) + c_{ji}H(a)\ (1-H(a))]$$

$$= -x_{ji}H^2(a)\ (1-c_{ji}H(a))^2 - c_{ji}a_{ji}H^2(a)\ (1-H(a)) + c_{ji}a_{ji}H^3(a)\ (1-c_{ji}H(a))$$

Then $\Sigma\ \Sigma\ d_j^2\ [\ ] \approx \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j^2\ H(a)\ (1-H(a)) - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^2 a_{ji} H(a)$

$$+ \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^2 a_{ji}\ H^2(a)$$

Finally

$$f''\,|_{H_o} = c. \int_0^1 \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-c_{lm}H)^{a_{lm}}\ H^{\alpha+x..-1}\ (1-H)^{\beta-1}\ .\ [(1-H)^2\ W_1^2\ -$$

$$-\ 2H\ (1-H)\ W_1 W_2\ +\ H^2 W_2^2 + H(1-H)W_3 - HW_4 + H^2 W_4]\ dH$$

$$= c. \sum_{j_{01}=0}^{a_{01}} \sum_{j_{rk_r}=0}^{a_{rk_r}} \binom{a_{01}}{j_{01}} (-c_{01})^{j_{01}} \ldots (-c_{r_{kr}})^{j_{rk_r}}\ \frac{\Gamma(\alpha+x..+j)\ \Gamma(\beta+2)}{\Gamma(\alpha+x..+j+\beta+2)}\ W_1^2$$

$$\frac{\Gamma(\alpha+x..+j+1)}{\Gamma(\alpha+x..+j+\beta+2)} \frac{\Gamma(\beta+1)}{} \quad (W_3-2W_1W_2)\ \frac{\Gamma(\alpha+x..+j+2)\ \Gamma(\beta)}{\Gamma(\alpha+x..+j+2+\beta)}\ (W_2^2+W_4)$$

$$-\ \frac{\Gamma(\alpha+x..+j+1)\ \Gamma(\beta)}{\Gamma(\alpha+x..+j+\beta+1)}\ W_4$$

Note that $\Gamma(\alpha+x..+j)\ \Gamma(\beta)/\Gamma(\alpha+x..+j+\beta)$ can be factored out to compute the three parts f, f, and f'' at once, also β can be replaced by β. and all terms associated with a_{jk_j} deleted. The latter is a considerable savings since the majority of deaths in each dose group will be at the end of the study.

The statistic should be a close approximation to the z statistic with a large savings in computation. The problem still exists that a computer is needed and an easier method is desirable.

3.4 An Approximation For Testing

The approximate statistic to follow depends on one mathematical approximation. Consider

$$\int_0^1 (1-ax)^n \, x^{\alpha-1} \, (1-x)^{\beta-1} \, dx \qquad a \varepsilon \, (0,1) \text{ then except}$$

for the constant this is the expected value of $(1-ax)^n$ where x is a random variable following a beta (α, β) distribution. Then

$$(1-ax)^n = \exp\{n \, \mathrm{Ln}\,(1-ax)\} = \exp\{n\,(-ax-1/2\, a^2 x^2 \; -\ldots)\} \approx \exp\{n\,(-ax-1/2\, a^2 x\;)\}$$

consider also

$$(1-x)^{an} = \exp\{an \ln (1-x)\} = \exp\{an\,(-x-\; 1/2 x^2 \ldots)\} \approx \exp\{an\,(-x-\; 1/2 x^2 \;)\}$$

The two expressions have the same first term and differ in the second by a factor of "a". When a=1 the two are the same and the closer to one the closer the approximation. Also note that the smaller the value of x the better the fit. When the random variable x has a small expectation, as is the case with a low background rate, most of the density mass is with small x, making the approximation good. So finally

$$\int_0^1 (1-ax)^n x^{\alpha-1} (1-x)^{\beta-1} dx = E[(1-ax)^n] \approx E[(1-x)^{an}] = \int_0^1 x^{\alpha-1} (1-x)^{\beta+an-1} dx$$

$$= \frac{\Gamma(\alpha)\,\Gamma(\beta+an)}{\Gamma(\alpha+\beta+an)}$$

The expectation will be small when β is large in comparison to α. For $\alpha=3$ and $\beta=5$ the expectation is .375, much larger than most tumor rates, and above where the approximation would be expected to be good, but even here for n=2 and a=.667, ignoring the constant $\Gamma(\alpha)$ term, the approximate and exact values are .00258 and .00141. Of the combinations tested this was the worst fit where as for a=.9 it improves to .00219 and .00179. For more likely rates such as $\alpha=3.95$ $\beta=391$ with expectation .01 when a=.75 the approximation was 3.155 and exact 3.17 both times, 10^{-10}, showing agreement up to the twelfth decimal place.

3.5 An Approximate Statistic and Exact Test

The above approximation will be applied here to the density and first derivative. The savings in computation is enormous and as will be discussed later almost no precision lost.

Recall from CH2 the density for the control group was

$$f_{x_o} = \prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} c_{oi}^{x_{oi}} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \int_0^1 \prod_{i=1}^{k_o} (1-c_{oi}H)^{a_{oi}} H^{\alpha+x_{o.}-1} (1-H)^{\beta-1} dH$$

$$\approx \prod_{i=1}^{k_o} \binom{n_{oi}}{x_{oi}} c_{oi}^{x_{oi}} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \frac{\Gamma(\alpha+x_{o.})\Gamma(\beta+\Sigma)}{\Gamma(\alpha+x_{o.}+\beta+\Sigma)} \text{ where } \Sigma = \sum_{i=1}^{k_o} c_{oi} a_{oi}$$

$$= C_1 \frac{\Gamma(\alpha+x_{o.})\Gamma(\beta+\Sigma)}{\Gamma(\alpha+x_{o.}+\beta+\Sigma)}$$

And the unconditional density under the null hypothesis

$$fx\,|_{H_o} = c_1 \prod_{j=1}^{r} \prod_{i=1}^{k_j} \binom{n_{ji}}{x_{ji}} c_{ji}^{x_{ji}} \int_0^1 \prod_{j=0}^{r} \prod_{i=1}^{k_j} (1-c_{ji}H)^{a_{ji}} H^{\alpha+x..-1} (1-H)^{\beta-1}\, dH$$

$$\approx C_1 \prod_{j=1}^{r} \prod_{i=1}^{k_j} \binom{n_{ji}}{x_{ji}} c_{ji}^{x_{ji}} \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)} \quad \text{where } \Sigma\,\Sigma = \sum_{j=0}^{r} \sum_{i=1}^{k_j} c_{ji}a_{ji}$$

$$= C_1C_3 \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)}$$

The resulting conditional likelihood, conditioning on X_o, is approximately

$$f\,(X;\,X_o,\,H_o) \approx C_3 \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma)\,\Gamma(\alpha+x_{o.}+\beta+\Sigma)}{\Gamma(\alpha+x_{o.})\,\Gamma(\beta+\Sigma)\,\Gamma(\alpha+x..+\beta+\Sigma\Sigma)}$$

Under the assumption of regularity the first derivative of the likelihood was found to be

$$f'(X;H_o) = C.\,[\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j \int_A \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-c_{lm}H(a))^{a_{lm}} H(a)^{\alpha+x..-2}$$

$$(a-H(a))^{\beta-1}(H'(a))^2 da$$

$$-\sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_ja_{ji} \int_A (1-c_{ji}H(a))^{-1} \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-c_{lm}H(a))^{a_{lm}} H(a)^{\alpha+x.-1}$$

$(1-H(a))^{\beta-1}\ (H'(a))^2\ da\ ]$

Letting H(.) be the logistic function the derivative of the density is the approximately

$$f'(X;H_o) \approx C.\ [\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j \frac{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma+1)}{\Gamma(\alpha+x.+\beta+\Sigma\Sigma+1)}$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_j a_{ji} \frac{\Gamma(\alpha+x..+1)\ \Gamma(\beta+\Sigma\Sigma+(1-c_{ji}))}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+1+(1-c_{ji}))}$$

The resulting approximate score statistic U. is then

$$U. = \frac{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma)} [\frac{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)} \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j \frac{\beta+\Sigma\Sigma}{\alpha+x..+\beta+\Sigma\Sigma}$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_j a_{ji} \frac{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma+\ (1-c_{ji}))}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+(1-c_{ji}))} \quad \frac{\alpha+x..}{\alpha+x..+\beta+\Sigma\Sigma+(1-c_{ji})}\ ]$$

The effect of treating all the $(1-c_{ji})$'s as zero was negligible on the statistic. Looking at the ratio of gamma functions treating $(1-c_{ji})$ as zero and exact was always almost one. Estimating x.. by 5, $\Sigma\Sigma$ by 130, the larger beta was, the closer to 1. Even for moderate beta (e.g. = 173) the ratio was .994 when c_{ji} = .75. No effect on the p-value (up to four places) was found for a wide range of alpha and beta.

With this further consideration the statistic is then

$$U. = \frac{\beta+\Sigma\Sigma}{\alpha+x..+\beta+\Sigma\Sigma} \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j - \frac{\alpha+x..}{\alpha+x..+\beta+\Sigma\Sigma} \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_j\,(n_{ji}-x_{ji})$$

If we let $\hat{q} = (\beta+\Sigma\Sigma) / (\alpha+x..+\beta+\Sigma\Sigma)$ and $\hat{P} = 1-\hat{q}$ this is

$$U. = \hat{q} \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j - \hat{P} \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_j\,(n_{ji}-x_{ji})$$

At this point an approximate-exact test can be performed conditioned on the control responses and the approximate conditional density. As a case when the test would be expected to behave poorly alpha and beta were selected to be 3 and 12 respectively. Using the same numbers in each dose group (dose = 0, 1, 2), 5 were assumed to have survive half the term, 5-80% of the term and 25 full term (i.e., almost 30% early mortality). In this case expecting the probability to sum to one .991 was observed. As beta increases, as the percent surviving full term increases, as the survival times increased, or with approximately similar survival proportions increasing the total sample size all had the effect of improving the approximation. If the significance probability is found by substraction then any error will be on the conservative side. Further results will be presented in a later chapter.

3.6 Asymptotic Variance

The score statistic has a normal limiting distribution, but to be useful an estimate of the variance is needed. Cox and Hinkley (1974) recommend using the negative of the second derivative of the log-likelihood evaluated at the null hypothesis as an estimate of the limiting variance.

Recall from Chapter 2, under the assumption of regularity, the second derivative of the density at the null hypothesis is equal to:

$$f''(X;H_o) = C.\Big[\Big\{\sum_{j=1}^{r}\sum_{i=1}^{k_j} x_{ji}d_j\Big)^2 \int_A \Big(\frac{H'(a)}{H(a)}\Big)^2 f\ da$$

$$-2\Big(\sum_{j=1}^{r}\sum_{i=1}^{k_j} x_{ji}d_j\Big)\sum_{j=1}^{r}\sum_{i=1}^{k_j} c_{ji}d_j a_{ji} \int_A \frac{(H'(a))^2}{H(a)\,(1-c_{ji}H(a))}\ f\ da$$

$$+\sum_{j=1}^{r}\sum_{i=1}^{k_j} c_{ji}^2 d_j^2 a_{ji}^2 \int_A \Big(\frac{H'(a)}{1-c_{ji}H(a)}\Big)^2 f\ da$$

$$+\sum_{j=1}^{r}\sum_{i=1}^{k_j}\sum_{(r,t)\neq(j,i)}^{r}\sum^{k_j} c_{ji}\,d_j\,a_{ji}\,c_{rt}\,d_r\,a_{rt} \int_A \frac{(H'(a))^2}{(1-c_{ji}H(a))\,(1-c_{rt}H(a))}\ f\ da$$

$$+\sum_{j=1}^{r}\sum_{i=1}^{k_j} x_{ji}d_j^2 \int_A \frac{H''(a)}{H(a)}\ f\ da - \sum_{j=1}^{r}\sum_{i=1}^{k_j} x_{ji}d_j \int_A \frac{H'(a)^2}{H(a)}\ f\ da$$

$$-\sum_{j=1}^{r}\sum_{i=1}^{k_j} c_{ji}d_j^2 a_{ji} \int_A \frac{H''(a)}{1-c_{ji}H(a)}\ f\ da - \sum_{j=1}^{r}\sum_{i=1}^{k_j} c_{ji}^2 d_j^2 a_{ji} \int_A \frac{H'(a)^2}{1-c_{ji}H(a)}\ f\ da\Big]$$

where $f = \prod_{l=0}^{r}\prod_{m=1}^{k_l} (1-c_{lm}H(a))^{a_{lm}}\, H(a)^{\alpha+x..-1}\,(1-H(a))^{\beta-1}\, H'(a)$

Then under the assumption of a logistic model for dose probabilities and using the previously mentioned approximation this becomes

$$f''(X_j H_0) \approx C.\left(\left(\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j\right)^2 \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma+2)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2)}\right.$$

$$- 2\left(\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j\right)\left(\sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \frac{\Gamma(\alpha+x..+1)\,\Gamma(\beta+\Sigma\Sigma+1+(1-c_{ji}))}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2+(1-c_{ji}))}\right)$$

$$+ \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}^2 d_j^2 a_{ji}^2 \frac{\Gamma(\alpha+x..+2)\,\Gamma(\beta+\Sigma\Sigma+2\,(1-c_{ji}))}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2+2(1-c_{ji}))}$$

$$+ \sum_{j=1}^{r} \sum_{i=1}^{k_j} \sum_{p=1}^{r} \sum_{q=1}^{k_{ji}} c_{ji} d_j a_{ji} c_{pq} d_p a_{pq} \frac{\Gamma(\alpha+x..+2)\,\Gamma(\beta+\Sigma\Sigma+(1-c_{ji})+(1-c_{pq}))}{\Gamma(\alpha+x.\ +\beta+\Sigma\Sigma+2+(1-c_{ji})+(1-c_{pq}))}$$

$$+ \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j^2 \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma+1)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+1)} - 2\sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j^2 \frac{\Gamma(\alpha+x..+1)\,\Gamma(\beta+\Sigma\Sigma+1)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2)}$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j^2 \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma+2)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2)} - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^2 a_{ji} \frac{\Gamma(\alpha+x..+1)\,\Gamma(\beta+\Sigma\Sigma+(1-c_{ji}))}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+1+(1-c_{ji}))}$$

$$+ 2\sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^2 a_{ji} \frac{\Gamma(\alpha+x..+2)\,\Gamma(\beta+\Sigma\Sigma+(1-c_{ji}))}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2+(1-c_{ji}))}$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}^{2} d_j^{2} a_{ji} \frac{\Gamma(\alpha+x..+2)\ \Gamma(\beta+\Sigma\Sigma+2\ (1-c_{ji}))}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2+2(1-c_{ji}))})$$

$$\approx C.\ \frac{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)} \left[\frac{\beta+\Sigma\Sigma}{\alpha+x..+\beta+\Sigma\Sigma} \quad \frac{\beta+\Sigma\Sigma+1}{\alpha+x..+\beta+\Sigma\Sigma+1} \quad W_1^{2} \right.$$

$$- 2\ \frac{\alpha+x..}{\alpha+x..+\beta+\Sigma\Sigma} \quad \frac{\beta+\Sigma\Sigma}{\alpha+x..+\beta+\Sigma\Sigma+1} W_1 W_2 + \frac{\alpha+x..}{\alpha+x..+\beta+\Sigma\Sigma} \quad \frac{\alpha+x..+1}{\alpha+x..+\beta+\Sigma\Sigma+1} \quad W_2^{2}$$

$$- \frac{\beta+\Sigma\Sigma}{\alpha+x..+\beta+\Sigma\Sigma} \quad \frac{\alpha+x..+1}{\alpha+x..+\beta+\Sigma\Sigma+1} \quad W_3 + \frac{\alpha+x..}{\alpha+x..+\beta+\Sigma\Sigma} \quad \frac{\alpha+x..+1}{\alpha+x..+\beta+\Sigma\Sigma+1} \quad W_4$$

$$\left. - \frac{\alpha+x..}{\alpha+x..+\beta+\Sigma\Sigma} \quad \frac{\beta+\Sigma\Sigma}{\alpha+x..+\beta+\Sigma\Sigma+1} W_4 - \frac{\alpha+x..}{\alpha+x..+\beta+\Sigma\Sigma} \quad \frac{\alpha+x..+1}{\alpha+x..+\beta+\Sigma\Sigma+1} \quad W_6 \right]$$

where $W_1 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \qquad W_2 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j\ (n_{ji}-x_{ji})$

$$W_3 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j^{2} \qquad W_4 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^{2} (n_{ji}-x_{ji})$$

$$W_6 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}^{2} d_j^{2}\ (n_{ji}-x_{ji})$$

Let $\hat{q} = (\beta+\Sigma\Sigma)\ /\ (\alpha+x..+\beta+\Sigma\Sigma) \qquad \hat{p} = 1-\hat{q}$

$q' = (\beta+\Sigma\Sigma+1)\ /\ (\alpha+x..+\beta+\Sigma\Sigma+1) \qquad p' = (\alpha+x..+1)\ /\ (\alpha+x..+\beta+\Sigma\Sigma+1)$

Then $\hat{i}.\ (\varepsilon = 0) = ((f')^2 - ff'') / f^2$

$$= \hat{q}\ (\hat{q}-q')\ W_1^{\ 2} + 2\ \hat{q}\ (1-q'-\hat{p})\ W_1W_2 + \hat{p}\ (\hat{p}-p')\ W_2^{\ 2}$$

$$+ \hat{q}\ (1-q')\ W_3 + \hat{p}\ (1-2p')\ W_4 + \hat{p}\ p'W_6$$

3.7 Asymptotic Statistic

The resulting statistic then is:

$z = U. / \sqrt{V}.$ which for the logistic case is:

$$z_{log} = (\hat{q}\ W_1 - \hat{p}\ W_2) / (\hat{q}\ (\hat{q} - q')\ W_1^{\ 2} + 2\hat{q}\ (1-q'-\hat{p})\ W_1W_2 + \hat{p}\ (\hat{p}-p')\ W_2^{\ 2}$$

$$+ \hat{q}\ (1-q')\ W_3 + \hat{p}\ (1-2p)\ W_4 + \hat{p}\ p'W_6)^{1/2}$$

Although too much to memorize, the statistic can easily be computed by hand with the W's usually involving about six terms. The first and third terms of the variance are always negative, omitting them could only make the test conservative and the result of doing so will be examined later.

3.8 One-Hit Model

Assume the one-hit model is appropriate, $H(a) = 1-e^{-a}$. Then $H'(a) = 1-H(a)$ and $H''(a) = -(1-H(a))$.

Recall under the regularity assumption:

$$f'(X;H_o) = C.\left[\sum_{j=1}^{r}\sum_{i=1}^{k_j} x_{ji}\, d_j \int_A \frac{H'(a)}{H(a)} \prod_{l=0}^{r}\prod_{m=1}^{k_l} (1-c_{lm}H(a))^{a_{lm}} H(a)^{\alpha+x_{..}-1}\right.$$

$$(1-H(a))^{\beta-1} H'(a)\, da - \sum_{j=1}^{r}\sum_{i=1}^{k_j} c_{ji}\, d_j\, a_{ji} \int_A \frac{H'(a)}{1-c_{ji}H(a)} \prod_{l=0}^{r}\prod_{m=1}^{k_l} (1-c_{lm}H(a))^{a_{lm}}$$

$$\left. H(a)^{\alpha+x_{..}-1} (1-H(a))^{\beta-1} H'(a)\, da\right]$$

which under the one-hit model is:

$$= C.\left[\sum_{j=1}^{r}\sum_{i=1}^{k_j} x_{ji}\, d_j \int_0^1 \prod_{l=0}^{r}\prod_{m=1}^{k_l} (1-c_{lm}H)^{a_{lm}} H^{\alpha+x_{..}-2} (1-H)^{\beta+1-1}\, dH\right.$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \int_0^1 (1-c_{ji} H)^{-1} \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1=c_{lm} H)^{a_{lm}} H^{\alpha+x..-1} (1-H)^{\beta+1-1} dH \ ]$$

$$\approx C. \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \frac{\Gamma(\alpha+x..-1)\,\Gamma(\beta+\Sigma\Sigma+1)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)} - c_{ji} d_j a_{ji} \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)}$$

$$= C. \frac{\Gamma(\alpha+x..)\,\Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)} \left[\frac{\beta+\Sigma\Sigma}{\alpha+x..-1} \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \right]$$

Letting $\hat{e} = (\beta+\Sigma\Sigma)/(\alpha+x..-1)$ then the score statistic is:

$$U_{one} \approx \hat{e} \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j - \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji}$$

Here as was the case with the logistic model an approximate exact test can be performed using U_{one} as the test statistic. Results using this are given later.

Recall, also under the assumption of regularity:

$$f''(X;H_o) = C.\ [W_1^2 \int_A \left(\frac{H'(a)}{H(a)}\right)^2 \Pi.\ da$$

$$- 2\ W_1 \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \int_A \frac{H'(a)}{H(a)} \frac{H'(a)}{1-c_{ji}H(a)} \Pi.\ da$$

$$+ \int_A \left(\sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j a_{ji} \frac{H'(a)}{(1-c_{ji}H(a))}\right)^2 \Pi.\ da$$

$$+ W_3 \int_A \frac{H''(a)}{H(a)} \Pi.\ da$$

$$- W_3 \int_A \frac{(H'(a))^2}{H(a)} \Pi.\ da$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^2 a_{ji} \int_A (1-c_{ji}H(a))^{-1} H''(a) \Pi.\ da$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}^2 d_j^2 a_{ji} \int_A \left(\frac{H'(a)}{(1-c_{ji}H(a)}\right)^2 \Pi.\ da\ ]$$

which under the one-hit model is approximated by, letting
$e' = (\beta+\Sigma\Sigma+1) / (x..+\alpha-2)$

$$f''(X;H_0) \approx C. \frac{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)} [\ \hat{e}\ e' W_1^2 - 2\ \hat{e}\ W_1 W_2 + W_2^2 - \hat{e}\ W_3$$

$$- \hat{e}\ e' W_3 + W_4 - W_6\ ]$$

Then

$$\hat{i}_{one} = ((f')^2 - ff'') / f^2$$

$$\approx \hat{e}\ (\hat{e} - e')\ W_1^2 + \hat{e}\ (1+e')\ W_3 - W_7$$

where $W_7 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j^2\ (n_{ji}-x_{ji})\ (1-c_{ji})$

The asymptotic statistic for the one-hit model is then $z_{one} = u_{one} / \sqrt{\hat{i}_{one}}$ which has a limiting standard normal distribution.

$$z_{one} = (\hat{e}\ W_1 - W_2) / (\hat{e}\ (\hat{e} - e')\ W_1^2 + \hat{e}\ (1+e')\ W_3 - W_7)^{1/2}$$

Examples using this statistic are given later.

3.9 A Linear Model Approximate Test

If the form of the increasing in dose probabilities is only to be estimated by $H(a+\varepsilon d_j) = a+\varepsilon d_j$ then $H'(a) = d_j$ $H''(a) = 0$

Then

$$f'(x;\ H_o) = C.\ \frac{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)}\ \left[\ \frac{(\alpha+x..+\beta+\Sigma\Sigma-1)}{(\alpha+x..-1)}\ \sum_{j=1}^{r}\ \sum_{i=1}^{k_j} x_{ji}d_j\right.$$

$$\left. -\ \frac{(\alpha+x..+\beta+\Sigma\Sigma-1)}{(\beta+\Sigma\Sigma-1)}\ \sum_{j=1}^{r}\ \sum_{i=1}^{k_j} c_{ji}d_j a_{ji}\right]$$

where $C. = \prod_{j=0}^{r}\ \prod_{i=1}^{k_j} \binom{n_{ji}}{x_{ji}} c_{ji}^{\ x_{ji}}\ \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}$

$$f''(x;\ H_o) = C.\ \frac{\Gamma(\alpha+x..)\ \Gamma(\beta+\Sigma\Sigma)}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma)}\ \left[\ \frac{\alpha+x..+\beta+\Sigma\Sigma-1}{\alpha+x..-1}\ \ \frac{\alpha+x..+\beta+\Sigma\Sigma-2}{\alpha+x..-2}\ (\ W_1^{\ 2} - W_3)\right.$$

$$-\ 2\ \frac{(\alpha+x..+\beta+\Sigma\Sigma-1)}{(\alpha+x..-1)}\ \ \frac{(\alpha+x..+\beta+\Sigma\Sigma-2)}{(\beta+\Sigma\Sigma-1)}\ \ W_1W_2$$

$$\left. +\ \frac{(\alpha+x..+\beta+\Sigma\Sigma-1)}{(\beta+\Sigma\Sigma-1)}\ \ \frac{(\alpha+x..+\beta+\Sigma\Sigma-2)}{(\beta+\Sigma\Sigma-2)}\ (W_2^{\ 2} - W_6)\right]$$

where w_k is as defined in 3.6.

$$U_{lin} = f'/\ f \approx \frac{\alpha+x..+\beta+\Sigma\Sigma-1}{\alpha+x..-1}\ \sum_{j=1}^{r}\ \sum_{i=1}^{k_j} x_{ji}d_j - \frac{\alpha+x..+\beta+\Sigma\Sigma-1}{\beta+\Sigma\Sigma-1}\ \sum_{j=1}^{r}\ \sum_{i=1}^{k_j} c_{ji}d_j a_{ji}$$

Here again an approximate-exact test can be used with the density as computed earlier.

An estimate of the variance of U_{lin} is given by

$$\hat{i}_{lin} = ((f')^2 - ff'')\ /\ f^2$$

$$\approx \frac{-(\alpha+x..)\ (\alpha+x..+\beta+\Sigma\Sigma-1)}{(\beta+\Sigma\Sigma-1)^2\ (\beta+\Sigma\Sigma-2)}\ W_2^{\ 2}\ \frac{-(\beta+\Sigma\Sigma)\ (\alpha+x..+\beta+\Sigma\Sigma-1)}{(\alpha+x..-1)^2\ (\alpha+x..-2)}\ W_1^{\ 2}$$

$$-\ 2\ [(\alpha+x..-1)^{-1} + (\beta+\Sigma\Sigma-1)^{-1} + ((\alpha+x..-1)\ (\beta+\Sigma\Sigma-1))^{-1}]\ W_1 W_2$$

$$+\ \frac{\alpha\ +x..+\beta+\Sigma\Sigma-1}{\alpha+x..-1}\ \frac{\alpha+x..+\beta+\Sigma\Sigma-2}{\alpha+x..-2}\ W_3\ \frac{\alpha+x..+\beta+\Sigma\Sigma-1}{\beta+\Sigma\Sigma-1}\ \frac{\alpha+x..+\beta+\Sigma\Sigma-2}{\beta+\Sigma\Sigma-2}\ W_6$$

$$z_{lin} \approx U_{lin} / \sqrt{V_{lin}} \sim N\ (0,\ 1)$$

Although the first three terms of the variance are negative all later examples using the linear model for dose-response probabilities will include all terms since, as will be seen, the linear tends to be more conservative than the two previously given models.

Chapter 4 - INCORPORATING HISTORICAL CONTROL INFORMATION IN MODELS UTILIZING TIME

4.1 Introduction

This chapter is presented as an example of how to incorporate historical control information in models that already account for time. As mentioned in Chapter I, the model to be used will be the one given by Dinse and Lagakos (1983). Their logistic model has the advantage over many others in that not only are time and weighting of treatment effect by time used but a set of covariables may be included.

As was the case with the test presented in Chapter II, the exact test here depends on evaluating integrals that are very cumbersome; here they are linear combinations of degenerate hypergeometric functions. Since this would render the test all but useless, only an approximation similar to the one in Chpater III is given. The resulting test then is an approximate asymptotic one, very close in values to similar non-approximate tests.

4.2 Model and Test Development

Recall from Chapter I that

$$\Pr\{Y=1;\ t,\ d,\ z\} = \exp\{\varepsilon dw(t) + bz + \partial(t)\}/[1+\exp\{\varepsilon dw(t) + bz + \partial(t)\}]$$

where Y = 1/0 presence/absence of response, d = dose, t = time of death, z = covariables.

Let t^* be the length of time for which historical control information is available. Redefine $\partial(t)$ if necessary such that z = 0 at $t = t^*$ for the control groups (i.e., mean values are adjusted to 0 when the corresponding information is unavailable for the historical control data or adjusted so that the historical value corresponds to 0).

Let P_0 denote the probability of response in the control group at $t = t^*$ and assume P_0 follows a beta distribution with parameters α and β. Then

$$P_0 = \frac{a}{1+a} \quad \text{where } a = \exp\{\partial(t^*)\}$$

If we let $c_i = \exp\{\varepsilon d_i w(t_i) + bz_i + \partial(t_i) - \partial(t^*)\}$ then the conditional density is

$$f(Y) = \int_0^1 \prod_{i=1}^{N} \frac{(c_i a)^{Y_i}}{1+c_i a} \quad \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \left(\frac{a}{1+a}\right)^{\alpha-1} \left(1 - \frac{a}{1+a}\right)^{\beta-1} d\,\frac{a}{1+a}$$

letting $x = \frac{a}{1+a}$ then $a = \frac{x}{1-x}$ and

$$f(Y) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{i=1}^{N} C_i^{Y_i} \int_0^1 \prod_{i=1}^{N} \left(\frac{1-x+c_i x}{1-x}\right)^{-1} \left(\frac{x}{1-x}\right)^{Y.} x^{\alpha-1} (1-x)^{\beta-1} \, dx$$

$$= \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{i=1}^{N} C_i^{Y_i} \int_0^1 \prod_{i=1}^{N} (1-b_i^* x)^{-1} x^{\alpha+Y.-1} (1-x)^{\beta+N-Y.-1} \, dx$$

where $b_i^* = -b_i = 1-c_i$

$$\approx \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{i=1}^{n} C_i^{Y_i} \frac{\Gamma(\alpha+Y.)\,\Gamma(\beta+N-Y.+\Sigma b_j)}{\Gamma(\alpha+\beta+N+\Sigma b_j)}$$

To evaluate the density under the null hypothesis below, replace C_i by $C_{io} = \exp\{bz_i + \partial(t_i) - \partial(t^*)\}$.

A test of no treatment effect is $H_0: \varepsilon=0$ vs $H_a: \varepsilon > 0$. Since there is only one point of concern in the null hypothesis, a locally most powerful test can be

obtained using the efficient score statistic:

$$T = \frac{\partial}{\partial\varepsilon} \ln(\text{lik}(\varepsilon)) = f'(\varepsilon = 0;\ Y)/f(\varepsilon = 0;\ Y)$$

$$f'(\varepsilon;\ Y) = \frac{\partial}{\partial\varepsilon} \int \prod_{i=1}^{N} \frac{(C_i a)^{Y_i}}{1+C_i a} \left(\frac{a}{1+a}\right)^{\alpha-1} \left(1-\frac{a}{1+a}\right)^{\beta-1} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}\ d\,\frac{a}{1+a}$$

Under regularity conditions the order of integration and differentiation may be changed. The derivative of the integrand being proportional to:

$$\frac{\partial}{\partial\varepsilon} \prod_{i=1}^{N} \frac{(c_i a)^{Y_i}}{1+c_i a} = \sum_{i=1}^{N} d_i w(t_i) \left\{Y_i - \frac{c_i a}{1+c_i a}\right\} \prod_{i=1}^{N} \frac{(c_j a)^{Y_i}}{1+c_j a}$$

Then,

$$f'(\varepsilon;\ Y) = \int \sum_{i=1}^{N} d_i w(t_i) \left\{Y_i - \frac{c_i a}{1+c_i a}\right\} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{j=1}^{N} \frac{(c_j a)^{Y_i}}{1+c_j a} \left(\frac{a}{1+a}\right)^{\alpha-1} \left(\frac{1}{1+a}\right)^{\beta-1} d\,\frac{a}{1+a}$$

$$= \sum_{i=1}^{N} d_i W(t_i)\ Y_i f(Y) - \sum_{i=1}^{N} d_i W(t_i) \int \frac{c_i a}{1+c_i a} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{j=1}^{N} \frac{(c_j a)^{Y_i}}{1+c_j a} \left(\frac{a}{1+a}\right)^{\alpha-1} \left(\frac{1}{1+a}\right)^{\beta-1} d\,\frac{a}{1+a}$$

Letting $x = \frac{a}{1+a}$ in the integral in the second sum then $a = \frac{x}{1-x}$ and the integral becomes

$$c_i \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{j=1}^{N} C_j^{Y_j} \int_0^1 \left(\frac{1-X+C_i X}{1-X}\right)^{-1} \prod_{j=1}^{N} \left(\frac{1-X+c_j X}{1-X}\right)^{-1} \left(\frac{X}{1-X}\right)^{Y.+1} X^{\alpha-1}(1-X)^{\beta-1}\ dx$$

$$= C_i \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod^{N} C_j^{Y_j} \int^{1} (1-b_i^{*} x)^{-1} \prod^{N} (1-b_j^{*} x)^{-1}\ x^{\alpha+Y.}\ (1-x)^{\beta+N-Y.-1}\ dx$$

$$j=1 \qquad 0 \qquad j=1$$

$$\approx C_i \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \prod_{j=1}^{N} C_j^{Y_j} \frac{\Gamma(\alpha+Y.+1)\Gamma(\beta+N-Y.+\Sigma b_j+b_i)}{\Gamma(\alpha+\beta+N+1+\Sigma b_j+b_i)}$$

Treating $b_i = 1 - C_i$ as zero yields

$$f'(Y) \approx \left[\sum_{i=1}^{N} d_i w(t_i) \left\{Y_i - C_i \frac{\alpha+Y.}{(\alpha+\beta+N+\Sigma b_j)}\right\}\right] f(Y)$$

To evaluate under H_o replace all C_i by C_{io}.

Then the efficient score statistic T, under the null hypothesis is

$$T \approx \sum_{i=1}^{N} d_i w(t_i) \left\{Y_i - C_{io} \frac{\alpha+Y.}{\alpha+\beta+N+\Sigma b_{jo}}\right\} \text{ where } \Sigma b_{jo} = \sum_{i=1}^{N} 1-C_{io}$$

As an estimate of the variance of the statistic the observed information matrix will be used.

$$i\ (\varepsilon = 0) = -\frac{\partial^2}{\partial\varepsilon^2} \ln \text{lik}\ (\varepsilon)$$

$$= \frac{\partial}{\partial\varepsilon}\ [f'/\ f] = \frac{(f')^2 - ff''}{f^2}$$

The density and first derivative have been found so only the second derivative is needed.

$$f'' = \frac{\partial^2}{\partial\varepsilon^2} \int_0^1 \prod_{i=1}^{N} \frac{(c_i a)^{Y_i}}{1+c_i a} \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)} \frac{a^{\alpha-1}}{1+a} \left(1 - \frac{a}{1+a}\right)^{\beta-1} d\frac{a}{1+a}$$

Again under the assumption of regularity we may change the order of differentiation and integration. The second derivative of the integrand is then proportional to:

$$\frac{\partial^2}{\partial\varepsilon^2}\left[\prod_{i=1}^{N}\frac{(c_i a)^{Y_i}}{1+c_i a}\right]=\frac{\partial}{\partial\varepsilon}\left[\sum_{i=1}^{N} d_i w(t_i)\left(Y_i-\frac{c_i a}{1+c_i a}\right)\prod_{j=1}^{N}\frac{(c_j a)^{Y_j}}{1+c_j a}\right]$$

$$=\left[\sum_{i=1}^{N} d_i w(t_i)\left(Y_i-\frac{c_i a}{1+c_i a}\right)\right]^2\prod_{j=1}^{N}\frac{(c_j a)^{Y_j}}{1+c_j a}$$

$$-\sum_{i=1}^{N} d_i\ w(t_i)\ \frac{c\ a}{(1+c_i a)^2}\prod_{j=1}^{\pi}\frac{(c\ a)^{Y_j}}{1+c_j a}$$

then f'' becomes

$$f''=\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}\left\{\sum_{i=1}^{N} d_i w(t_i)\int_0^1\left(Y_i-\frac{c_i a}{1+c_i a}\right)^2\prod_{j=1}^{N}\frac{(c_j a)^{Y_j}}{1+c_j a}\left(\frac{a}{1+a}\right)^{\alpha-1}\left(1-\frac{a}{1+a}\right)^{\beta-1}d\frac{a}{1+a}\right.$$

$$\left.-\sum_{i=1}^{N} d_i^2 w(t_i)^2\int_0^1\frac{c_i a}{(1+c_i a)^2}\prod_{j=1}^{N}\frac{(c_j a)^{Y_j}}{1+c_j a}\left(\frac{a}{1+a}\right)^{\alpha-1}\left(1-\frac{a}{1+a}\right)^{\beta-1}d\frac{a}{1+a}\right\}$$

$$=\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}\left[\sum_{i=1}^{N} d_i w(t_i)\int_0^1\left(Y_i-2Y_i\frac{c_i a}{1+c_i a}+\frac{c_i a}{1+c_i a}^2\prod_{j=1}^{N}\frac{(c_j a)^{Y_j}}{1+c_j a}\frac{a}{1+a}^{\alpha-1}\frac{1}{1+a}^{\beta-1}d\frac{a}{1+a}\right.\right.$$

$$\left.-\sum_{i=1}^{N} d_i^2 w(t_i)^2\int_0^1\frac{c_i a}{(1+c_i a)^2}\prod_{j=1}^{N}\frac{(c_j a)^{Y_j}}{1+c_j a}\frac{a}{1+a}^{\alpha-1}\left(1-\frac{a}{1+a}\right)^{\beta-1}d\frac{a}{1+a}\right]$$

$$\approx f(Y)\{\sum_{i=1}^{N} d_i w(t_i)Y_i - 2\sum_{i=1}^{N} d_i w(t_i)Y_i\ C_i \frac{\alpha+Y.}{\alpha+\beta+N+\Sigma b_j}$$

$$+\sum_{i=1}^{N} d_i w(t_i)\ C_i^{\ 2}\ \frac{(\alpha+Y.)}{\#}\ \frac{(\alpha+Y.+1)}{(\#+1)}\ \frac{(\beta+N-Y.+\Sigma b_j)}{(\#+2)}\ \frac{(\beta+N-Y.+\Sigma b_j+1)}{(\#+3)}$$

$$-\sum_{i=1}^{N} d_i^{\ 2} w(t_i)^2 c_i\ \frac{(\alpha+Y.)}{\#}\ \frac{(\beta+N-Y.+\Sigma b_j)}{(\#+1)}\}$$

where $\# = \alpha+\beta+N+\Sigma b_j$

$$\hat{i}.\ (\varepsilon=0) \approx \sum_{i=1}^{N} d_i w(t_i)\ (Y_i - C_i\ \frac{\alpha+Y.}{\#})^2] - \sum_{i=1}^{N} d_i w(t_i)Y_i$$

$$+\ 2\ \frac{\alpha+Y.}{\#}\sum_{i=1}^{N} d_i w(t_i)Y_i C_i + \frac{\alpha+Y.}{\#}\ \frac{(\beta+N-Y.+\Sigma b_j)}{(\#+1)}\ \sum_{i=1}^{N} d_i^{\ 2} w(t_i)^2\ c_i$$

$$-\frac{\alpha+Y.}{\#}\ \frac{\alpha+Y.+1}{\#+1}\ \frac{\beta+N-Y.+\Sigma b_j}{\#+2}\ \frac{\beta+N-Y.+\Sigma b_j+1}{\#+3}\ \sum_{i=1}^{N} d_i w(t_i)\ c_i^{\ 2}$$

with C_i replaced by C_{io} under the null hypothesis.

The statistic $\hat{T} / \sqrt{T}$. then has an asymptotic chi-squared distribution with one degree of freedom for testing an increasing trend in dose while accounting for time and covariables.

This same technique can be applied to similar models, but as was the case here, an approximation may be necessary. If covariable information is not available for the historical data as will usually be the case then the current experiment and historical information must be assumed to have had similar values.

Chapter 5 EXAMINATION OF APPROXIMATE: EXACT AND ASYMPTOTIC TESTS

5.1 Introduction

Almost all of the work that follows will use a logistic model for the dose-response probabilities. Similar results should hold for others, except much of what follows examines the effect of omitting a negative term present only in the logistic model from the variance estimate. Besides the acceptability of the logistic model in practice, it's use will allow a fair comparison with Tarone's test which also assumes a logistic model.

Simulations are used to compare the two statistics, with/without the negative term, with regard to the normality assumption and the Type I error. Significance levels are then compared against the corresponding exact p-values only in the case where intercurrent information is excluded. The reason for doing so is that the exact test incorporating censored data requires so much computation time as to make it prohibitive for the number of values needed. The approximate exact test does allow censored data and is used in comparing the asymptotic tests.

5.2 Two Asymptotic Test Statistics

Recall from chapter 3 that the asymptotic test statistic is

$Z_{log} = U_{log}/i_{log}^{1/2}$ where

$U_{log} = \hat{q}w_1 - \hat{p}w_2$

$i_{log} = \hat{q}\,(\hat{q}-q')\,w_1^2 + \hat{P}\,(\hat{P}-P)\,w_2^2 + 2\hat{q}\,(1-q'-\hat{p})\,w_1w_2 + \hat{q}\,(1-q')\,w_3 + \hat{P}(1-2P')w_4 + \hat{P}P'w_6$

$\hat{q} = (\beta+\Sigma\Sigma)/(\alpha+x..+\beta+\Sigma\Sigma) \quad \hat{P} = 1-\hat{q}$

$q' = (\beta+\Sigma\Sigma+1)/(\alpha+x..+\beta+\Sigma\Sigma+1) \quad P' = (\alpha+x..+1)/(\alpha+x..+\beta+\Sigma\Sigma+1)$

$W_1 = \Sigma\Sigma\ xd \qquad W_2 = \Sigma\Sigma\ cd\ (n-x) \qquad W_3 = \Sigma\Sigma\ xd^2$

$W_4 = \Sigma\Sigma\ cd^2\ (n-x) \qquad W_6 = \Sigma\Sigma\ c^2\ d^2\ (n-x)$

Since the first two terms of the variance are negative omitting them would give more conservative p-values. The statistic using all the terms is referred to here as APP-ASY and the test omitting the terms APP-ASY1 with corresponding significance values P and P1.

The limiting distribution of the efficient score is normal, but simulations are used here to compare the two statistics for samples of size 50. Figures 1.3.0 through 8.5.1 are graphs of the empirical distribution function of the statistics with the standard normal or chi-square for reference. The functions are the results of 10,000 simulated samples from the distribution under the null hypothesis. Each sample is from a population with 40 surviving full-term and only one censored group of 10. The alpha and beta values correspond to expected control rates of .2 to .01, with coefficients of variation (CV) from .25 to .50. The scalar values for the probability in the censored group are .33, .5, .8 and .9. See figure chart in appendix for guide to figure numbers.

5.3 Normality

Figures 1.3.0 through 1.9.1 use $\alpha = 5.655$ $\beta = 28.106$, with an expected value of .1675 and CV = .378. These parameter estimates represent the maximum likelihood estimates from the historical control data for lung tumors in male mice.

The APP-ASY statistic, for all scalar choices, appears to be symmetrical about 0, and slightly tail heavy beyond about 2 standard deviations. As the scalars decrease the tail weight increases, but only slightly.

For APP-ASY 1 the fit is nearly perfect to the normal but with the possibility of a slight shift of the mean below 0 as the scalars decrease. In

all cases the APP-ASY1 appears closer to standard normal.

Examining the figures corresponding to fixing the mean at .1675 and scalar at .5 allowing the CV to change, we find that for both statistics as the variance decreases the weight in the tails also decreases. When CV = .25 APP-ASY is very close to normal whereas APP-ASY1 uses an overestimate of the variance making the distribution too light in the tails. When the standard deviation is half the mean both are tail heavy but APP-ASY1 much closer. Fixing the CV at .5 and scalar at .5, we can see the effect of changes in the mean on the statistics. For larger background rates .2 - .1 APP-ASY is relatively normal in shape and centered about 0, as the mean increases the tail heaviness increases. For lower rates .05 and especially .025 the normality assumption is in question, but from about 1 standard deviation and above it is very close to the normal. In the larger means .2-.1 APP-ASY1 is relatively close to the normal, very tail heavy at .2 but a good fit at .1675. For .05 and .025 APP-ASY1 underestimates the tail area and does not appear to be normal at .025. Overall APP-ASY1 appears closer to normal for larger rates, .1 and above, APP-ASY better for smaller rates.

For low control rates, most of the probability mass is associated with very small numbers of tumors. To help smooth the data the square of the statistics is used, and compared with a chi-squared with one degree of freedom.

For a rate of .05 APP-ASY is very close to the chi-square, for .025 good but not as good. For both these rates APP-ASY1 underestimates the tail density. In the case of a very low rate (e.g., .01), the data again appear discreet. In all cases for the lower rates APP-ASY is closer to the chi-squared distribution.

5.4 Type I Errors

Simulations were again used to estimate the true significance levels of APP-ASY and APP-ASY1. Table 4 gives the results for several alpha and beta with different scalar values for test significance levels of .05, .01 and .005.

For means of .01 and larger APP-ASY ranges from two to four times the specified levels. When below .1 the range is 50% above the level to just below. For all means as the scalars get larger the true significance levels of both APP-ASY and APP-ASY1 drop. And for both as the c.v. increases the significance levels do also.

In almost all cases APP-ASY1's true significance levels are below those specified. For the larger rates the levels are very close. When the rates drop below .10, for higher c.v.'s the true levels tend to be about half that specified.

If the significance level is a major concern then APP-ASY1 is to be preferred since it generally is the more conservative test.

5 5.1 P-values: Full-Term Data

The most important consideration is not whether a test will conform to a set of theoretical assumptions, but rather will give useful, reliable information. In this case p-values are the desired information and their accuracy will be measured against the exact test. Table 3 gives p-values for a range of mean control rates and observed responses chosen for significance levels in a usable range.

An overview is dependent on the mean rates. In all cases APP-ASY and Tarone's test are almost identical as would be expected, and APP-ASY1 by design larger than APP-ASY.

For large to moderate mean rates ($\geq$ .03) independent of c.v., APP-ASY and

the exact are very close with APP-ASY the larger making it conservative to use. APP-ASY1 tends to be too conservative with values sometimes more than twice the exact. For smaller rates, down to .0175, APP-ASY is very close to the exact when the standard deviation is half or more the mean, although slightly aggressive. When the c.v. is .25 or less APP-ASY1 is close to the exact but aggressive. Neither test is very close for means about .01 with c.v. $\geq$ .75. The exact is usually bounded by them and within .01 of APP-ASY for pertinent levels. When the c.v. is smaller but not below .5 APP-ASY1 is close to the exact but aggressive. If the mean is below .01, APP-ASY1 is usable for large variances and too aggressive otherwise.

From this the choice between APP-ASY and APP-ASY1 can be seen to depend on μ and the c.v. A test labeled ASY is also presented in table 3. ASY represents the above choices between APP-ASY and APP-ASY1 with the transition linearly in c.v. Although not presented the linear transition appears to be a very adequate approximation, and is quite easy to compute.

Considering values with a mean = .17, it is easy to see that as the variability in the mean increases the p-value increases. For example, an observed (8, 12, 16) goes from a p of .010 for c.v. = .25 to p=.022 with double the standard deviation. The table also shows how the test relies on the historical data. If no dose effect is present then you would expect about 8 tumors in each group. An observed (8, 10, 12) represents the expected with increases of 2 per dose unit, yielding a significance level of .119 for c.v. = .25. When the control group has 20 tumors, 2.5 times the expected, with the same increases of 2 per dose, the p-value now drops to .001 less than 1% of .119 for the same increases. If the mean value is correct then the probability of observing 20 or more in the control group is <0.001, so such an example is unlikely. The Cochran-Armitage test not incorporating historical information,

measuring increases relative to the total number of tumors, gives a larger p-value for more tumors in the control group. That the decreased variability increases the weight of the historical mean, can be seen by noting that for c.v. = .25 increasing the control number of tumors by 2.5 times the p=value was less than 1% the original; c.v. = .38 it is 13% and with c.v. = .5, 38%.

Another example of the problem alluded to above is seen in an observed (5, 5, 3) μ=.01 c.v. = .5. Here the significance level is less than .01 for all the tests with historical information, when the suspect substance actually appears to possibly be beneficial. The problem exists when the observed control response is outside what is probable assuming the prior distribution. Here the historical data can be of use as a quality control check, and should not be incorporated directly in the test when the observed is outside the expected range. The Cochran-Armitage test yields a p-value of .76 in the above situation, more in line with what is intuitively expected.

5.5.2 P-values: One Censored Group

The exact test in order to accommodate even one censored group per dose requires a tremendous amount of computer time. To compare the asymptotic results with an exact value two approximate exact tests APP1 and APP2 will be used. APP1 is closer to the exact but APP2 is easier computationally. In most of the examples presented the approximations required from 30 to 60 minutes cpu time on a VAX780. The second requiring much less time, but since they have been computed simultaneously no estimate is given here. The derivation of APP1 and APP2 is presented in Appendix 1. APP1 is very close to the exact, increasing in accuracy as the scalars approach 1. Generally summing from .99 to .995 rather than 1.0 the approximation is slightly aggressive. Tables 5 and 6 give the significance level for both approximations, the three asymptotic tests

and the exact where possible. The first uses the prior for lung tumors in male mice with a background rate of .1675. Here due to the large expected number of tumors, the responses are fixed and the scalar varies.

For the observed (9, 3-7, 9-5) APP2 is very aggressive compared to all the other results with the greater discrepancy for the smaller scalars. APP-ASY gives slightly larger values than APP1 but for all scalar values the difference is nearly constant at .01. This could be due to the aggressive nature of the APP1 approximation. When the censored groups are combined and APP1 is exact APP-ASY amd APP1 agree closely as was noted earlier.

The second example in that table uses smaller samples to facilitate computation of the exact values, each requiring over four hours cpu time on a VAX 780. For all scalar values, APP1 yields smaller but close to the exact values, APP-ASY is close and slightly conservative. APP-ASY1 appears to be way too conservative for this large of a background rate. This is the same as the uncensored results. The ASY value, representing the recommendations from the uncensored data, is merely equal to APP-ASY here.

Table 6 uses alpha=3.95 and beta=391 for a mean rate of .01. The number at risk is the same throughout the table (50, 10-40, 20-30) with the scalar also constant at .5 chosen to be the worst likely case. ASY, for this mean rate, is the APP-ASY1 statistic. Compared to APP1, APP-ASY is too aggressive but ASY is usually very close but not consistently in either direction.

Line 1 reflects the addition of one tumor in the censored dose 2 group over Line 2. The probability of a tumor in the censored group is small and the test reflects this with ASY dropping from .27 to .04. The approximate and asymptotic results are very similar. Increasing one tumor in the second dose group is shown in line 6 with all probabilities less than .01. If the second tumor in

line 2 had instead been in the first dose full-term group as in line 3 then the tumor being more likely, the tests' values increase to between .12 and .14. Similar results can be seen throughout the table, with the tests reacting as would be expected and generally in close agreement.

The ASY test appears to behave properly with conclusions similar to the exact test. The use of the ASY value rather than the derived APP-ASY is only in the conservative direction and is recommended.

5.6 Probability Estimates Prior to Full-Term

A basic assumption was that the probabilities prior to full-term could be estimated. At present there is not a sufficient database to accurately model all tumor types, but the inclusion of time to tumor information in future studies will hopefully solve this problem. The very rare tumors require more data to estimate the scalars with little variability but a conservative approach can be used reliably for any background rate. Portier (1984) has found a Weibull distribution to closely fit most tumor types tested. If we let P(t) be the probability of tumor at time t then the model is:

$P(t) = 1- \exp\{-a\ (t-w)^c\}$.

The model has three unknown parameters but generally w, the earliest possible occurrence of a tumor, can be accurately estimated. When the probability is constrained by $P(104) = \alpha/(\alpha+\beta)$ for a given tumor type then only one free parameter remains. I chose to allow the shape parameter c to vary solving for a.

Portier (1984) noted that for some tumors more than one Weibull adequately fit the data. An example is adrenal cortical adenomas in female rats. Here with P(104) = .0233, w=58, and c=3 fitting the best, models with $0 \leq c \leq 7$ also fit well. Figures 9.1 through 11.1 display the Weibull distribution for

different combinations of c and P(104) all with w=52 for comparison.

If you examine figures 9.1, 10.1, and 11.1 it is easy to see that with c fixed, .21 here, that the probability at full-term affects the scale of the distribution but not the shape. Only one case need be examined here then: $\alpha/(\alpha+\beta) = .1675$.

Figures 11.1 through 11.4 represent a Weibull with shape parameters c = .21, 1, 2, and 5. As c goes to 0 the distribution approaches a constant function equal to the full-term probability. Linear at c=1 and concave upward for larger c, the distribution assigns values closer to 0 as c goes to infinity.

C equal 0 is the same as grouping all observations into one time interval and assuming that a tumor was just as likely to occur anytime prior to full-term as full-term. Choosing large c is equivalent to saying that the tumor has almost no chance of occurring prior to full-term. Applying a larger probability to earlier tumors intuitively reduces the impact of their occurrence making the use of smaller c's the conservative choice. The fact that the distribution is stochastically larger for smaller c's confirms the intuition that the smaller the c used the more conservative the test. Since most of the distributions are presented with either an estimate of the variance or range of acceptable values; then the lower bounds of c's should be used.

For the example presented earlier, lung tumors in male mice, the best fitting Weibull distribution is one with w=52, full-term probability .1675 and shape parameter c = .21. Using these the significance level from the asymptotic test is .028, for c=1 p=.019, c=2 p=.015, and c=5 p=.010. As can be seen the larger the c used the more aggressive the test. These compare with considering all the data to be full-term p=.032 and .034 for the asymptotic and exact tests.

5.7 Two Examples

Two examples will be presented to show the effect of using the censoring information versus not including it and to see the changes caused by grouping the data in time.

The first example is from the National Toxicology Program's Technical Report Series No. 259. The data are reproduced in table 1 and represent the findings of the effect of Ethyl Acrylate on the occurrence of lung tumors in male mice. It is important to note that an excess of tumors was found in the control group so to put the significance level in a desirable range the dose 2 group and control group were switched. Therefore, no conclusions reached should be applied to Ethyl Acrylate. The study began with 50 mice in each of the three groups; with the second dose twice that of the first. All full-term data are considered to have occurred at week 104, only 31, 31, and 29 surviving at least that long.

The second example is presented in table 2. It is the censoring information for female mice in the study of Allyl Isovalerate, Technical Report Series No. 253. Tumors in the forestomach were found to be very significant with the other tumors not in a desired range. The censoring information was therefore used, but with the responses fictitious. In this study only 27, 35, and 27 survived to full-term, indicating that some means of including the time-to-tumor information must be included. In this case, it will be assumed that the tumor has a background rate of .01 and doses 1 and 2 used.

For more complete information on either study see the technical reports.

5.8 The Effect of Grouping in Time

The two examples described earlier will be used to examine the effect on the significance level of grouping into time intervals. The first example, lung tumors in male mice, has prior distribution parameters estimated by α=5.655 and

β=28.106 for a mean of .1675. Using a Weibull with location w=52 and shape c=.21 on all the data ungrouped the significance level is .028. If the test is to be programmed then there is no reason to group into possibly arbitrary time intervals, and the full data should be used. A possible exception is to exclude all non-tumor deaths prior to what was deemed the earliest possible time for a tumor to occur. In this example deleting 8, 7, and 4 from the control through dose 2 groups respectively produced no change in the p-value for at least five places. Observing no tumors when it is assumed none are possible adds no information. Should a tumor occur then the data or location parameter may be suspect rather than having a very significant result.

The first grouping scheme used time endpoints: 0, 53, 65, 85, and 104 with corresponding scalars: 0.0, .459, .764, .916, and 1.0. Two choices for a scalar to represent each interval were considered, the mean and median. Since in all cases these were almost identical, only the mean is used. The table below gives the data for the grouping scheme.

Scalar	Control	dose 1	dose 2
.0	0/8	0/7	0/4
.690		0/2	0/2
.864	0/3	0/2	2/5
.960	2/7	1/8	2/10
1.0	3/31	5/31	9/29
	5/49	6/50	13/50

The second grouping scheme merely combines the last two groups using 1.0 for the scalar. The p-values changed very little: .028 ungrouped, .029 5 groups and .030 4 groups. The effect of grouping is slight enough to warrant

grouping the data when hand calculations are necessary, supported by the fact that using fewer groups yields more conservative results. The approximate exact results are almost identical with APP1 yielding p=.028 and APP2 .029 in the last case.

The data in the table below represent a tumor with α=3.95 and β=391 yielding a much smaller background rate, μ=.01, than in the previous example. For comparison, the prior probabilities are modeled using the same Weibull shape. The same interval groupings are used but with the scalar determined by the data.

Scalar	Control	dose 1	dose 2
.0	0/2		0/4
.612	0/3	0/1	
.864	0/3	0/4	0/5
.963	1/15	1/9	1/12
1.0	0/27	1/35	1/27
	1/50	2/49	2/48

Here the effect of grouping is not detectable in three significant digits. Ungrouped, 5 and 4 groups gave a p=value of .024. And as above deleting the responses prior to 52 weeks had no effect since no tumors were observed. The two exact approximations, APP1 and APP2 yielded p=values .027 and .030 respectively on the 4 group data. Here again the asymptotic results are very close to the exact with a considerable savings in computer time. In each example the exact approximations required about 30 minutes cpu time on a VAX 780.

The asymptotic test appears to be relatively robust to grouping and minor changes in the scalar estimates. The use of conservative scalars and grouping

on time make it feasible for hand calculation and justify its inclusion in testing results to account for possible survival differences.

5.9 Comparison of the Asymptotic Results with Other Tests, Including and Excluding Censored Observations.

The table below gives significance levels for the two examples presented earlier. First, all the data are considered as if they survived full-term, secondly, only those that did. In example 1, it can be seen that the tumors occurred at about the same rate as those in the full-term sacrifice. The exact ranging from .027 to .034, including the time-to-tumor information in the asymptotic test gives only a slightly different value .028. Note again the closeness of the asymptotic to exact for large background rates, also not much is gained by including historical control information over the Cochran-Armitage test.

				Asy	Exact	Tarone	C-A
Example 1				.028			
All Data	5/49	6/50	13/50	.032	.034	.033	.016
Full Term	3/31	5/31	9/29	.026	.027	.026	.017
Example 2				.024			
All Data	1/50	2/49	2/48	.033	.036	.023	.276
Full Term	0/27	1/35	1/27	.073	.090	.062	.179

In example 2, however, the decision as to how much and what data to include does make a difference. The exact could be argued to be either .036 or .090, a difference which could alter the conclusion. The formal inclusion of time is able to account for the early occurrence of the tumors and does so without any arbitrariness as to how to handle the data. Here again the asymptotic test gives results very close to the exact and closer than Tarone's test. The large

values of the Cochran-Armitage test point out its inappropriateness for tumors with low background rates.

The effect of including or excluding the time information depends on the amount of censoring and the model used for the prior scalars. In both the examples presented the Weibull increases very rapidly so that by the 76th week the probability of a tumor is already 85% of what it is full-term. In example 2, if 10 of the full-term dosed tumorless responses are moved to the 76th week then the probability drops slightly from .024 to .020. Although only a small change it reflects that the dosed animals were now at risk less than before. In the case where survival is better in the dosed groups then the significance level will be lower.

Inclusion of the time information may change the p-value in either direction with the degree depending on many factors. Since this is the case it seems an unreasonable approach to exclude some information and try to estimate the effect.

5.10 Effect of Variability in Estimation of Prior Parameters

The test has assumed that the parameters of the beta prior are known. In reality alpha and beta are estimated from the historical control data using maximum likelihood methods. Since the test depends on these $\hat{\alpha}$ and $\hat{\beta}$ estimates the effect of their variability on the test will be considered.

First, 95% confidence intervals of $\theta=\alpha/(\alpha+\beta)$ and $\alpha+\beta$ are obtained. Two methods are considered. The first method, referred to here as the unconditional method, is to construct the confidence intervals directly from the maximum likelihood estimates of α and β, and their asymptotic variance and covariance matrix. The second or conditional method is to utilize the pooled historical control rate which is generally considered acceptable by toxicologists.

Consider the historical control rates $p_j=y_j/M_j$, where M_j is the size of the jth control group and y_j is the number of animals with a tumor in the organ of interest in the jth control group, j=1,...,k. Let y./M. estimate the pooled historical control rate. Assume that $y_1,\ldots y_k$ are mutually independent and that y_1 is distributed as a beta-binomial with parameters M_i, α and β. Then, the expectation and variance of y./M. are

$$E(y./M.) = \theta$$

$$V(y./M.) = \{\theta(1-\theta)/M.^2\} \sum_{i=1}^{k} M_i\{1+\gamma(M_i-1)\},$$

where $\gamma=(\alpha+\beta+1)^{-1}$. Replacing y./M. by $\hat{\theta}$ which is generally very close and also replace θ by $\hat{\theta}$ and γ by $\hat{\gamma} = (1+\hat{\alpha}+\hat{\beta})^{-1}$, a 95% confidence interval of θ may be approximated by

$$CI_1 = [\hat{\theta}-A, \hat{\theta}+A], \qquad (1)$$

where

$$A = (1.96/M.)[\hat{\theta}(1-\hat{\theta})\sum_{i=1}^{k} M_i\{1+\hat{\gamma}(M_i-1)\}]^{1/2} \qquad (2)$$

This interval is referred to as the parametric confidence interval.

Alternatively, we may construct a confidence interval on θ without assuming the beta-binomial distribution. Assume that y_i, conditioned on p_i, follows a binomial distribution with parameters m_i and p_i, i=1,...,k, and that $P_1,\ldots,P_k$ are independently and identically distributed. Let

$$S^2 = \sum_{i=1}^{k} \left(\frac{M_i}{M.}\right)\left(\frac{y_i}{M_i} - \frac{y.}{M.}\right)^2$$

then we have

$$E(y./M.) = \theta$$

$$V(y./M.) = \frac{\theta(1-\theta)}{M.} + \sigma^2\{ \sum_{i=1}^{k} (\frac{M_i}{M.})^2 - \frac{1}{M.}\} \qquad (3)$$

$$E(S^2) = (k-1)\ \{\theta(1-\theta)/M.\} + \sigma^2 Q,$$

where

$$Q = 1 - \{(k-1)/M.\} - \sum_{i=1}^{k} (\frac{M_i}{M.})^2$$

and σ^2 is the unknown variance of the distribution of P_1. Thus by approximating $E(S^2)$ by S^2 we may estimate σ^2 by

$$\hat{\sigma}^2 = Q^{-1}[S^2 - \{ (k-1)\mu(1-\mu)\}/M.].$$

Substituting this into (3) we have an analogous confidence interval for θ, a nonparametric confidence interval. For obtaining the confidence interval of $\alpha+\beta$, condition on the pooled historical estimate y./M. and estimate α and β by $\hat{\alpha}$ and β subject to the restriction that $\hat{\alpha}/(\hat{\alpha}+\beta) = y./M.$. Using an approximation to the variance of log $(\hat{\alpha} + \beta)$, V, given in Appendix 2, a confidence interval for $\alpha+\beta$ is given by

$$CI_2 = [\exp\{\log(\hat{\alpha}+\beta)-1.96\sqrt{V}\}, \exp\{\log (\hat{\alpha}+\beta)+1.96\sqrt{V}\}].$$

Table 9 gives the conditional and unconditional parametric and nonparametric intervals for three examples of tumors with background rates .017, .088 and .189. From this it is easy to see that the four methods provide almost identical results, so any one could be used.

Let

$$R = \{\alpha',\beta'): \frac{\alpha'}{\alpha'+\beta'} \varepsilon\ CI_1,\ (\alpha'+\beta')\varepsilon\ CI_2\}$$

and consider the maximum and minimum significance probabilities, $SP(\alpha',\beta')$, over the region; that is

$$MSP = \text{Max}\{ SP(\alpha',\beta') : (\alpha',\beta')\varepsilon\ R \}$$

$$mSP = \text{Min}\{ SP(\alpha',\beta') : (\alpha',\beta')\varepsilon\ R \}.$$

Although found through computations these maxima and minima are attained at the four boundary points (α', β') satisfying:

$$\{\alpha'/(\alpha'+\beta')\} = \text{lower (upper) confidence limits of } \theta$$
$$\{\alpha'+\beta') = \text{lower (upper) confidence limits of } \alpha+\beta. \qquad (4)$$

Columns 2, 3, 4 and 5 of Table 2 display values of $SP(\alpha', \beta')$ for these four boundary points when $(\alpha, \beta) = (3.95, 391)$ and $(3, 12)$ with $\sqrt{V}$ estimated by 7.7625 and 249.2237, respectively. The values in the table are computed by supposing the incorporation of 50 historical experiments, each consists of 50 control animals; that is $k=50$ and $M_i=50$ for $i=1,2,\ldots,50$. The first column of the tables shows the corresponding values of $SP(\alpha', \beta')$.

Table 7 shows, at least numerically, that when $\alpha+\beta$ is small the significance probability changes very little over the region. For example, the worst case is the first line (2,2,9) with an estimated SP(3, 12) = .041 with a range of (.023, .076).

In this case the confidence interval for θ is $\hat{\theta} \pm 16\%$ of $\hat{\theta}$ which is not a large variation. Columns 2 with 3 and 4 with 5 represent a confidence interval conditioning on the θ. Conditioned on θ there is more variability than displayed by the corresponding intervals given in Table 8.

Table 8 gives wider confidence intervals for SP(3.95, 391) but most of this appears to be due to the variability of θ. Here a range is $\hat{\theta} \pm 40\%$ of $\hat{\theta}$. With this much variability for small background rates, the true results can vary greatly, but conditioned on θ the intervals are very tight.

A possible solution is to compute the four significance probabilities and use the range. What is recommended here instead is to assume that enough is known about the tumor to judge whether the mean from the historical data is accurate or not. If the historical estimates are not in keeping with what was expected, then do not include the historical data in testing until a sufficient

database is available.

If the historical mean is close to what is expected then include the information in testing, ignoring the variability in the prior estimates.

Chapter 6 CLOSING REMARKS

6.1 Summary

Historical control information, if available, can provide more sensitivity to increased risk of a tumor. Rather than subjectively using this information it needs to be formally incorporated into the testing procedure. Survival time is another factor that must be included when attempting to determine risk differences. A survival difference should void any conclusions reached if not accounted for. The estimates of probabilities of a tumor prior to full term are presently available for many types and should be soon for all. In many cases a conservative approach can be taken.

With the probability estimates available the test developed can formally include historical control information while accounting for differences in survival. A major feature of the test is that it does so without the need for cause of death determination, or classification of the tumor as lethal, incidental or somewhere in between.

The exact procedures are too cumbersome to be widely applied. The approximations are very close and as shown can be reliably used. The asymptotic test is very easy to compute, yielding conclusions almost identical to the exact test; the asymptotic test is therefore the recommended test.

Any test is merely a point estimate of a probability. With this in mind and recalling that the asymptotic test is relatively robust to variability in the prior estimates, a point estimate rather than a confidence interval for the probability is to be used.

With a formal means of including historical control information while accounting for survival differences available there is no reason to merely do so subjectively. The asymptotic test is a relatively robust and reliable way to do so without the problem of subjective inclusions.

6.2 Future Research

The test developed is ready for use. Further applications and evaluation to real data are to be desired. The test assumptions were made to account for the extra-binomial variability present in the historical control data. In the case of less than binomial variability Tarone recommends modifying the alpha and beta estimates used. He sets the first moments equal arbitrarily restricting the second. Possibly, a better choice is the alpha and beta estimates found from the method of moments? Another possibility in these cases is a Poisson trend test incorporating historical information and survival times.

The test also has assumed a nondecreasing probability of tumor with increasing dose. In some cases a dampening effect may be present in the high doses with a need for possibly a different type of test.

Finally although some ground work has been done here, the use of covariables in testing needs to be completely examined. The Dinse model with historical data included may prove very useful when other factors are felt to affect the risk.

Appendix 1 APP1 and APP2

Recall the test statistic is:

$$C_3T = \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{n_{lm}-x_{lm}} H(a)^{x_{..}+\alpha-2} (1-H(a))^{\beta-1}$$

$$(H'(a))^2 \, da$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j (n_{ji}-x_{ji}) \quad (1-C_{ji}H(a))^{-1} \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{n_{lm}-x_{lm}}$$

$$H(a)^{x_{..}+\alpha-1} (1-H(a))^{\beta-1} (H'(a))^2 \, da$$

$$= \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{n_{lm}-x_{lm}} H(a)^{x_{..}+\alpha-2} (1-H(a))^{\beta-1}$$

$$(H'(a))^2 (1-C_{ji}H(a))^{-1} \, da$$

$$- \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji} d_j n_{ji} \quad (1-C_{ji}H(a))^{-1} \prod_{l=0}^{r} \prod_{m=1}^{k_l} (1-C_{lm}H(a))^{n_{lm}-x_{lm}} H(a)^{x_{..}+\alpha-1}$$

$$(1-H(a))^{\beta-1} (H'(a))^2 \, da$$

For H logistic:

$$\doteq \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji} d_j \frac{\Gamma(x_{..}+\alpha)\Gamma(\beta+\Sigma\Sigma+1-c_{ji})}{\Gamma(\alpha+x_{..}+\beta+\Sigma\Sigma+1-c_{ji})}$$

$$- \sum_{j=1} \sum_{i=1} \frac{\Gamma(x..+\alpha+1)\Gamma(\beta+\Sigma\Sigma+1-c_{ji})}{\Gamma(\alpha+x..+\beta+\Sigma\Sigma+2-c_{ji})}$$

$$C_3 \doteq \frac{\Gamma(x..+\alpha)\Gamma(\beta+\Sigma\Sigma)}{\Gamma(x..+\alpha+\beta+\Sigma\Sigma)}$$

Then

$$APP1 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} \frac{\Gamma(\beta+\Sigma\Sigma+1-c_{ji})\Gamma(x..+\alpha+\beta+\Sigma\Sigma)}{\Gamma(\beta+\Sigma\Sigma)\Gamma(x..+\alpha+\beta+\Sigma\Sigma+1-c_{ji}} \{ x_{ji}d_j$$

$$- \frac{(x..+\alpha)}{(x..+\alpha+\beta+\Sigma\Sigma+1-c_{ji})} \quad c_{ji}d_jn_{ji}\}$$

If we want to assume that $1-c_{ji} \approx 0$

$$APP2 = \sum_{j=1}^{r} \sum_{i=1}^{k_j} x_{ji}d_j - \frac{(x..+\alpha)}{(x..+\alpha+\beta+\Sigma\Sigma)} \sum_{j=1}^{r} \sum_{i=1}^{k_j} c_{ji}d_jn_{ji}$$

Note that APP2 is in the form of an observed minus expected.

Appendix 2: Unconditional Variance of log $(\hat{\alpha}+\hat{\beta})$

Since $\hat{\alpha}$ and $\hat{\beta}$ are restricted by $\hat{\alpha}/(\hat{\alpha}+\hat{\beta})=\hat{\theta}=y./M.$, we have approximately

$$\log(\hat{\alpha}+\hat{\beta}) \approx \log(\beta) + [(\hat{\beta}-\beta)/\beta] + \hat{\theta}.$$

Therefore

$$E[\log(\hat{\alpha}+\hat{\beta}) \mid \hat{\theta}] \approx \log(\beta) + \hat{\theta}.$$

Further

$$\begin{aligned} Var[\log(\hat{\alpha}+\hat{\beta}) \mid \hat{\theta}] &\approx Var(\hat{\beta} \mid \hat{\theta})/\beta^2 \\ &= (1-\hat{\theta})^2 \, Var(\hat{\alpha} \mid \hat{\theta})/(\theta\beta)^2 \\ &\approx (1-\hat{\theta})^2 \, Var(\hat{\alpha} \mid \hat{\theta})/(\theta\beta)^2, \end{aligned}$$

since the variance of $\hat{\theta}$ is very small. Now we approximate $E[Var(\hat{\alpha} \mid \hat{\theta})]$ by the conditional variance of $\hat{\alpha}$, say ν. Then we have

$$E\{Var[\log(\hat{\alpha}+\hat{\beta}) \mid \hat{\theta}]\} \approx \nu\{(1-\theta)/(\beta\theta)\}^2.$$

Thus

$$\begin{aligned} Var[\log(\hat{\alpha}+\hat{\beta})] &= E[Var\{\log(\hat{\alpha}+\hat{\beta}) \mid \hat{\theta}\}] + Var[E\{\log(\hat{\alpha}+\hat{\beta}) \mid \hat{\theta}\}], \\ &\approx \nu\{(1-\theta)/(\beta\theta)\}^2 + Var(\hat{\theta}) \equiv V \end{aligned}$$

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TABLES

Table 1

Individual Animal Pathology For Lung Tumors Of Male

Mice In A Two-Year Study Of Ethyl Acrylate

***Note the contol and dose 2 data were switched to create p-values in a more usable range.

***Alveolar/bronchiolar adenoma & carcinoma combined

weeks on study	tumor(s)/death(s) control	dose 1	dose 2
5	0/1		
7		0/1	0/1
12	0/1	0/1	
13			0/2
14	0/1		
18	0/1		
19	0/1		
21		0/1	
22	0/1	0/2	
23	0/2	0/1	
33			0/1
34		0/1	
54			0/1
63		0/2	
64			0/1
71			0/1
72			0/1
73	0/1		
74		0/1	
75		0/1	
78	0/1		
79			1/1
80	0/1		
81			1/1
84			0/1
87			0/1
88			1/1
90	0/1	1/2	
91	1/2	0/1	
92		0/1	0/2
93	1/2		
94			0/1
95			0/1
96		0/1	0/1
97		0/1	0/1
98		0/1	
99		0/1	1/1
100	0/1		0/1
101	0/1		
104+	3/31	5/31	9/29
	5/49	6/50	13/50

Table 2

Individual Animal Pathology Of Female Mice

In A Two-Year Study Of Allyl Isovalerate

***Note the data make use of the censoring times but the responses were selected for proper significance

weeks on study	tumor(s)/death(s) control	dose 1	dose 2
7	0/1		
14	0/1		0/1
29			0/1
31			0/1
50			0/1
54	0/1		
57		0/1	
58	0/1		
61	0/1		
70		0/1	
71		0/1	
76		0/1	0/1
77	0/1		
78	0/1		
79			0/1
80			0/2
82	0/1		
84		0/1	0/1
86			1/2
87	0/1		
88	0/1	0/1	0/1
90	0/2		
92		1/2	
93			0/2
94			0/1
95	0/1		0/1
96	0/1	0/3	0/1
98	0/1		0/1
99	0/1		
100	0/1		
101	1/3		0/1
102	0/1	0/3	0/2
103	0/1		
104+	0/27	1/35	1/27
	1/50	2/49	2/48

Table 3

P-VALUES FOR UNCENSORED DATA

ALPHA	BETA	U	C.V.	XO	X1	X2	P	P1	** ASYMPTOTIC ** ASY	EXACT	TARONE	C-A
12.6	50.40	.2	.25	10	10	14	.148	.193	.148	.145	.148	.170
				10	15	15	.062	.099	.062	.058	.062	.129
				10	15	20	.003	.011	.003	.003	.003	.015
				20	15	20	.093	.131	.093	.093	.093	.500
12.87	63.97	.17	.25	8	10	12	.119	.162	.119	.116	.120	.159
				8	10	14	.044	.075	.044	.045	.044	.072
				8	12	16	.010	.024	.010	.011	.010	.031
				14	18	22	.001	.003	.001	.001	.001	.048
				20	22	24	.001	.004	.001	.001	.001	.210
5.656	28.11	.17	.38	8	10	12	.136	.194	.136	.127	.137	.159
				8	10	14	.055	.103	.055	.053	.056	.072
				8	12	16	.017	.045	.017	.016	.017	.031
				14	18	22	.006	.020	.006	.006	.006	.048
				20	22	24	.018	.043	.018	.018	.018	.210
3.996	15.39	.17	.5	8	10	12	.144	.211	.144	.132	.145	.159
				8	10	14	.061	.119	.061	.057	.062	.072
				8	12	16	.022	.059	.022	.019	.022	.031
				14	18	22	.019	.049	.019	.018	.019	.048
				20	22	24	.055	.100	055	.053	.055	.210
3.428	30.85	.1	.5	2	6	8	.037	.086	.037	.030	.037	.026
				5	7	8	148	.212	.148	.131	.148	.189
				5	9	11	.027	.066	.027	.022	.027	.054
				5	10	15	.002	.010	.002	.001	.002	.006
				8	10	14	.020	.051	.020	.018	.020	.072
				10	15	13	.061	.109	.061	.051	.062	.245
3.674	69.81	.05	.5	1	4	6	.021	.051	.021	.018	.021	.028
				2	4	5	.085	.136	.085	.074	.085	.125
				2	5	8	.006	.021	.006	.006	.006	.023
				3	5	6	.059	.104	.059	.053	.060	.151
				3	5	7	.028	.060	.028	.025	.028	.091
15.26	595.26	.025	.25	0	2	3	.047	057	.057	.066	.047	.047
				1	1	3	.104	.118	.118	.118	.105	.133
				1	2	4	.012	.017	.017	.024	.013	.078
				1	3	5	.001	.001	.001	.004	.001	.046
				2	3	4	.001	.012	.012	.018	.001	.200
				4	4	5	.001	.002	.002	.005	.001	.361

P-VALUES FOR UNCENSORED DATA

(continued)

ALPHA	BETA	U	C.V.	X0	X1	X2	** ASYMPTOTIC ** P	P1	ASY	EXACT	TARONE	C-A
3.797	148.08	.025	.5	0	2	3	.051	.083	.051	.052	.052	.047
				1	1	3	.119	.158	.119	.125	.119	.133
				1	2	4	.030	.054	.030	.034	.030	.078
				1	3	5	.006	.016	.006	.008	.006	.046
				2	3	4	.041	.068	.041	.041	.041	.200
				4	4	5	.031	.054	.031	.031	.031	.361
3.950	391.00	.01	.5	0	0	2	.058	.074	.075	.081	.058	.041
				0	1	2	.028	.040	.040	.045	.028	.077
				1	1	3	.007	.011	.012	.016	.007	.133
				5	5	3	.006	.010	.010	.008	.006	.761
1.750	173.00	.01	.75	0	0	2	.057	.088	.058	.077	.057	.041
				0	1	2	.041	.068	.042	.043	.041	.077
				1	1	3	.021	.040	.022	.029	.021	.133
				5	5	3	.067	.097	.068	.051	.067	.761

Table 4

SIMULATED SIGNIFICANCE LEVELS FOR APP AND APP1

APP-ASY = FULL VARIANCE
APP-ASY1 = VAR LESS QH(QH-QPRIME)W1**2 + PH(PH-PPRIME)W2**2
U = MEAN OF DIST'N C = SCALAR FOR CENSORED GROUP

					SIGNIFICANCE LEVEL					
					*** APP-ASY ****			*** APP-ASY1 ***		
ALPHA	BETA	U	C.V.	C	.050	.010	.005	.050	.010	.005
12.60	50.400	.2	.25	.33	.091	.027	.018	.055	.012	.006
				.5	.094	.027	.016	.051	.010	.003
				.8	.073	.021	.013	.042	.008	.004
				.9	.069	.018	.010	.037	.006	.004
5.655	28.106	.1675	.378	.33	.099	.043	.029	.053	.013	.007
				.5	.101	.039	.027	.060	.014	.009
				.8	.097	.036	.023	.051	.012	.006
				.9	.095	.033	.023	.050	.012	.007
12.87	63.968	.1675	.25	.5	.078	.022	.012	.048	.009	.004
3.096	15.387	.1675	.5	5	.141	.068	.049	.080	.026	.015
3.428	30.852	.1	.5	.5	.100	.036	.023	.054	.013	.007
3.674	69.806	.05	.5	.5	.071	.024	.014	.038	.008	.004
3.797	148.083	.025	.5	.5	.055	.014	.008	035	.005	.001
3 950	391.000	.01	.5	.33	.064	.015	.011	.047	.011	.004
				.5	.068	.019	.013	.041	.013	.007
				.8	.051	.013	.011	.040	.013	.006
				.9	.049	.015	.006	.039	.012	.006
1.750	173.000	.01	.75	.33	.065	.015	.008	.035	.005	.004
				.5	.063	.014	.006	.029	.006	.004
				.8	.044	.016	.006	.029	.005	.004
				.9	.040	.016	.005	.024	.004	.004

Table 5

Significance Levels For Several Tests

With At Most One Censored Group

alpha=5.655 beta=28.106

Tumor(s)/At Risk					APP-ASY			APP-EXACT	
Control	Dose1	Dose2	Scalar	Exact	Asy	P	P1	APP1	APP2
9/50	7/40	5/30	1.00						
	3/10	9/20	.33		.026	.026	.057	.016	.005
			.5		.036	.036	.073	.023	.011
			.8		.059	.059	.107	.045	.038
			.9		.069	.069	.120	.058	.053
9/50	10/50	14/50	1.0	.077	.080	.080	.133	.077	.077
4/25	5/20	6/20	1.0						
	0/5	1/5	.33	.062	.065	.065	.099	.055	.053
			.5	.071	.076	.076	.116	.064	.065
			.8	.092	.099	.099	.140	.085	.092
			.9	.099	.107	.107	.145	.094	.101
4/25	5/25	7/25	1.0	.112	.116	.116	.160	112	.112

Table 6

SIGNIFICANCE PROBABILITIES: ASYMPTOTIC & APPROXIMATE TESTS

Alpha = 3.95 Beta = 391 Mean = .01 C.V. = .495

At Risk : control 50
dose 1 10/40 scalar = .5
dose 2 20/30 scalar = .5

	TUMOR(S)			ASYMPTOTIC			APPROXIMATE	
Line #	Control	Dose1	Dose2	Asy	P	P1	APP1	APP2
1:	0	0/0	0/1	.272	.257	.272	.259	.296
2:	0	0/0	1/1	.043	.032	.043	.058	.044
3:	0	0/1	0/1	.144	.126	.144	.119	.140
4:	0	0/1	1/1	.037	.027	.037	.027	.022
5:	0	0/1	0/2	.019	.013	.019	.022	.029
6:	0	0/0	1/2	.004	.002	.004	.009	.008
7:	0	0/0	0/2	.042	.031	.042	.047	.059

Table 7

Significance Probabilities Of Selected Outcomes

For Asymptotic And Cochran-Armitage Tests

CONTROL	DOSE 1	DOSE 2		ASYMPTOTIC TEST					C-A TEST
			ALPHA	3.000	4.176	2.784	3.024	2.016	
			BETA	12.00	13.82	9.22	14.98	9.98	
			MEAN	.200	.232	.232	.168	.168	
			C.V.	.495	.413	.500	.505	.611	
2	2	9		.041	.076	.042	.036	.023	.006
2	2	11		.011	.022	.011	.009	.005	.001
2	6	9		.047	.077	.049	.039	.029	.014
2	6	11		.013	.024	.014	.011	.008	.003
2	11	9		.050	.074	.055	.041	.035	.024
2	11	10		.029	.044	.032	.023	.020	.013
11	8	19		.029	.037	.035	.021	.024	.033
11	8	21		.010	.013	.012	.007	.008	.012
11	16	18		.042	.049	.053	.030	038	.063
11	16	20		.015	.019	.021	.011	.014	.026
11	21	17		.059	.066	.075	.043	.056	.100
11	21	20		.014	.016	.019	.009	.013	.029
11	21	21		.008	.009	.012	.005	.008	.018
21	18	27		.038	.039	.055	.025	.041	.113
21	18	29		.015	.015	.022	.009	.016	.054
21	18	30		.009	.009	.014	.005	.009	.036
21	21	27		.035	.035	.051	.022	.038	.114
21	21	29		.013	.013	.021	.008	.015	.055
21	21	30		.008	008	.012	.004	.009	.036
21	25	26		.049	.046	.069	.030	.053	.159
21	25	29		.011	.011	.018	.006	.013	.055

Table 8

Significance Probabilities Of Selected Outcomes

For Asymptotic And Cochran-Armitage Tests

CONTROL	DOSE 1	DOSE 2		ASYMPTOTIC TEST					C-A TEST
			ALPHA	3.950	6.635	4.423	2.844	1.896	
			BETA	391.0	467.3	311.5	471.1	314.1	
			MEAN	.010	.014	.014	.006	.006	
			C.V.	.495	.381	.467	.585	.716	
0	0	2		.075	.155	.149	.025	.029	.041
0	0	3		.010	.033	.035	.002	.003	.016
0	1	2		.040	.090	.095	.012	.017	.077
0	1	3		.005	.017	.021	.001	.002	.031
0	2	2		.022	.050	.060	.005	.010	.107
0	2	3		.003	.009	.013	.000	.001	.047
1	1	2		.068	.122	.140	.025	.040	.267
1	1	3		.012	.027	.038	.003	.006	.133
1	1	4		.001	.004	.009	.000	.001	.063
1	2	2		.038	.072	.092	.012	.024	.289
1	2	3		.006	.015	024	.001	.004	.157
2	0	3		.038	.072	.092	.012	.024	.289
2	0	4		.006	.015	.024	.001	.004	.154
2	1	3		.021	.041	.060	.006	.015	.305
2	1	4		.003	.008	.015	.001	.002	.172
2	3	2		.035	.058	.088	.012	.028	.500
2	3	3		.006	.012	.025	.001	.005	.328
2	4	2		.020	.033	.058	.006	.017	.500
2	4	3		.003	.007	.016	.001	.003	.337

Table 9

Estimated Beta-Binomial Parameters

(a) For Thyroid I[1] Tumors in Male Fisher 344 Rats

(i) Conditional estimates:

$\theta = .0175$, $\alpha = 2.9807$ (3.19)[2], $\beta = 167.4543$ (179.28)

$\alpha + \beta = 170.44$ (185.02)

95% confidence interval of θ: parameteric = (.0113, .0236); nonparametric = (.0114, .0236)

95% confidence interval of $\alpha + \beta$ = (21.77, 1334.06)

(ii) Unconditional estimates:

$\theta = .0174$, $\alpha = 2.9541$ (3.13), $\beta = 167.1140$ (178.39)

$\alpha + \beta = 170.07$ (181.47)

95% confidence interval of θ = (.0112, .0235)

95% confidence interval of $\alpha + \beta$ = (21.01, 1376.91)

(b) For Thyroid II[3] Tumors in Male Fisher 344 Rats

(i) Conditional estimates:

$\theta = .0879$, $\alpha = 8.1127$ (4.89), $\beta = 84.1904$ (50.76)

$\alpha + \beta = 92.30$ (56.19)

95% confidence interval of θ: parametric = (.0734, .1024); nonparametric = (.0833, .1025)

95% confidence interval of $\alpha + \beta$ = (28.32, 300.88)

---

[1] All thyroid tumors except adenoma, c-cell adenoma and c-cell carcinoma.

[2] ( ) standard deviation.

[3] c-cell adenoma and c-cell carcinoma.

Estimated Beta-Binomial Parameters

(continued)

(b) For Thyroid II Tumors in Male Fisher 344 Rats

(ii) Unconditional estiamtes:

θ = .0886, α = 8.1145 (4.89), β = 83.4606 (50.97)

$\alpha + \beta$ = 91.58 (55.81)

95% confidence interval of θ = (.0740, .1032)

95% confidence interval at $\alpha + \beta$ = (27.73, 302.37)

(c) All Lymphomas and Leukemias in Female Fisher 344 Rats

(i) Conditional estiamtes:

θ = .1980, α = 15.7621 (8.87), β = 67.6221 (38.05)

$\alpha + \beta$ = 83.38 (47.14)

95% confidence interval of θ — parametric = (.1691, .2089)

nonparametric = (.1690, .2091)

95% confidence interval of $\alpha + \beta$ = (27.69, 251.13)

(ii) Unconditional estiamtes:

θ = .1889, α = 15.7294 (8.83), β = 65.5346 (38.06)

$\alpha + \beta$ = 83.26 (46.84)

95% confidence interval of θ = (.1690, .2088)

95% confidence interval of $\alpha + \beta$ = (27.64, 250.82)

FIGURE LEGEND

Fig. A.B.C.

A = 1-8 Simulated distribution (10,000 simulations), of the asymptotic statistic and a standard distribution.

A	ALPHA	BETA	MEAN
1	5.655	28.106	.1675
2	12.871	63.968	.1675
3	3.096	15.387	.1675
4	3.428	30.852	.10
5	3.674	69.806	.05
6	3.797	148.083	.025
7	3.95	391	.01
8	3	12	.20

.B = Scalar used in censored group

C = 0 full variance used APP-ASY

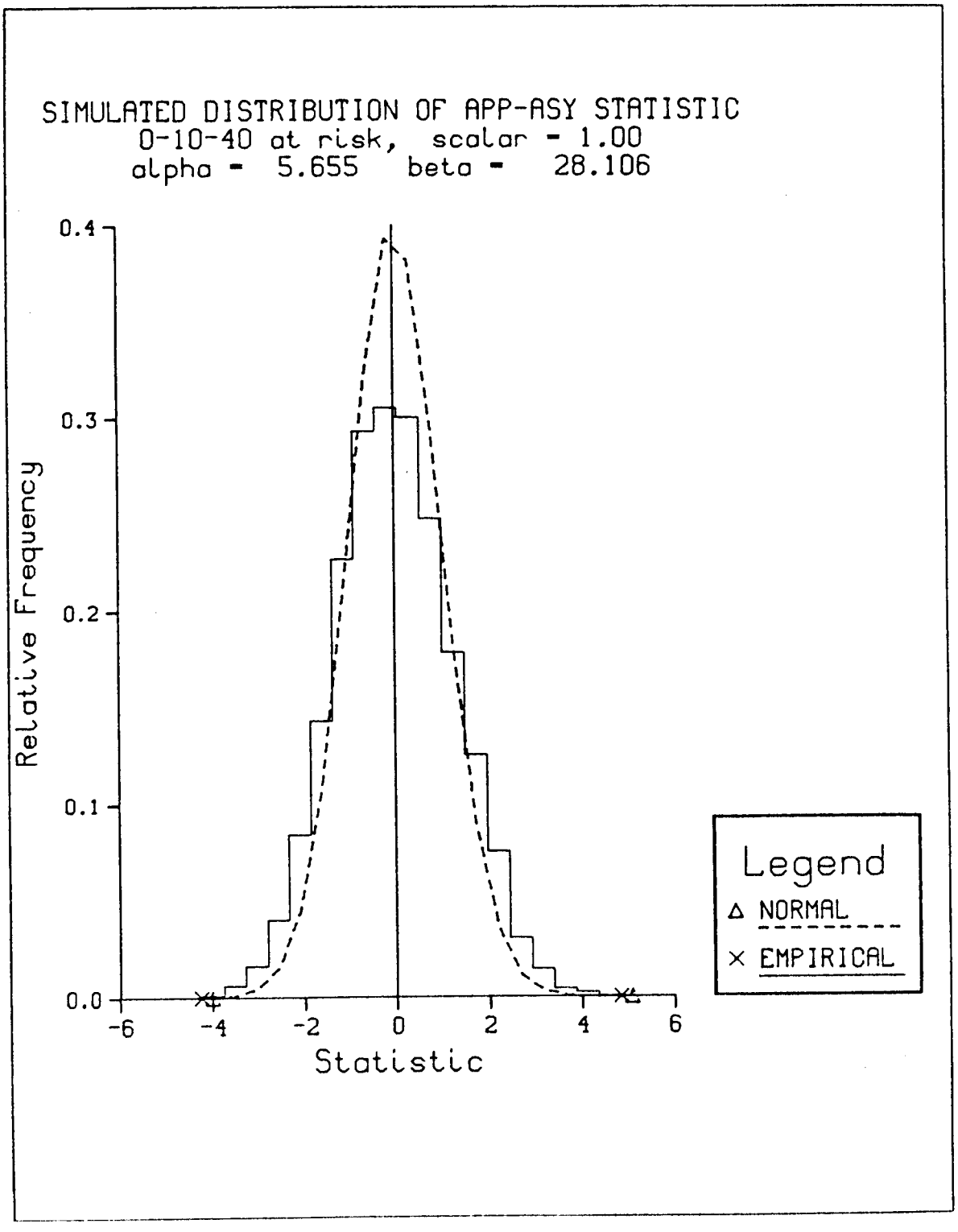
= 1 only positive terms used APP-ASY1

A = 9, 10, 11 Weibull distribution modeling the probability of response prior to full-term

A	Probability at Full-Term
9	.01
10	.006
11	.1675

B	Shape Parameter
1	.21
2	1.0
3	2.0
4	5.0

Fig. 1.10


SIMULATED DISTRIBUTION OF APP-ASY STATISTIC
0-10-40 at risk, scalar - 1.00
alpha - 5.655 beta - 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-6
-4
-2
0
2
4
6
Statistic
Legend
NORMAL
EMPIRICAL

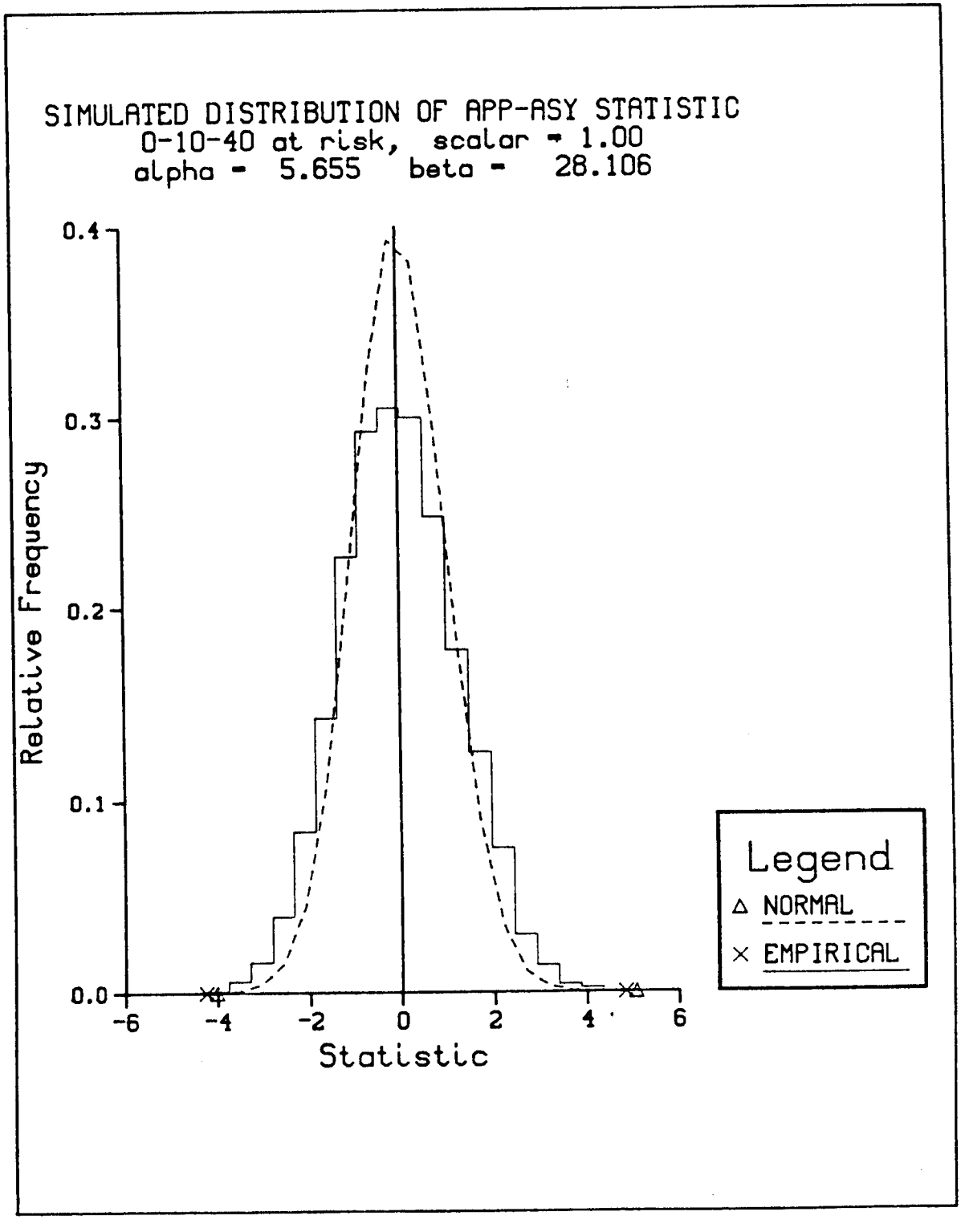

SIMULATED DISTRIBUTION OF APP-ASY STATISTIC
0-10-40 at risk, scalar = 1.00
alpha = 5.655 beta = 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-6
-4
-2
0
2
4
6
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 1.9.0

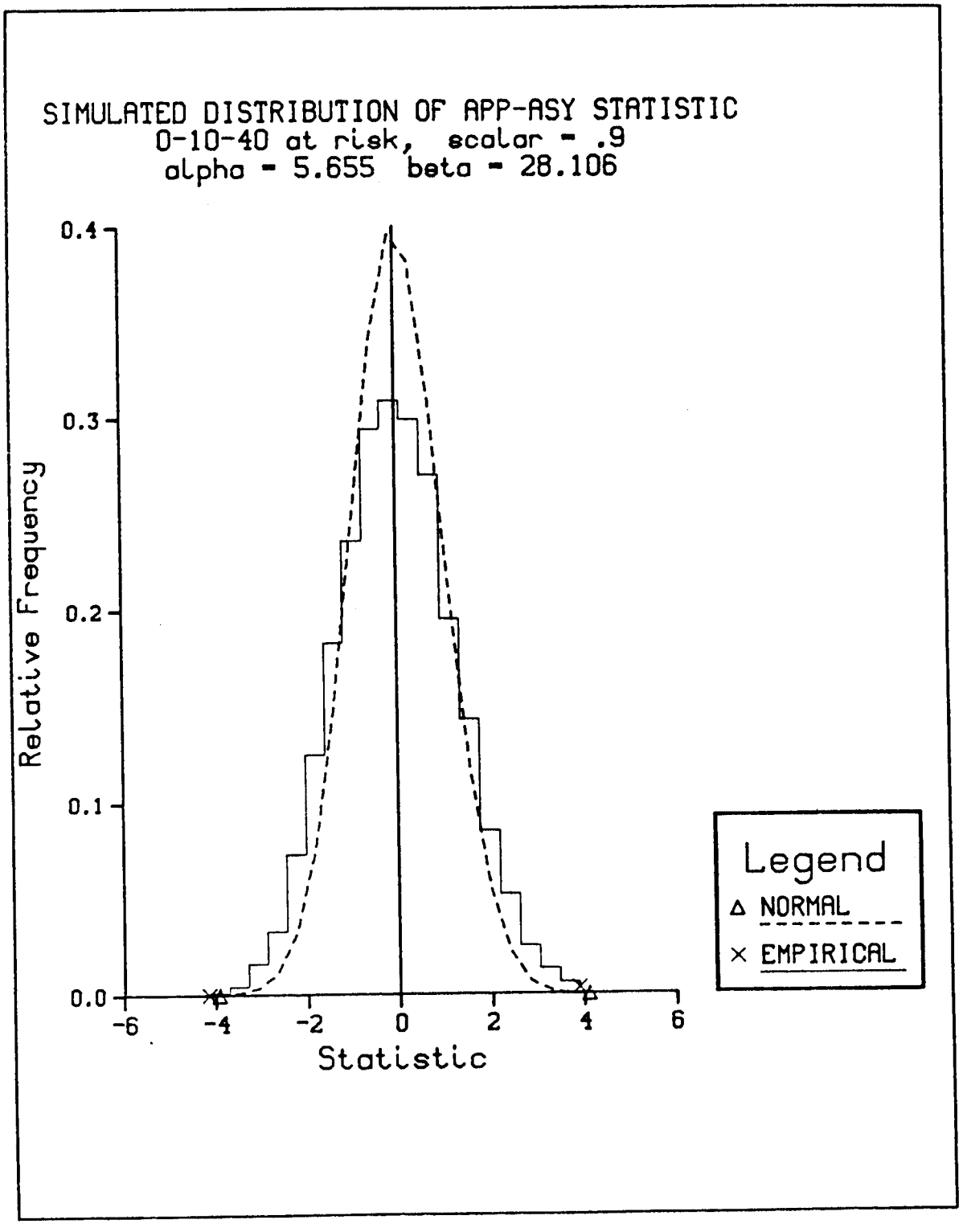

SIMULATED DISTRIBUTION OF APP-ASY STATISTIC
0-10-40 at risk, scalar = .9
alpha = 5.655 beta = 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-6
-4
-2
0
2
4
6
Statistic
Legend
Δ NORMAL
× EMPIRICAL

Fig. 1.8.0

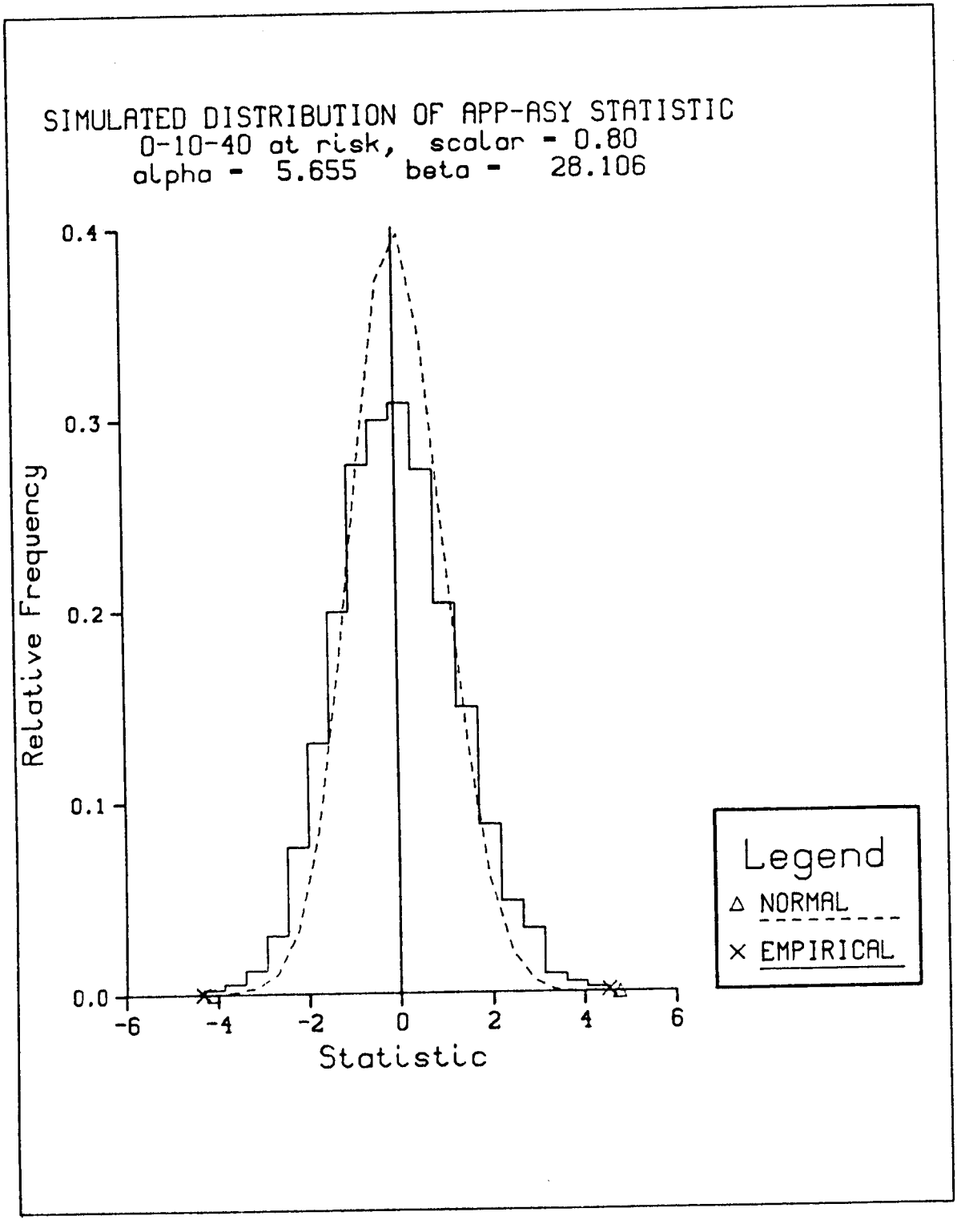

SIMULATED DISTRIBUTION OF APP-ASY STATISTIC
0-10-40 at risk, scalar = 0.80
alpha = 5.655 beta = 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-6
-4
-2
0
2
4
6
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 1.5.0

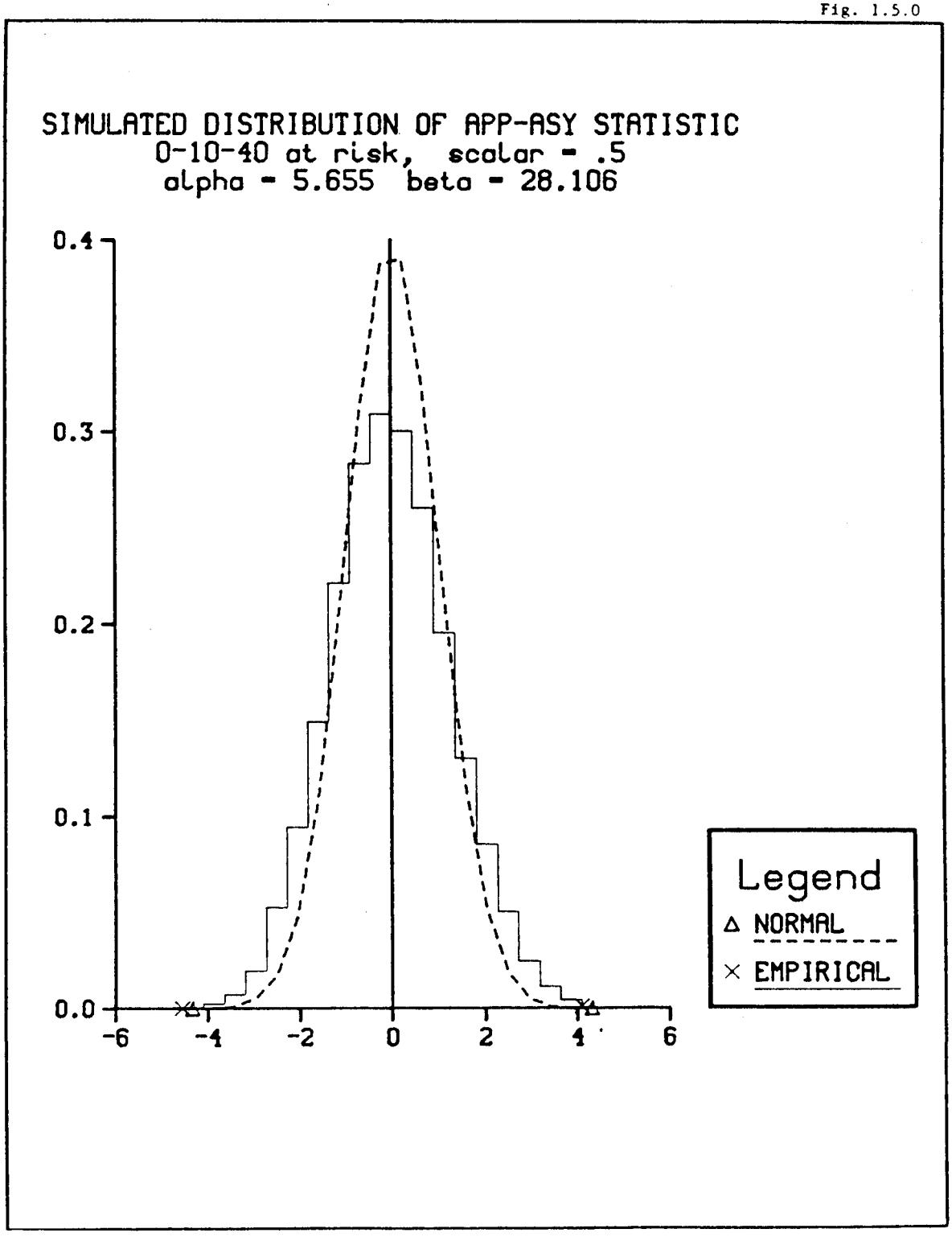

SIMULATED DISTRIBUTION OF APP-ASY STATISTIC
0-10-40 at risk, scalar = .5
alpha = 5.655 beta = 28.106
0.4
0.3
0.2
0.1
0.0
-6
-4
-2
0
2
4
6
Legend
NORMAL
EMPIRICAL

Fig. 1.3.0

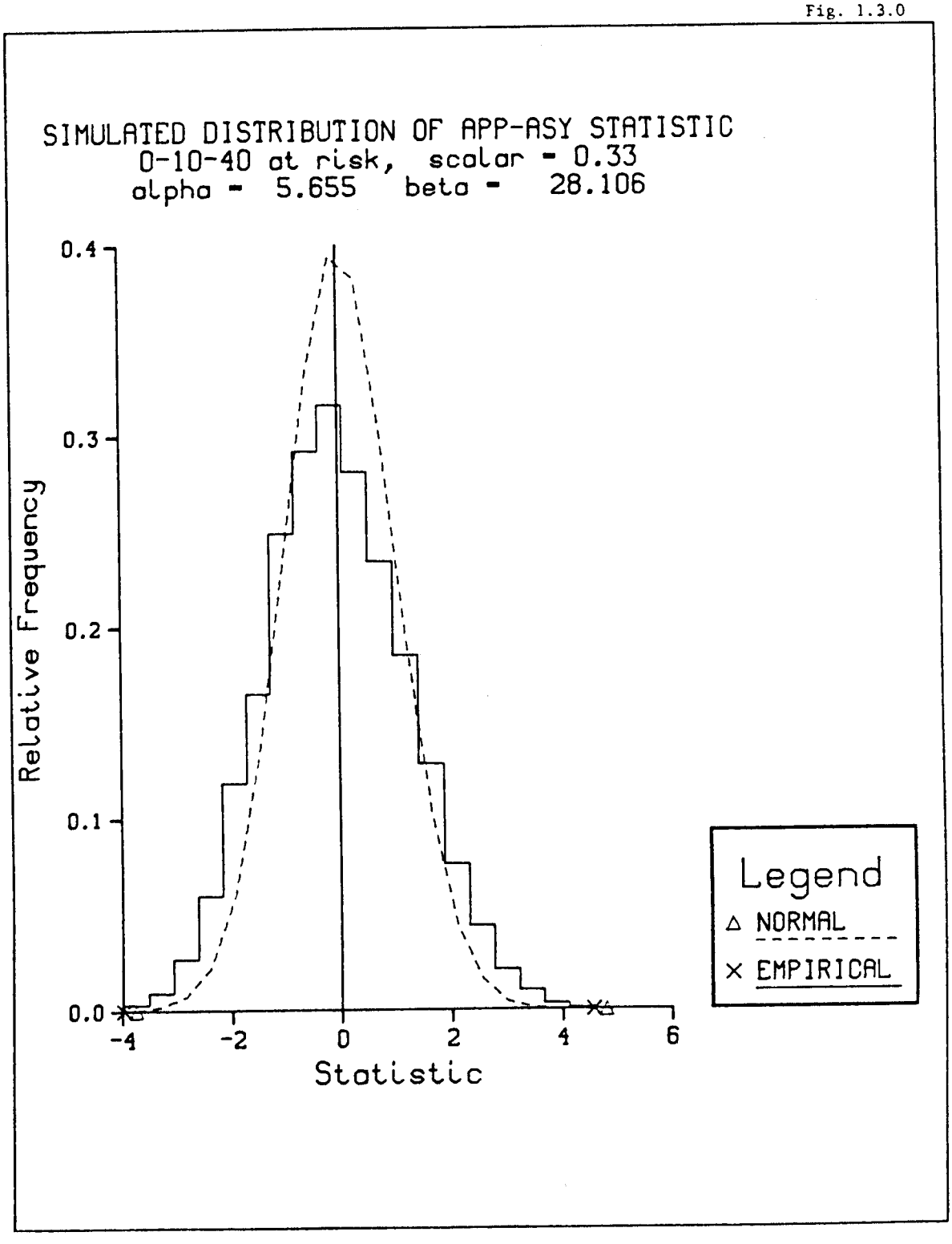

SIMULATED DISTRIBUTION OF APP-ASY STATISTIC
0-10-40 at risk, scalar = 0.33
alpha = 5.655 beta = 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
6
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 1.1.1

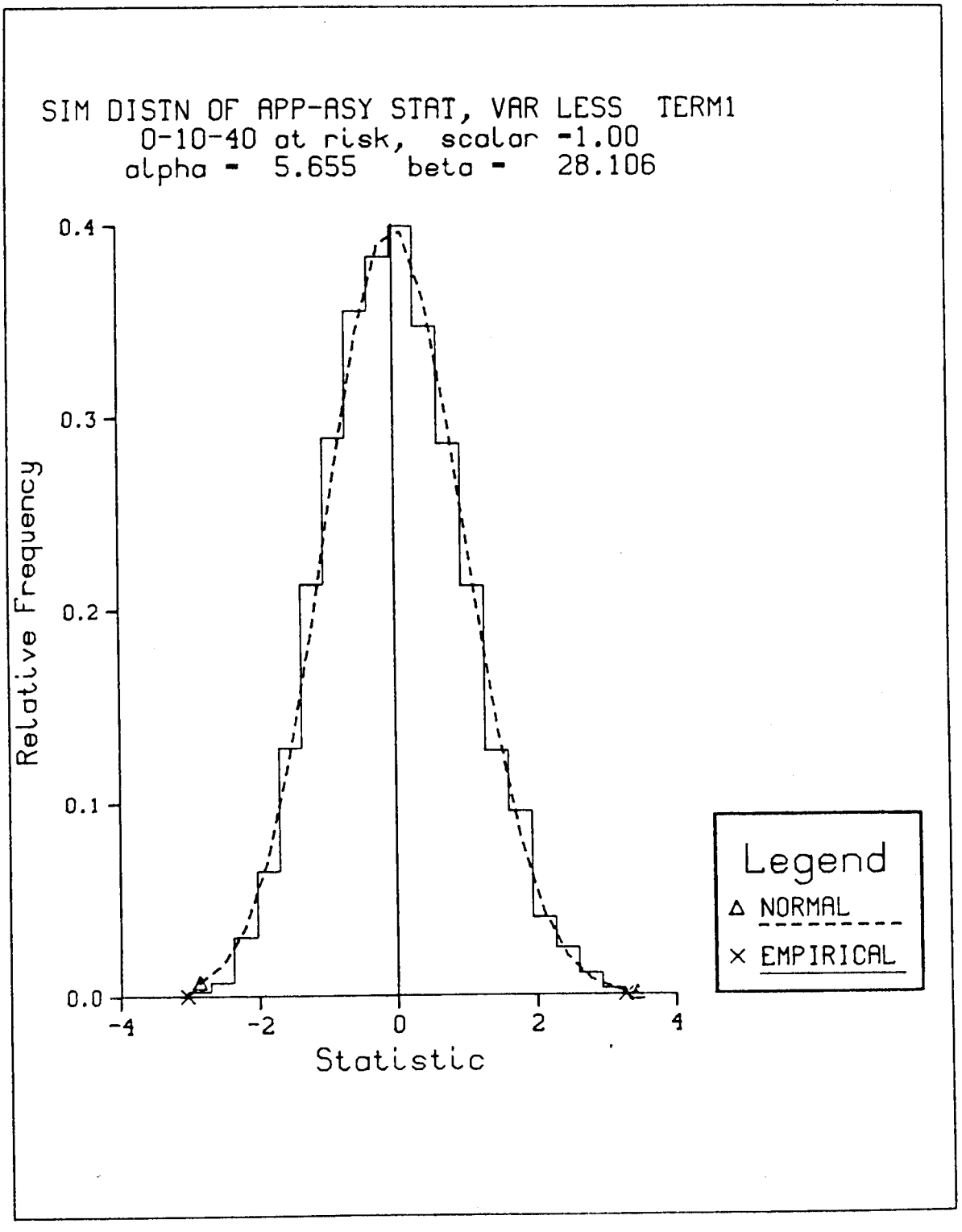

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar -1.00
alpha = 5.655 beta = 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 1.9.1

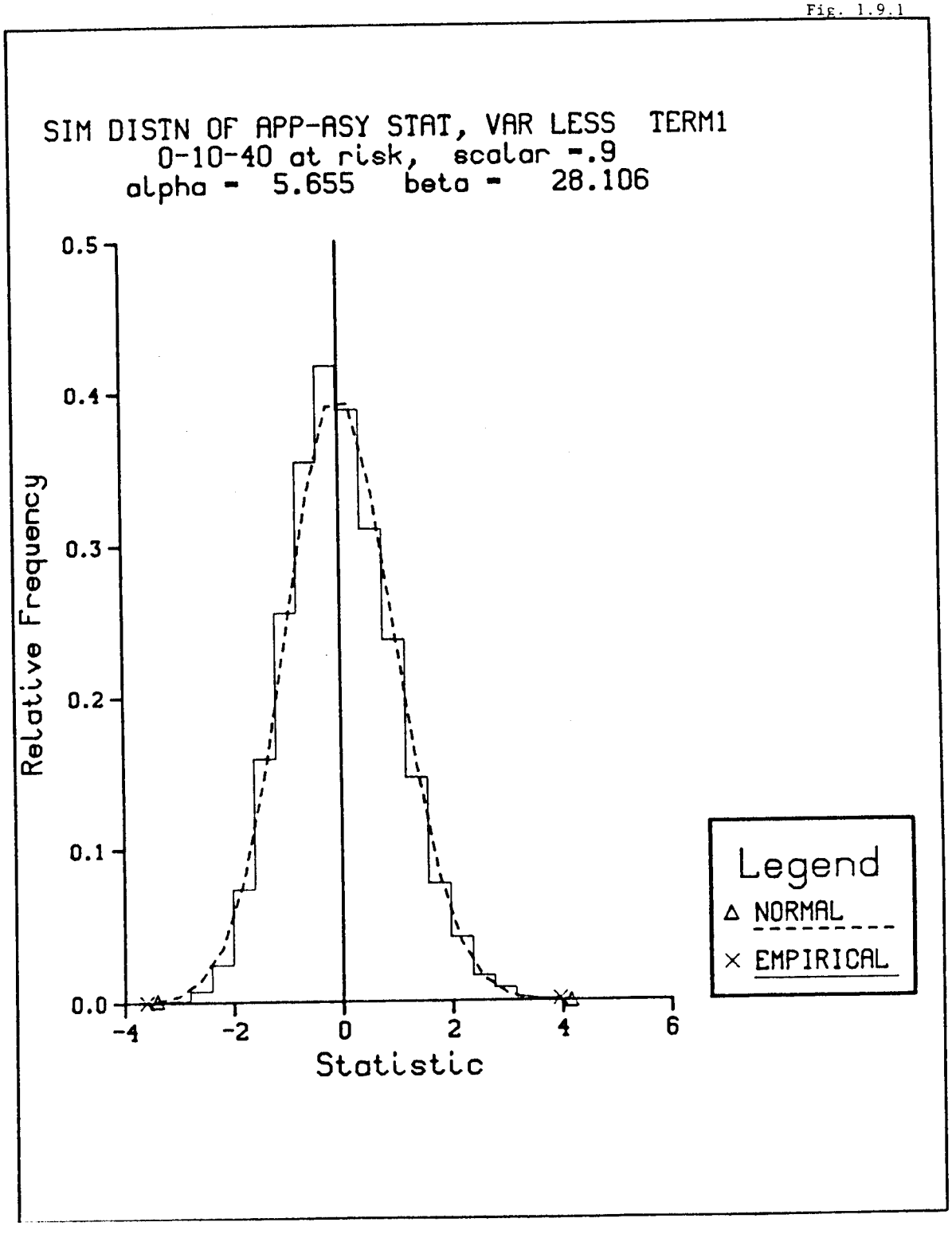

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar =.9
alpha = 5.655 beta = 28.106
Relative Frequency
0.5
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
6
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 1.8.1

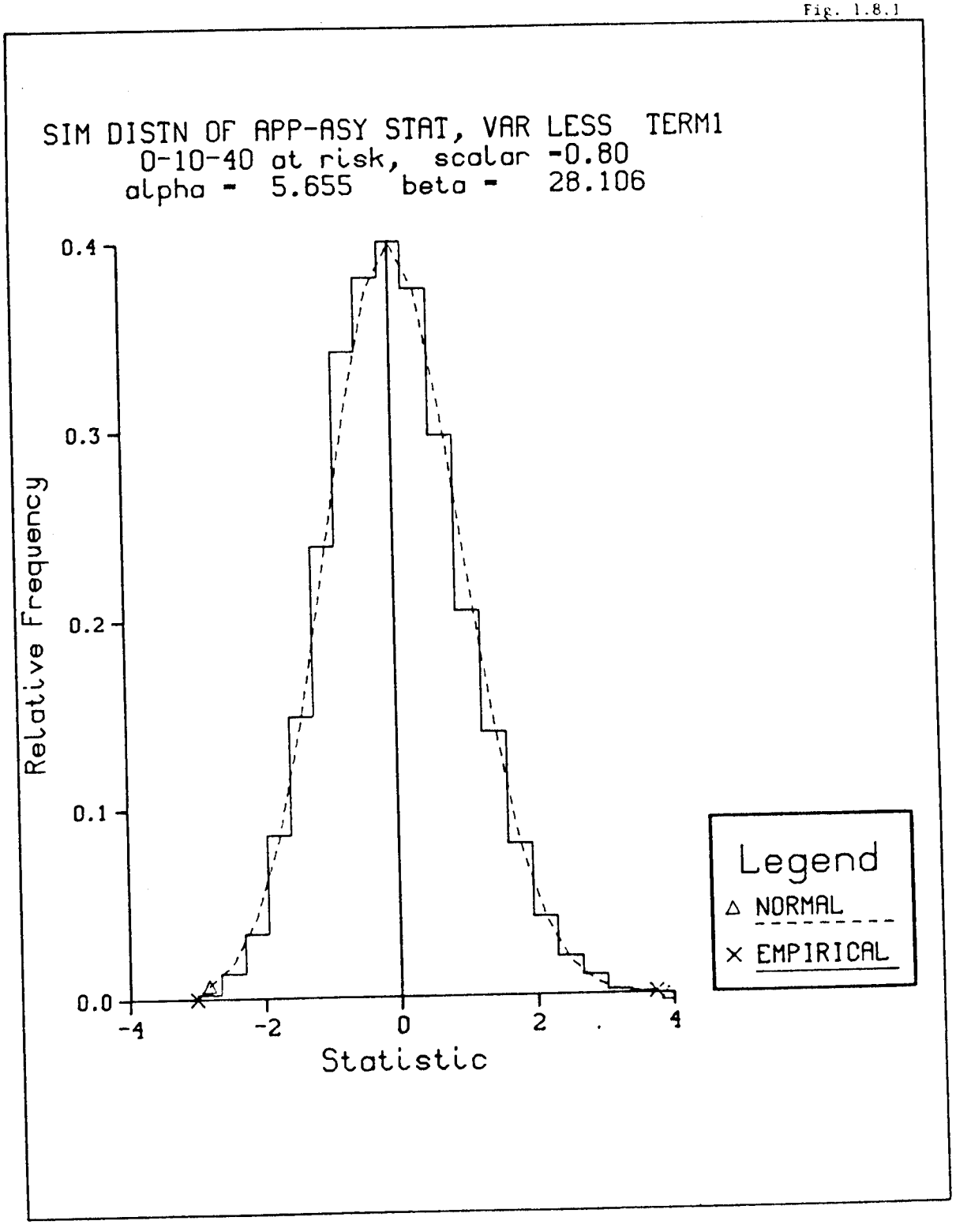

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar -0.80
alpha - 5.655 beta - 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 1.5.1

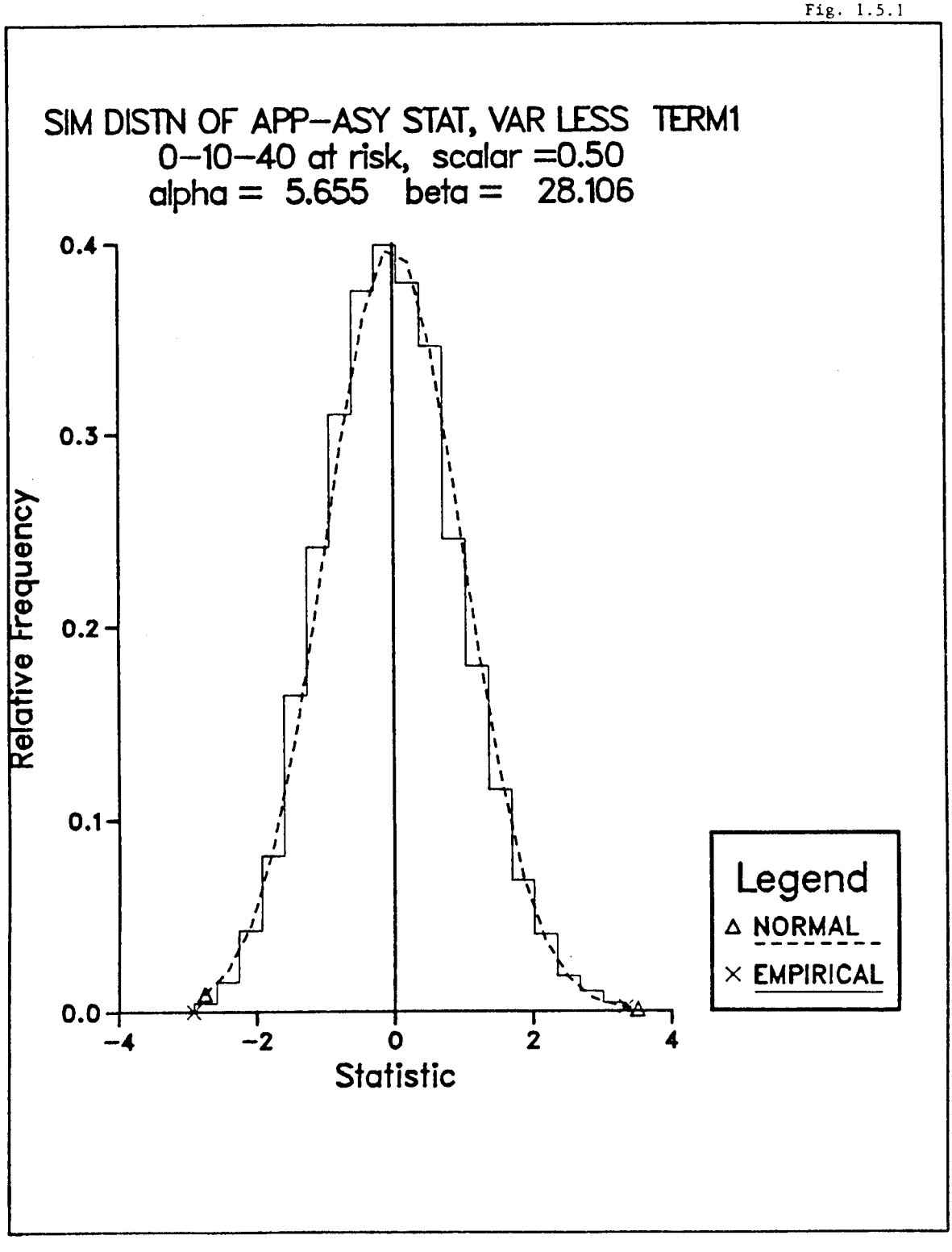

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar =0.50
alpha = 5.655 beta = 28.106
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 1.3.1

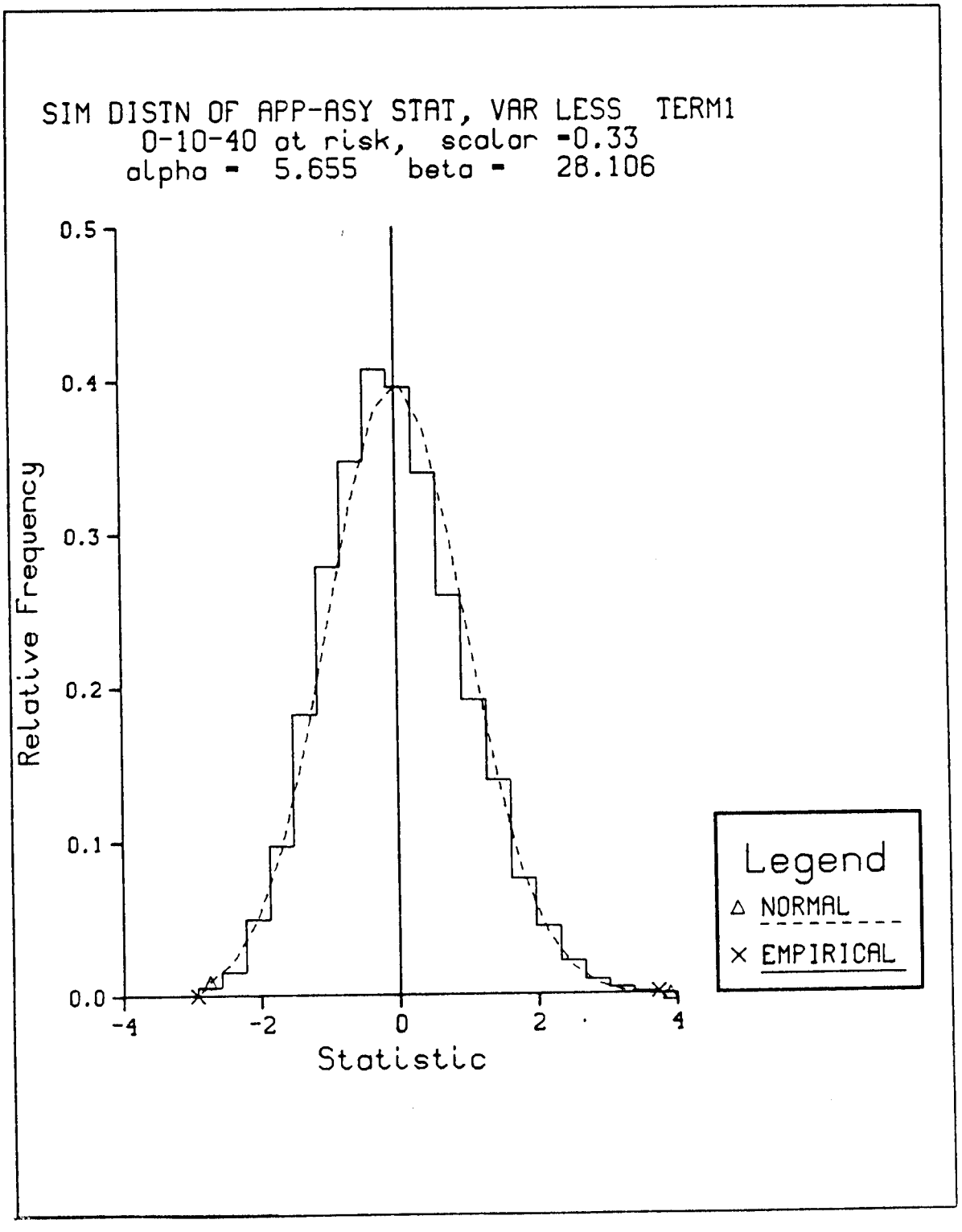

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar =0.33
alpha = 5.655 beta = 28.106
Relative Frequency
0.5
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 2.5.0

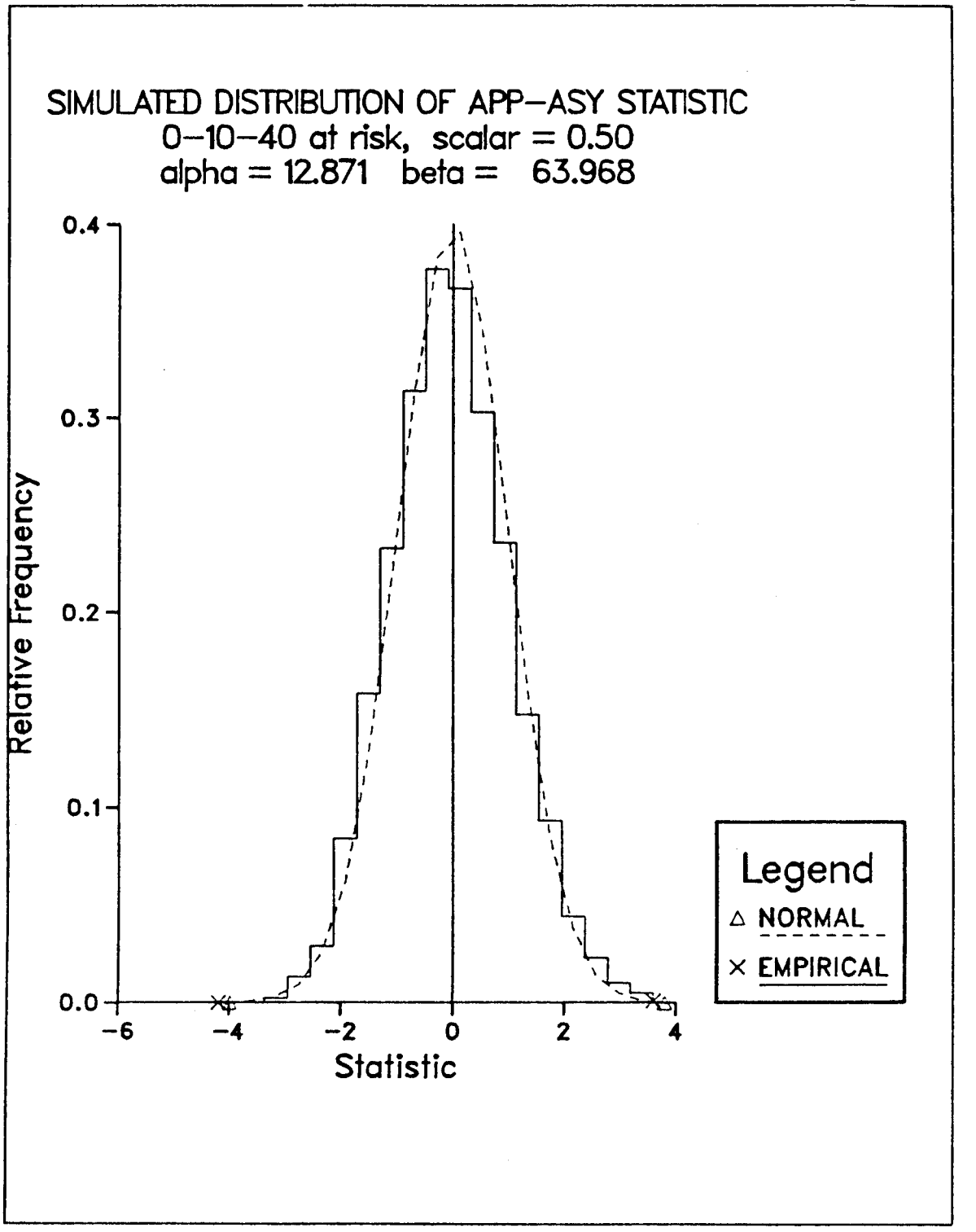

SIMULATED DISTRIBUTION OF APP–ASY STATISTIC
0–10–40 at risk, scalar = 0.50
alpha = 12.871 beta = 63.968
Relative Frequency
0.4
0.3
0.2
0.1
0.0
−6
−4
−2
0
2
4
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 2.5.1

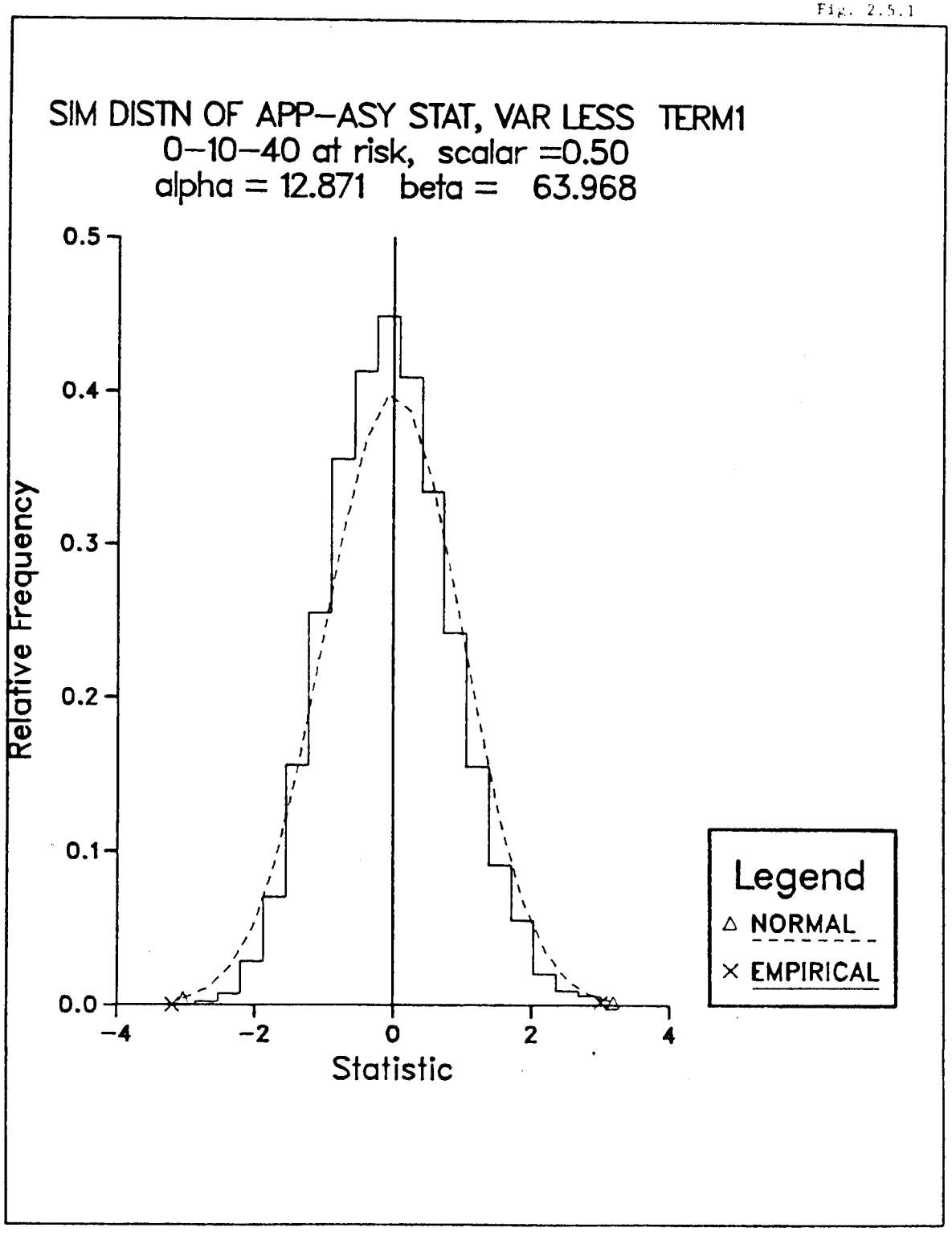

SIM DISTN OF APP–ASY STAT, VAR LESS TERM1
0–10–40 at risk, scalar =0.50
alpha = 12.871 beta = 63.968
Relative Frequency
0.5
0.4
0.3
0.2
0.1
0.0
–4
–2
0
2
4
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 3.5.0

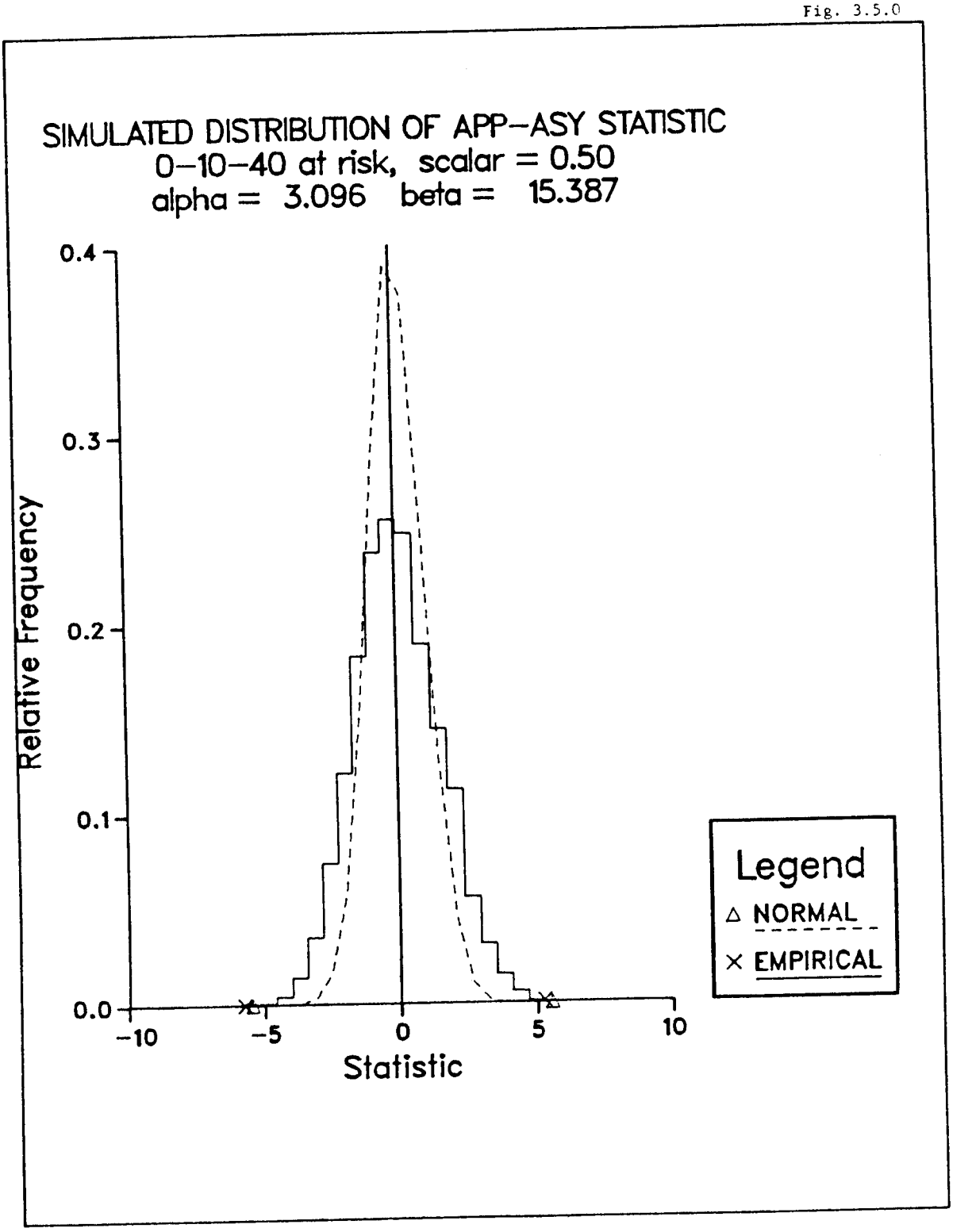

SIMULATED DISTRIBUTION OF APP–ASY STATISTIC
0–10–40 at risk, scalar = 0.50
alpha = 3.096 beta = 15.387
Relative Frequency
0.4
0.3
0.2
0.1
0.0
−10
−5
0
5
10
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 3.5.1

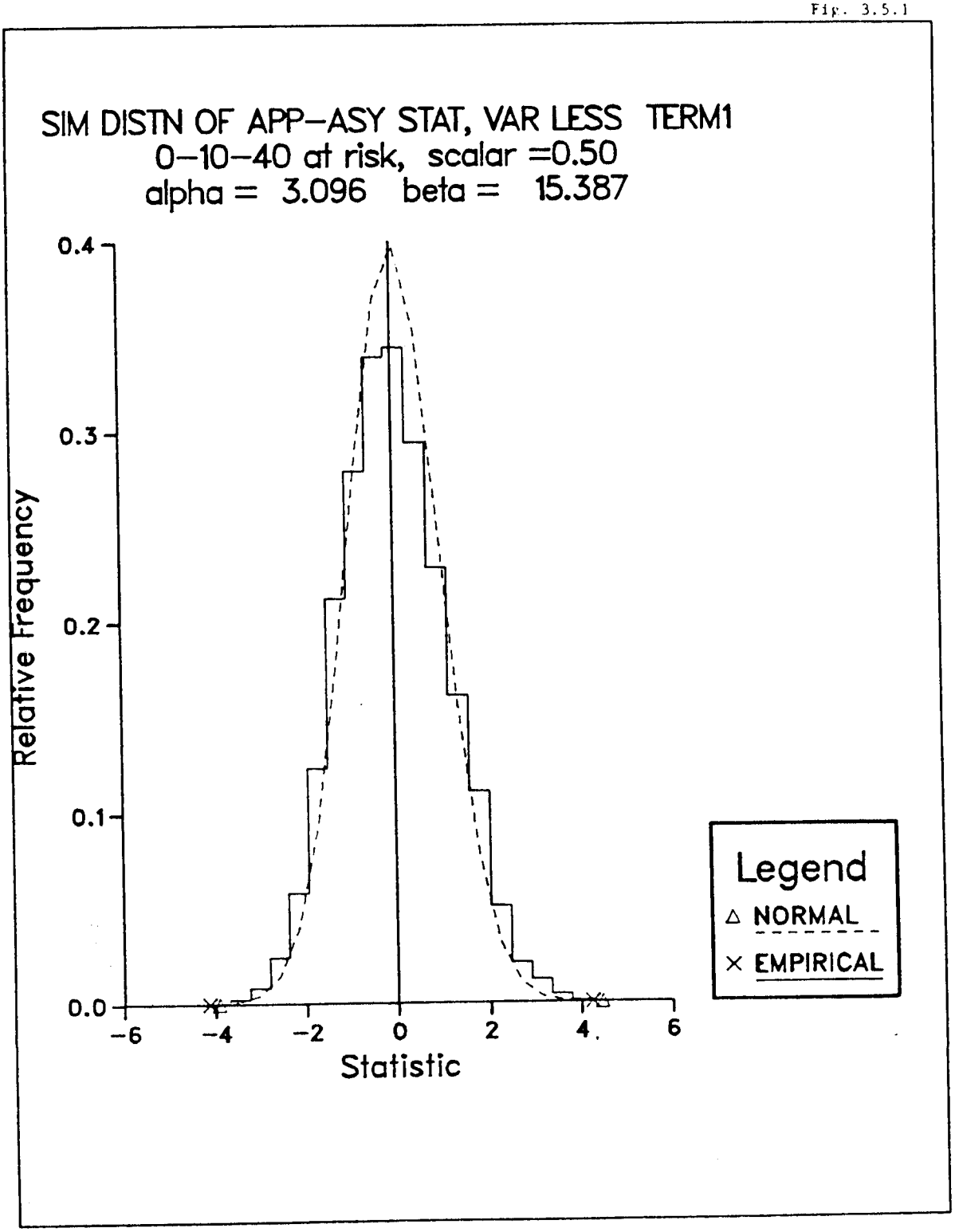

SIM DISTN OF APP–ASY STAT, VAR LESS TERM1
0–10–40 at risk, scalar =0.50
alpha = 3.096 beta = 15.387
Relative Frequency
0.4
0.3
0.2
0.1
0.0
–6
–4
–2
0
2
4
6
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 4.5.0

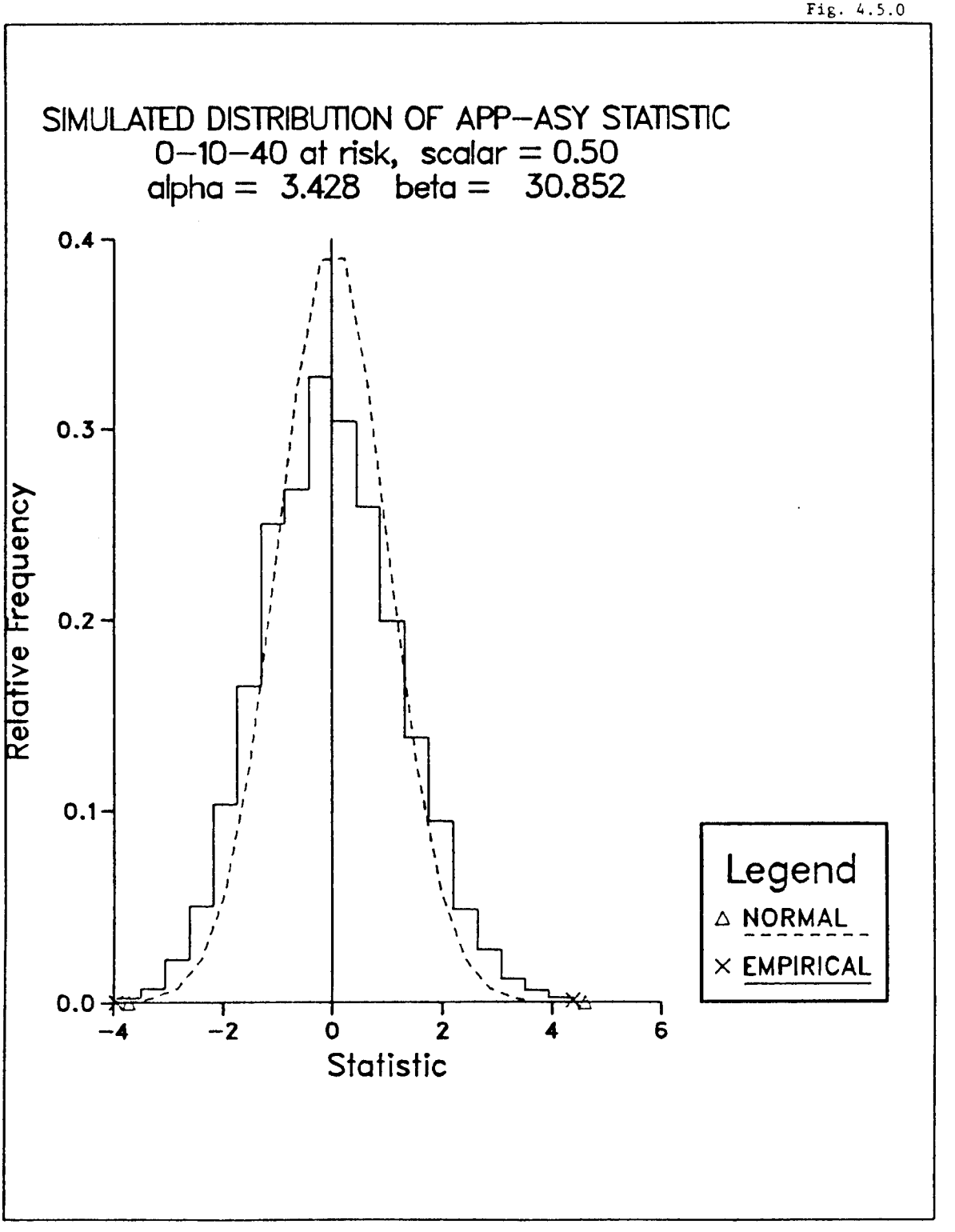

SIMULATED DISTRIBUTION OF APP–ASY STATISTIC
0–10–40 at risk, scalar = 0.50
alpha = 3.428 beta = 30.852
Relative Frequency
0.4
0.3
0.2
0.1
0.0
−4
−2
0
2
4
6
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 4.5.1

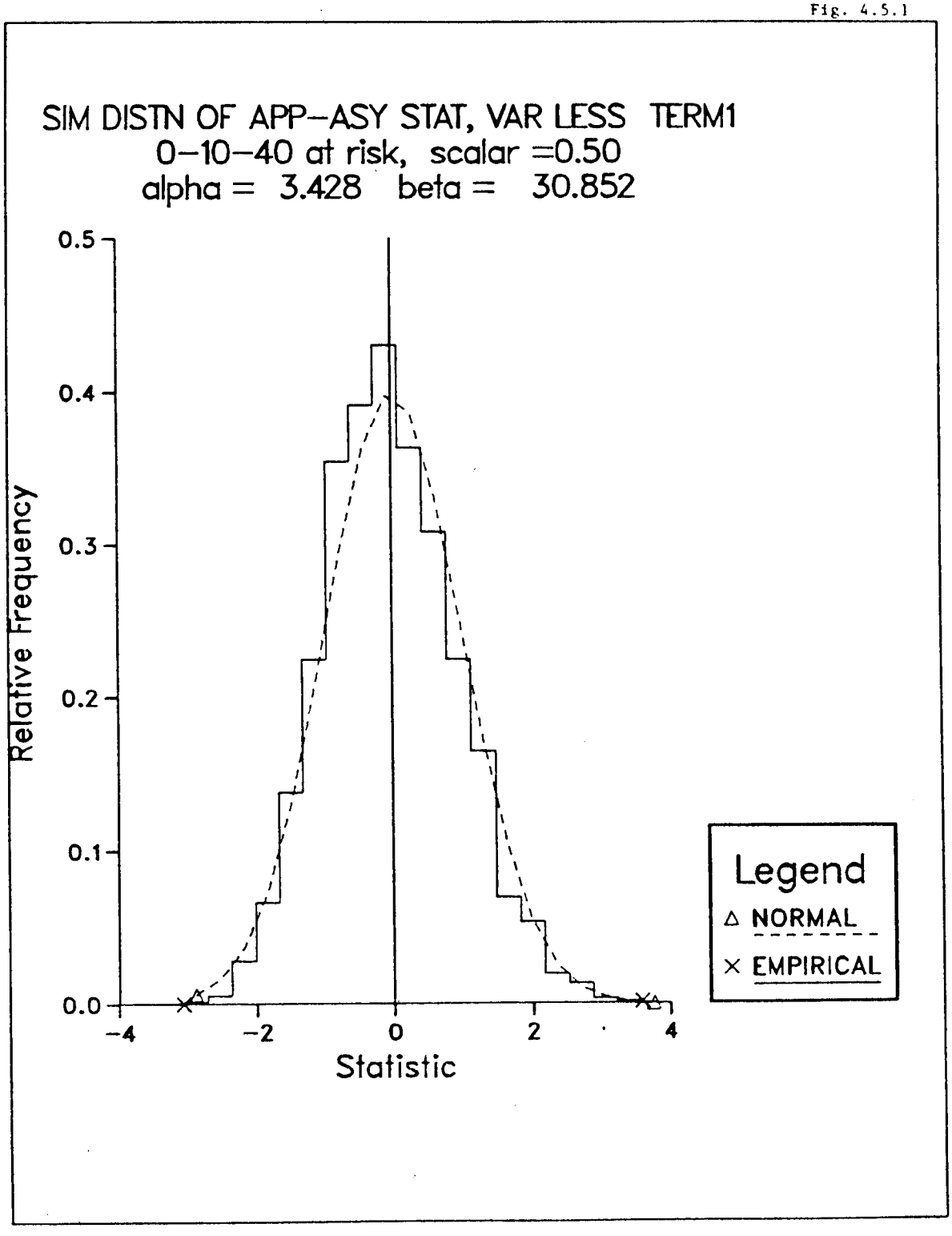

SIM DISTN OF APP–ASY STAT, VAR LESS TERM1
0–10–40 at risk, scalar =0.50
alpha = 3.428 beta = 30.852
Relative Frequency
0.5
0.4
0.3
0.2
0.1
0.0
−4
−2
0
2
4
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 5.5.0-N

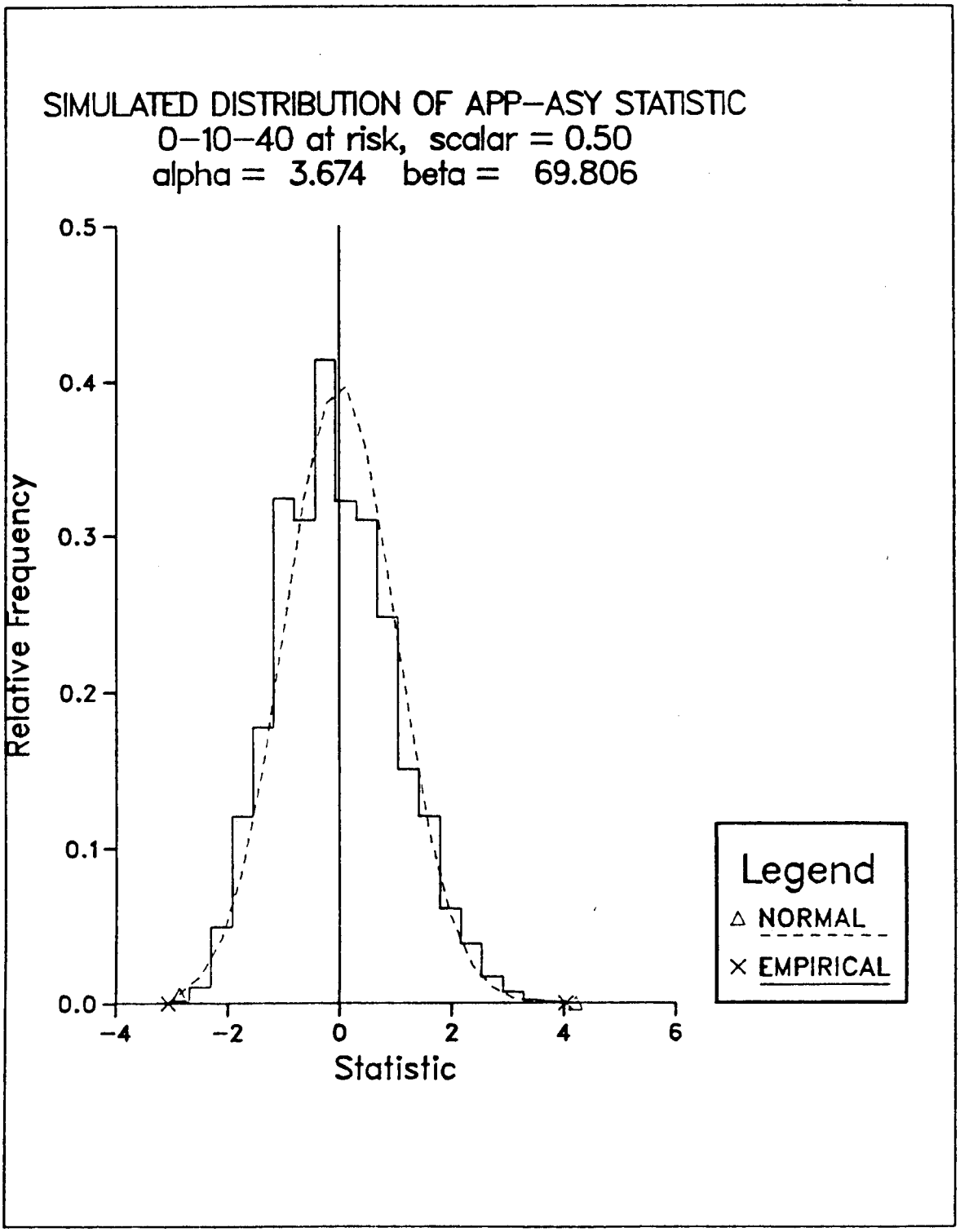

SIMULATED DISTRIBUTION OF APP–ASY STATISTIC
0–10–40 at risk, scalar = 0.50
alpha = 3.674 beta = 69.806
Relative Frequency
0.5
0.4
0.3
0.2
0.1
0.0
–4
–2
0
2
4
6
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 5.5.1-N

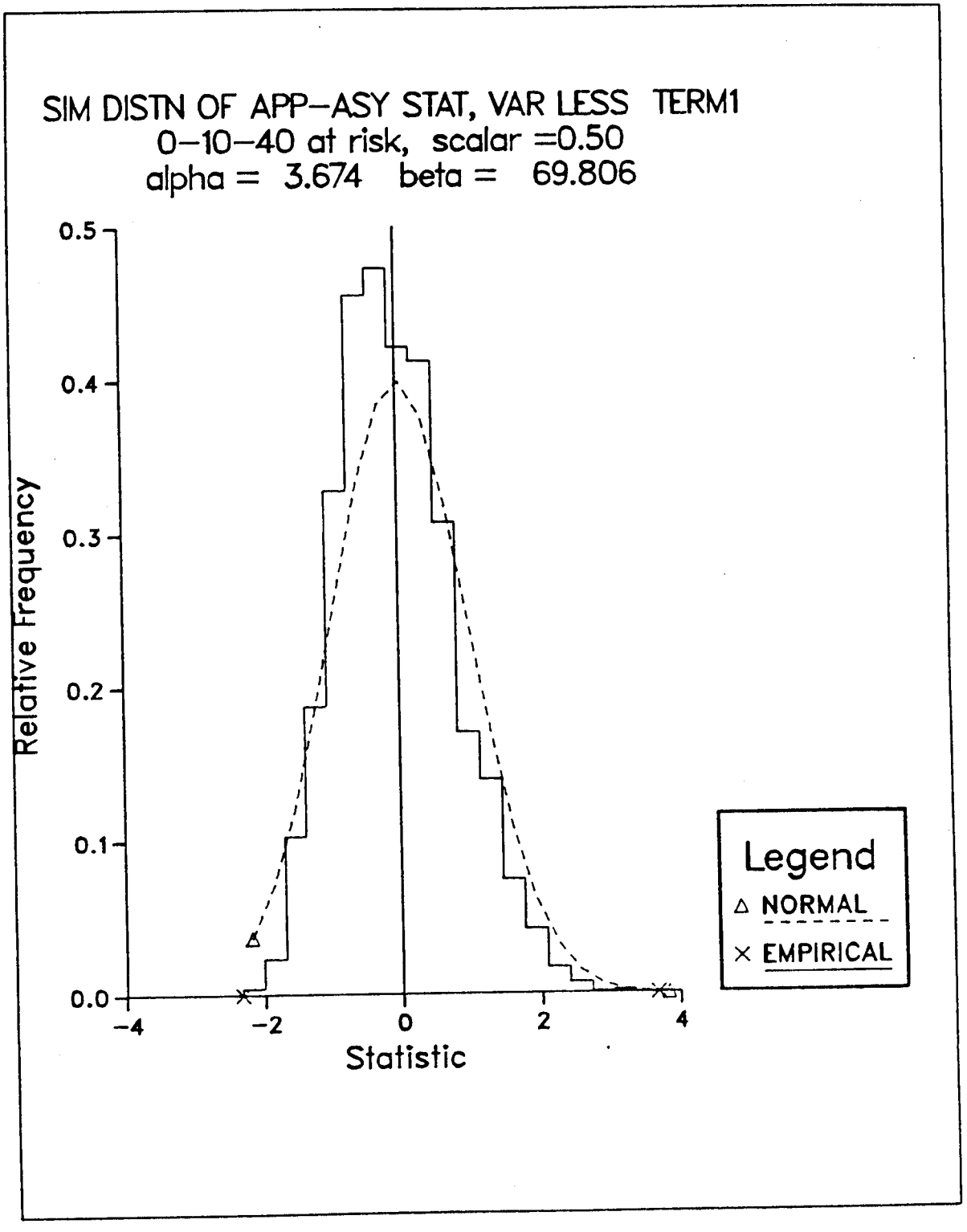

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar =0.50
alpha = 3.674 beta = 69.806
Relative Frequency
0.5
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 5.5.0-C

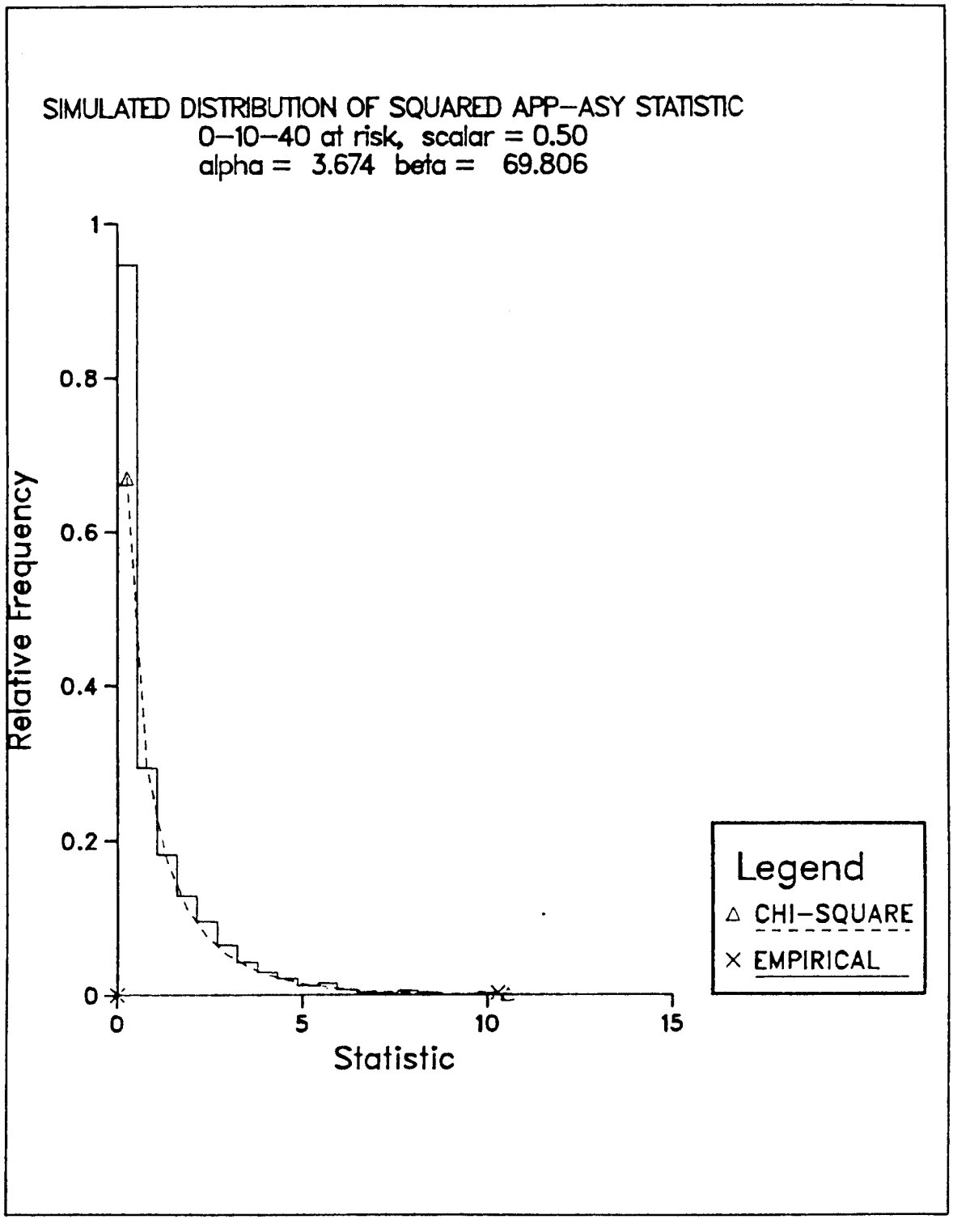

SIMULATED DISTRIBUTION OF SQUARED APP-ASY STATISTIC
0-10-40 at risk, scalar = 0.50
alpha = 3.674 beta = 69.806
Relative Frequency
1
0.8
0.6
0.4
0.2
0
0
5
10
15
Statistic
Legend
CHI-SQUARE
EMPIRICAL

Fig. 5.5.1-C

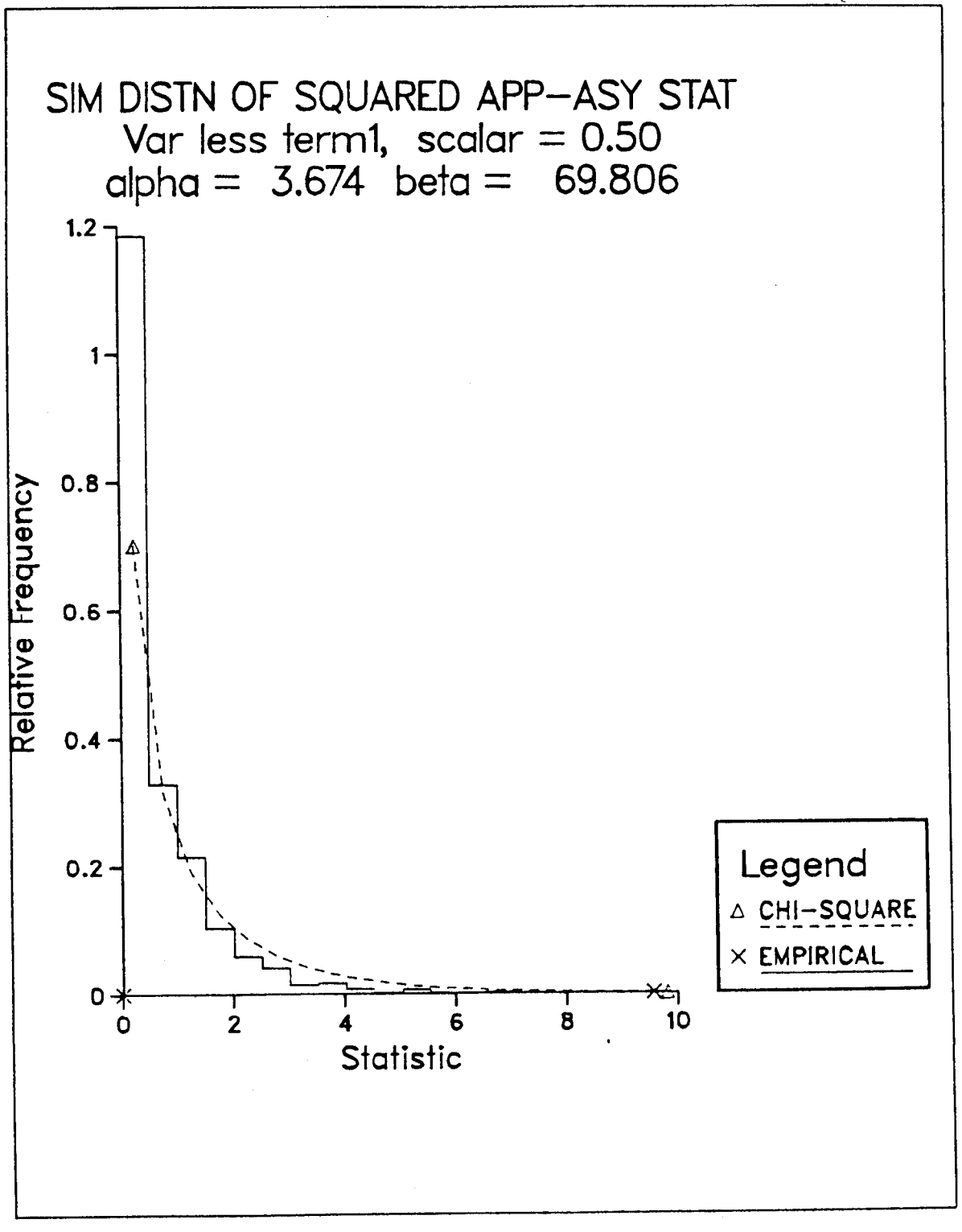

SIM DISTN OF SQUARED APP-ASY STAT
Var less term1, scalar = 0.50
alpha = 3.674 beta = 69.806
Relative Frequency
1.2
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Statistic
Legend
CHI-SQUARE
EMPIRICAL

Fig. 6.5.0-N

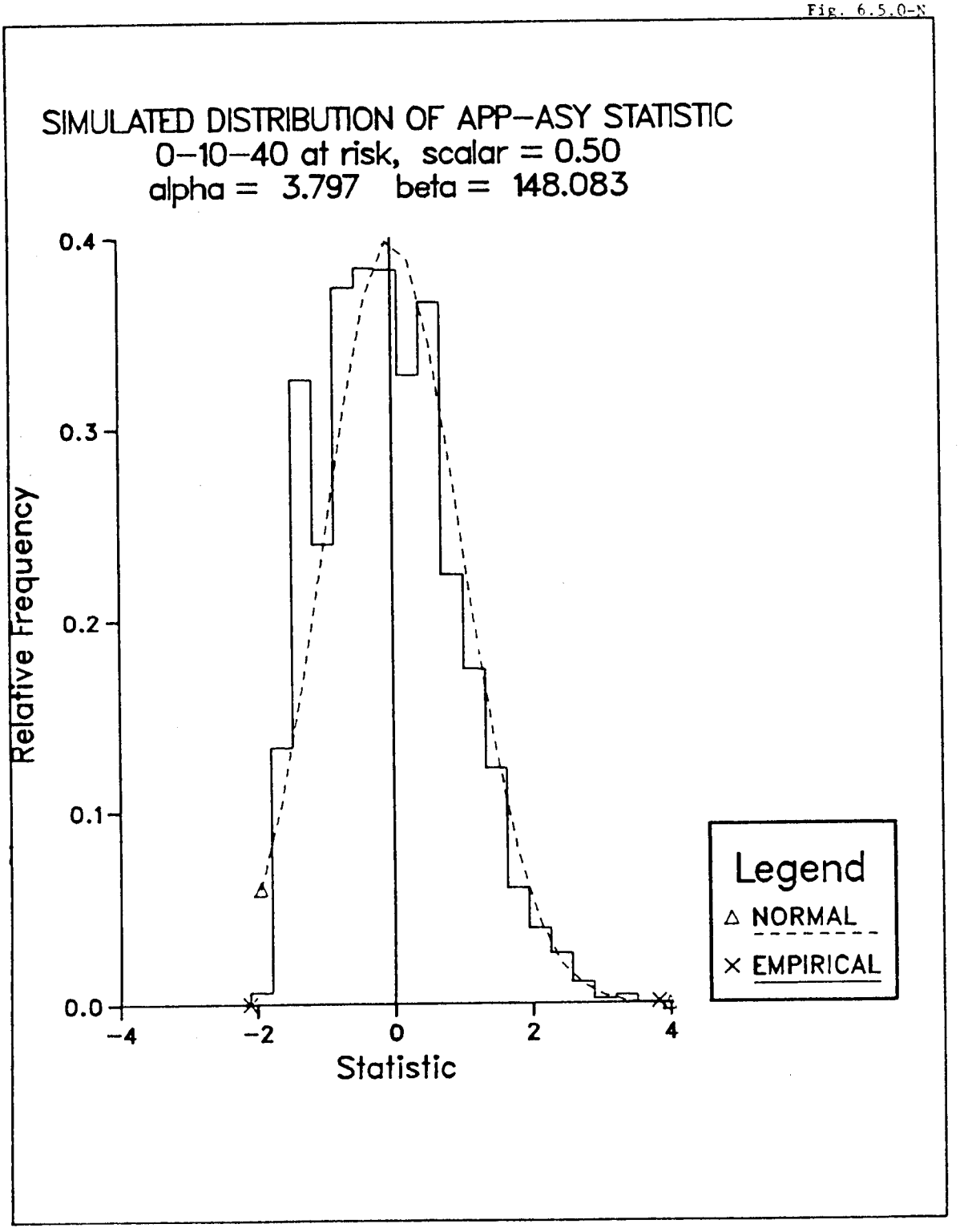

SIMULATED DISTRIBUTION OF APP–ASY STATISTIC
0–10–40 at risk, scalar = 0.50
alpha = 3.797 beta = 148.083
Relative Frequency
0.4
0.3
0.2
0.1
0.0
−4
−2
0
2
4
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 6.5.1-N

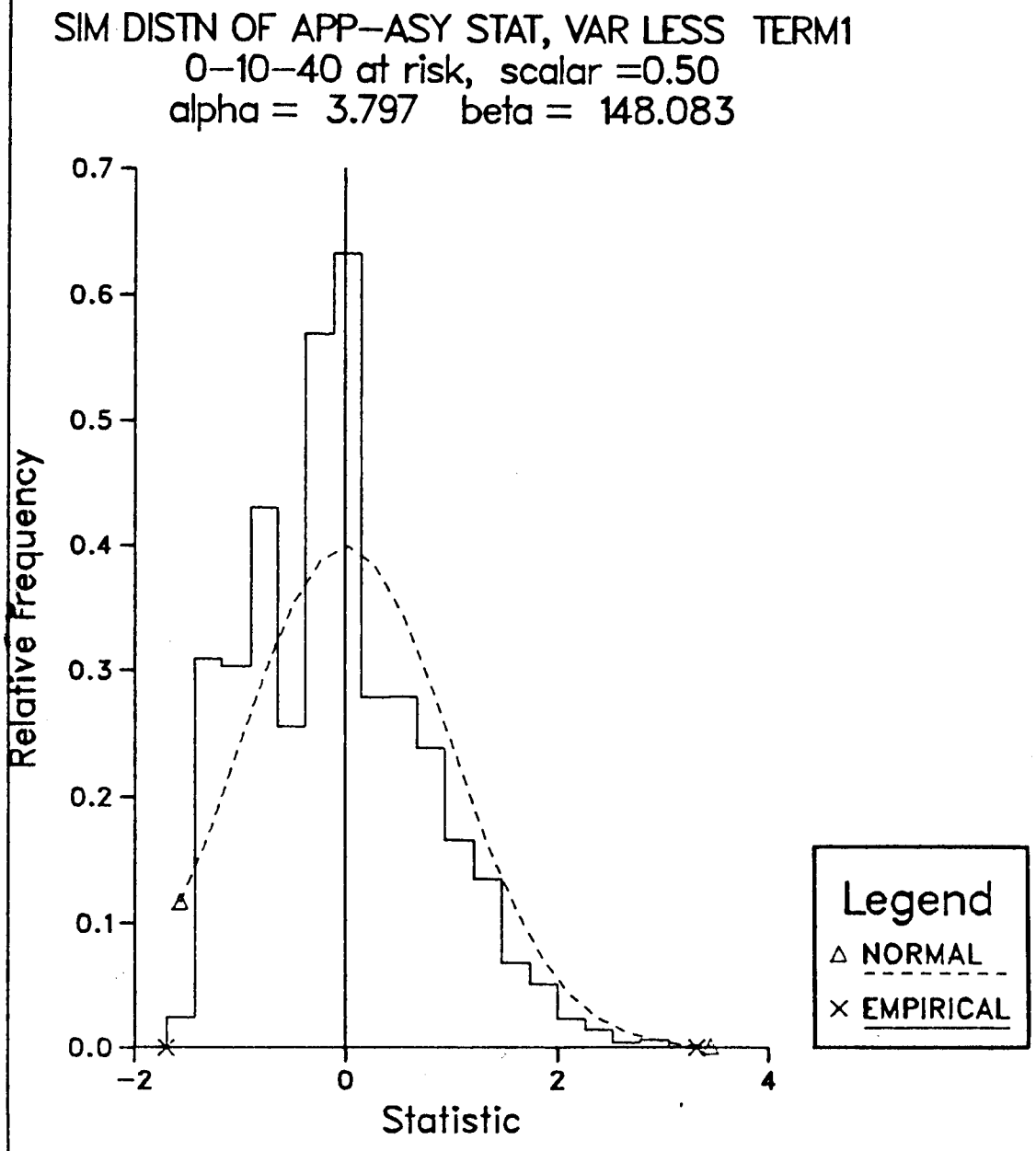

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar =0.50
alpha = 3.797 beta = 148.083
Relative Frequency
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-2
0
2
4
Statistic
Legend
NORMAL
EMPIRICAL

Fig. 6.5.0-C

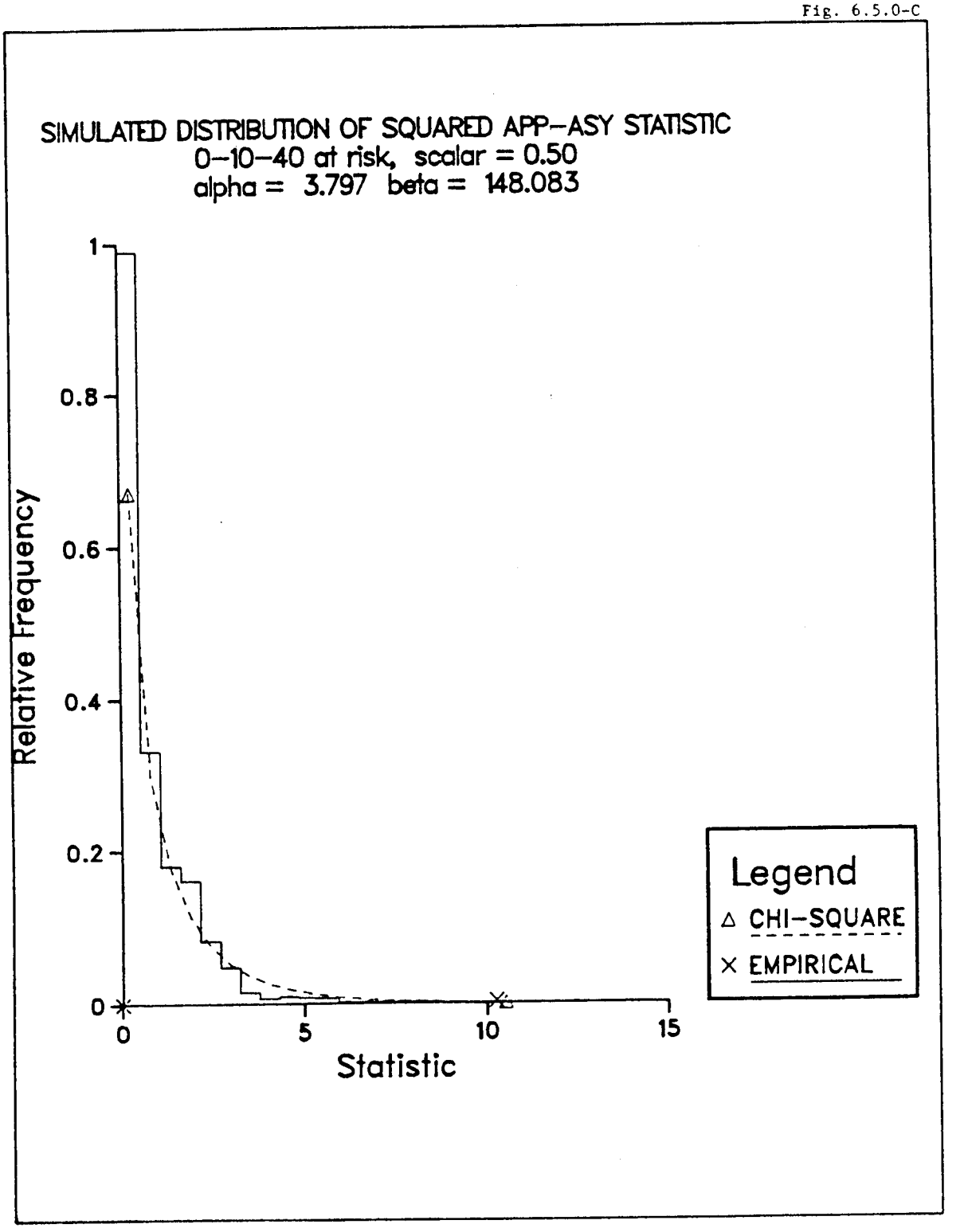

SIMULATED DISTRIBUTION OF SQUARED APP-ASY STATISTIC
0-10-40 at risk, scalar = 0.50
alpha = 3.797 beta = 148.083
Relative Frequency
1
0.8
0.6
0.4
0.2
0
0
5
10
15
Statistic
Legend
CHI-SQUARE
EMPIRICAL

Fig. 6.5.1-C

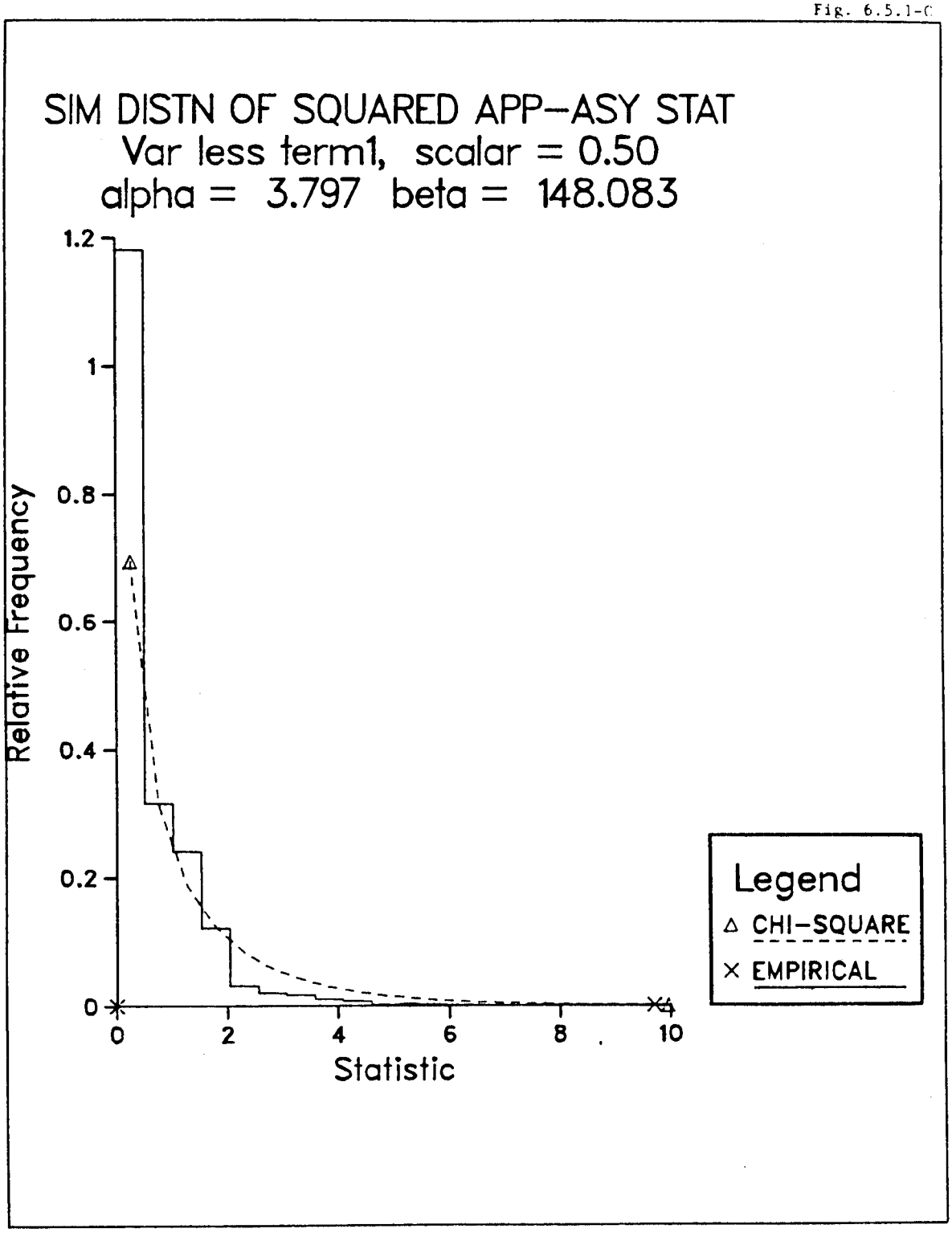

SIM DISTN OF SQUARED APP-ASY STAT
Var less term1, scalar = 0.50
alpha = 3.797 beta = 148.083
Relative Frequency
1.2
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
Statistic
Legend
CHI-SQUARE
EMPIRICAL

Fig. 7.5.0

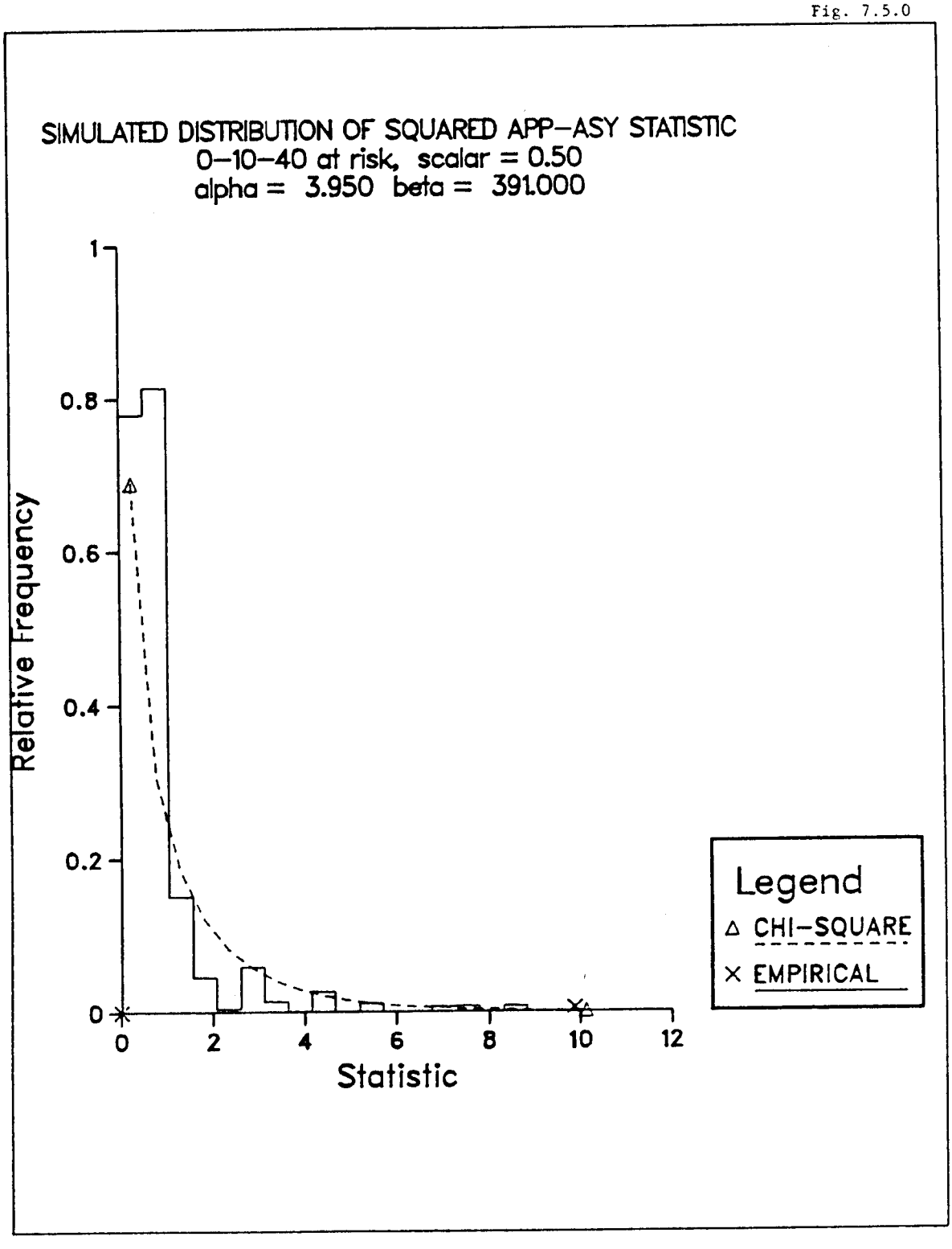

SIMULATED DISTRIBUTION OF SQUARED APP-ASY STATISTIC
0-10-40 at risk, scalar = 0.50
alpha = 3.950 beta = 391.000
Relative Frequency
1
0.8
0.6
0.4
0.2
0
0
2
4
6
8
10
12
Statistic
Legend
CHI-SQUARE
EMPIRICAL

Fig. 7.5.1

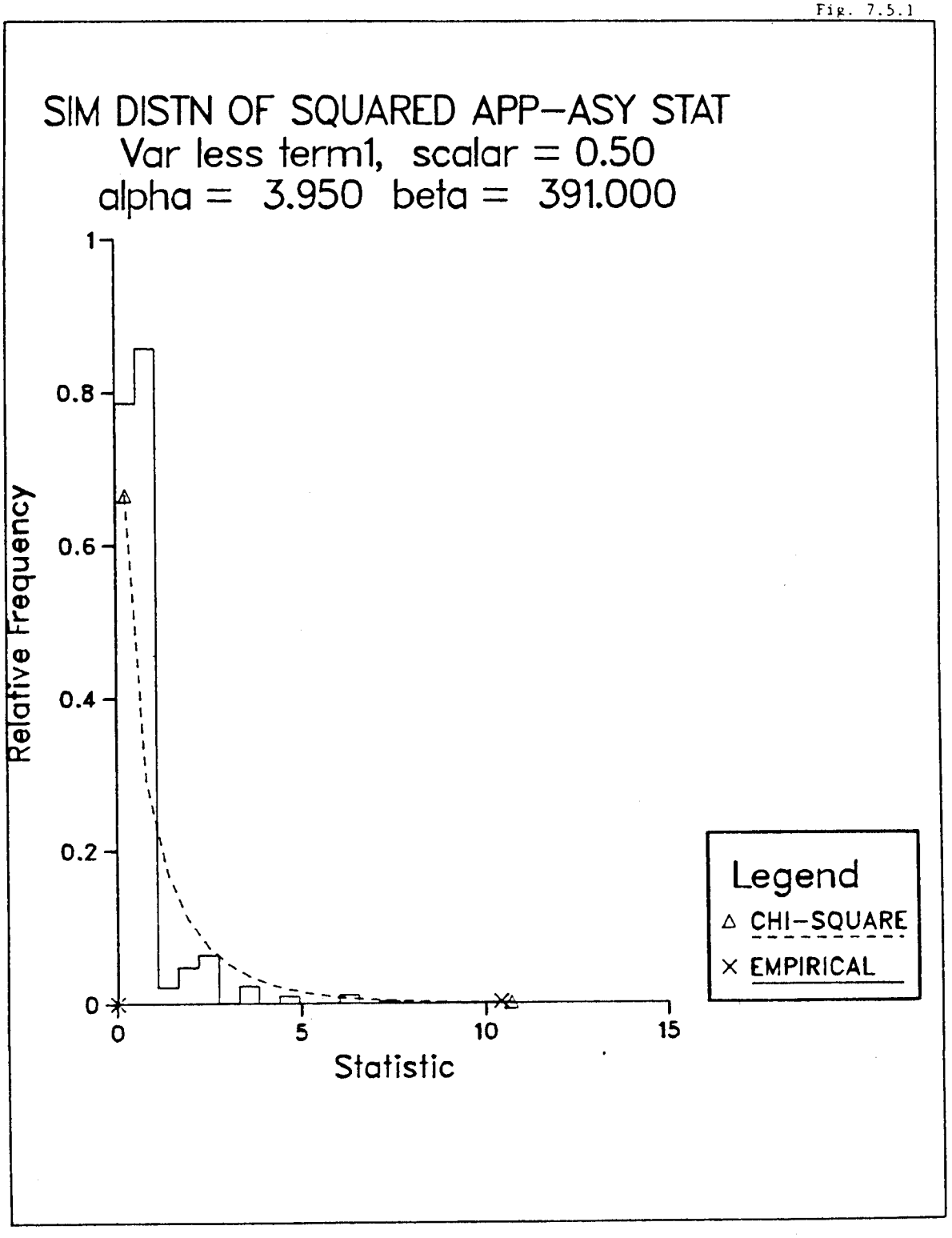

SIM DISTN OF SQUARED APP-ASY STAT
Var less term1, scalar = 0.50
alpha = 3.950 beta = 391.000
Relative Frequency
1
0.8
0.6
0.4
0.2
0
0
5
10
15
Statistic
Legend
CHI-SQUARE
EMPIRICAL

Fig. 8.5.0

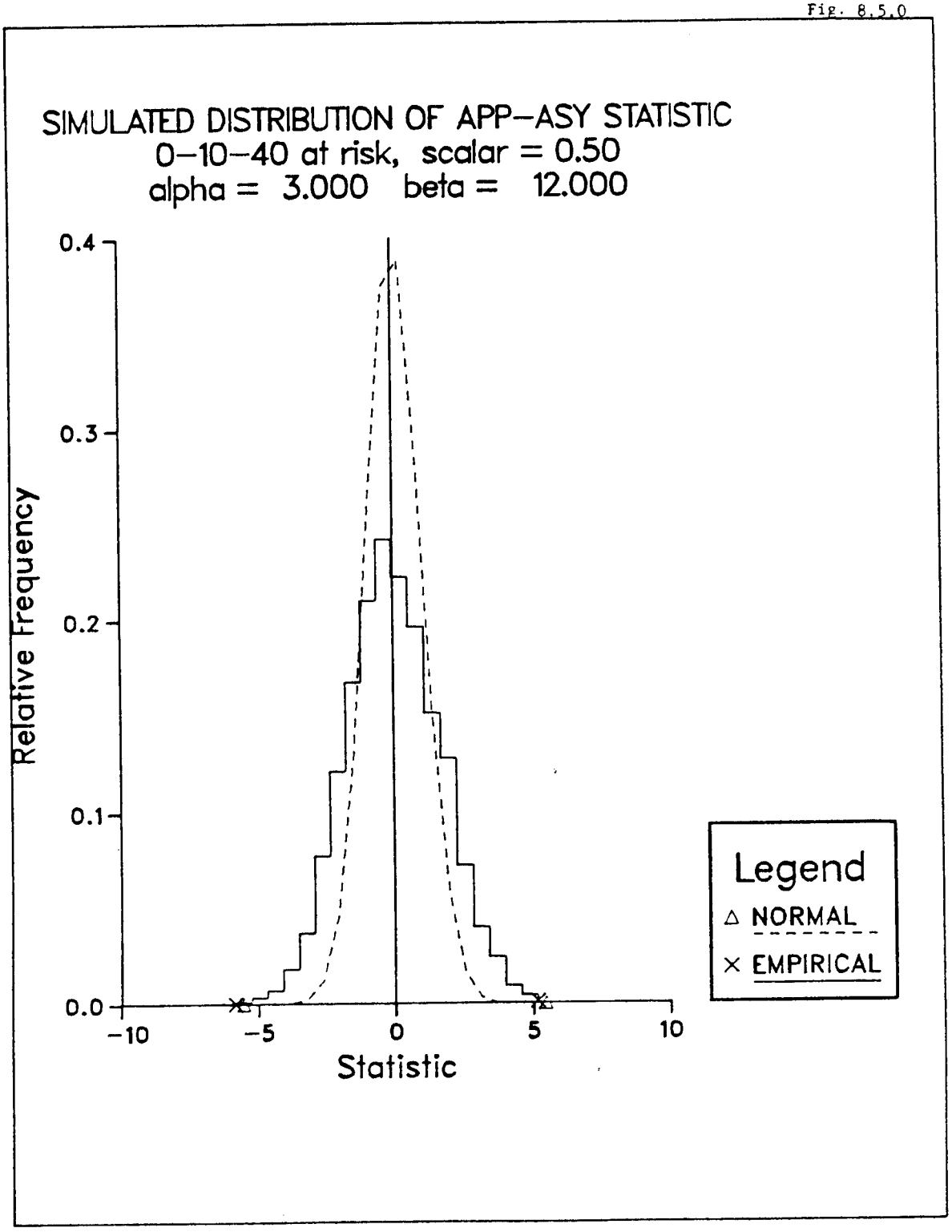

SIMULATED DISTRIBUTION OF APP-ASY STATISTIC
0-10-40 at risk, scalar = 0.50
alpha = 3.000 beta = 12.000
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-10
-5
0
5
10
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 8.5.1

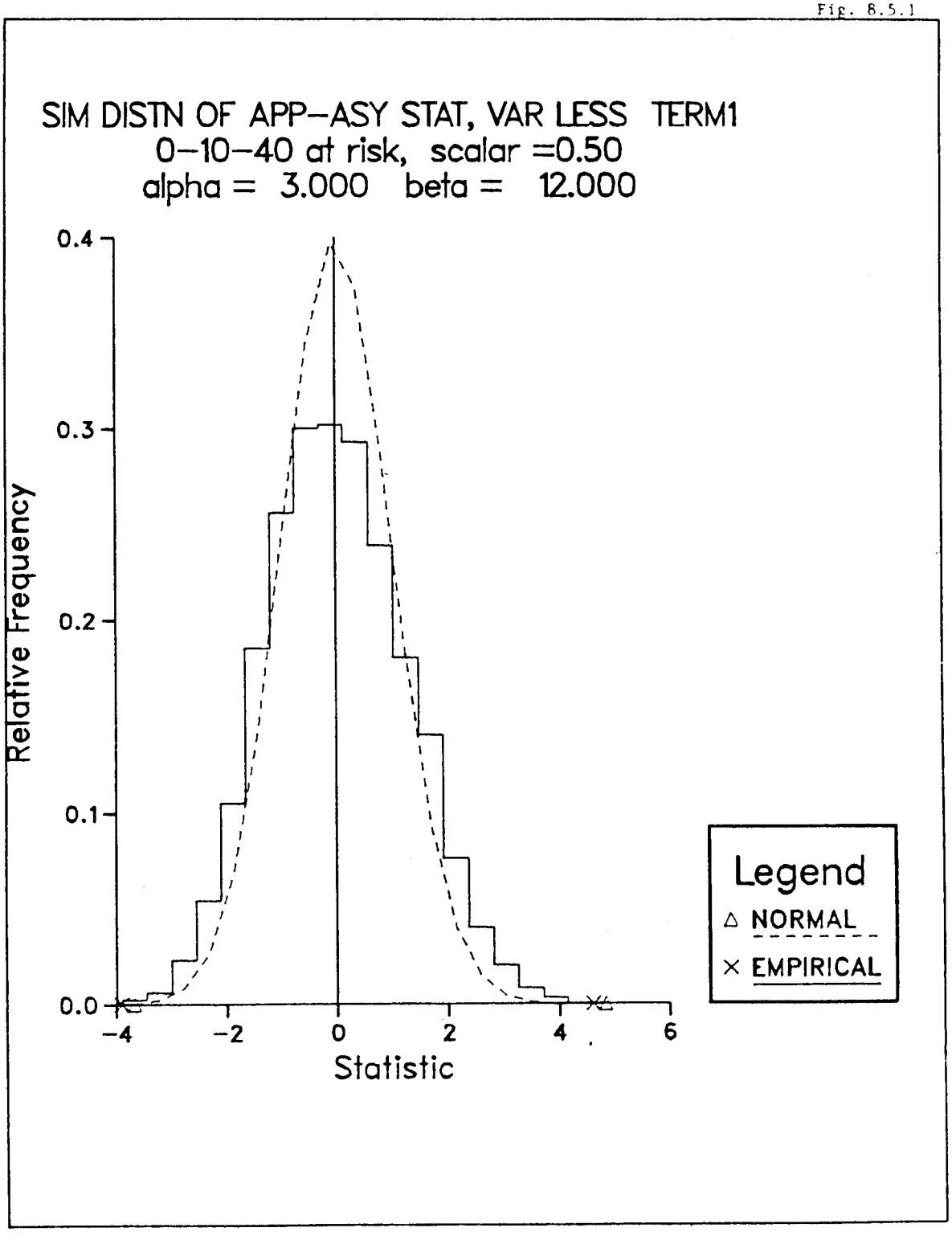

SIM DISTN OF APP-ASY STAT, VAR LESS TERM1
0-10-40 at risk, scalar =0.50
alpha = 3.000 beta = 12.000
Relative Frequency
0.4
0.3
0.2
0.1
0.0
-4
-2
0
2
4
6
Statistic
Legend
△ NORMAL
× EMPIRICAL

Fig. 9.1

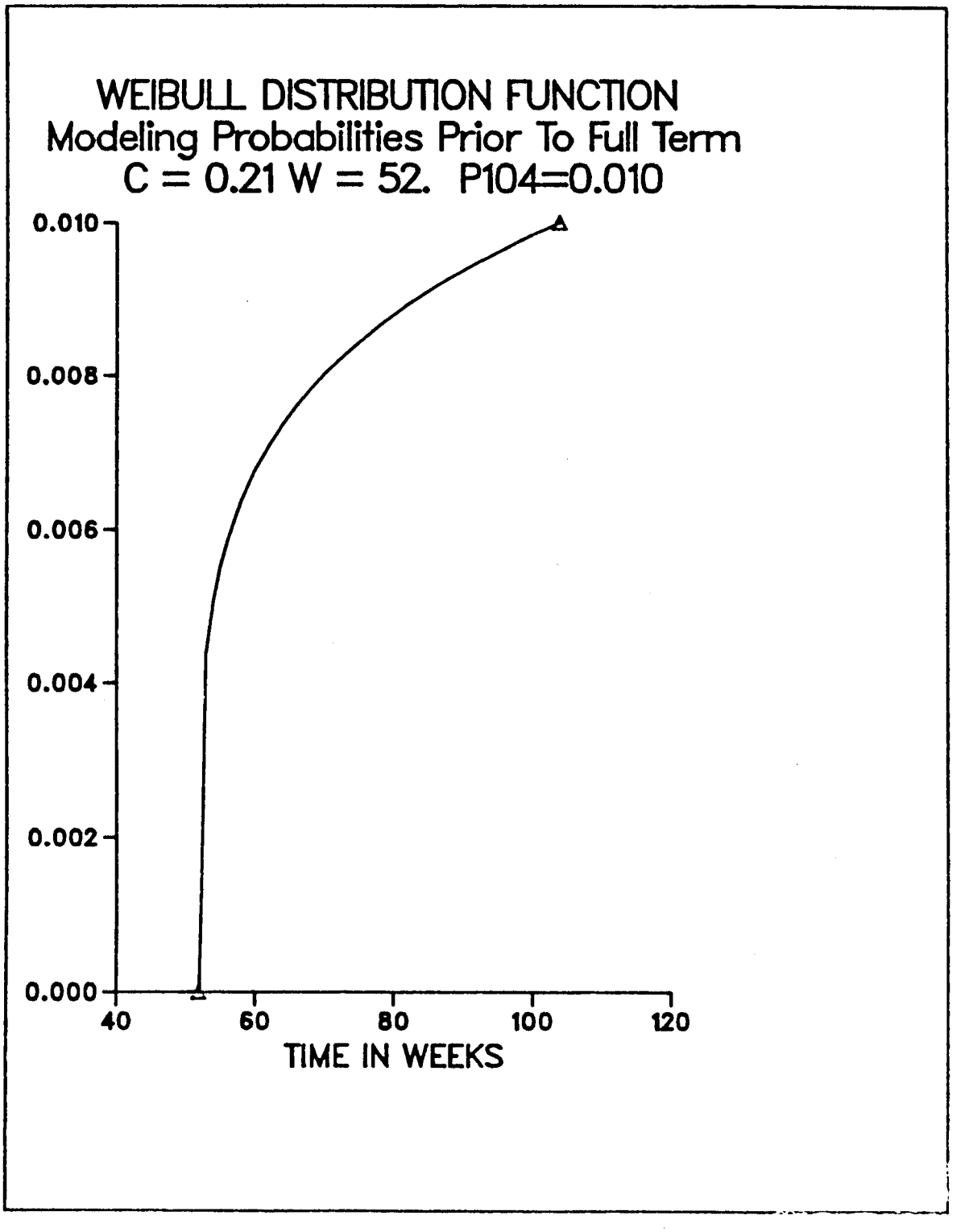

WEIBULL DISTRIBUTION FUNCTION
Modeling Probabilities Prior To Full Term
C = 0.21 W = 52. P104=0.010
0.010
0.008
0.006
0.004
0.002
0.000
40
60
80
100
120
TIME IN WEEKS

Fig. 10.1

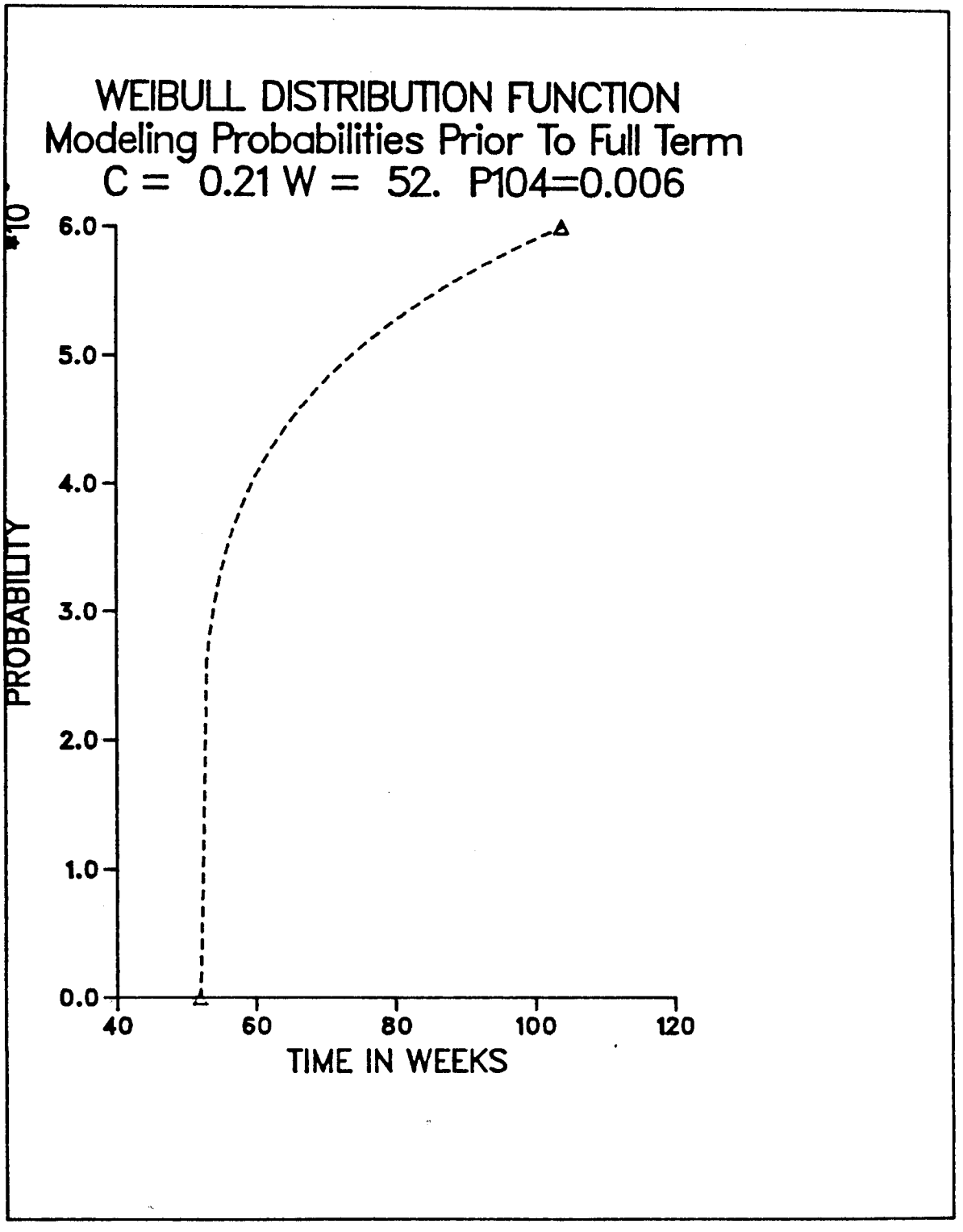

WEIBULL DISTRIBUTION FUNCTION
Modeling Probabilities Prior To Full Term
C = 0.21 W = 52. P104=0.006
PROBABILITY *10
6.0
5.0
4.0
3.0
2.0
1.0
0.0
40
60
80
100
120
TIME IN WEEKS

Fig. 11.1

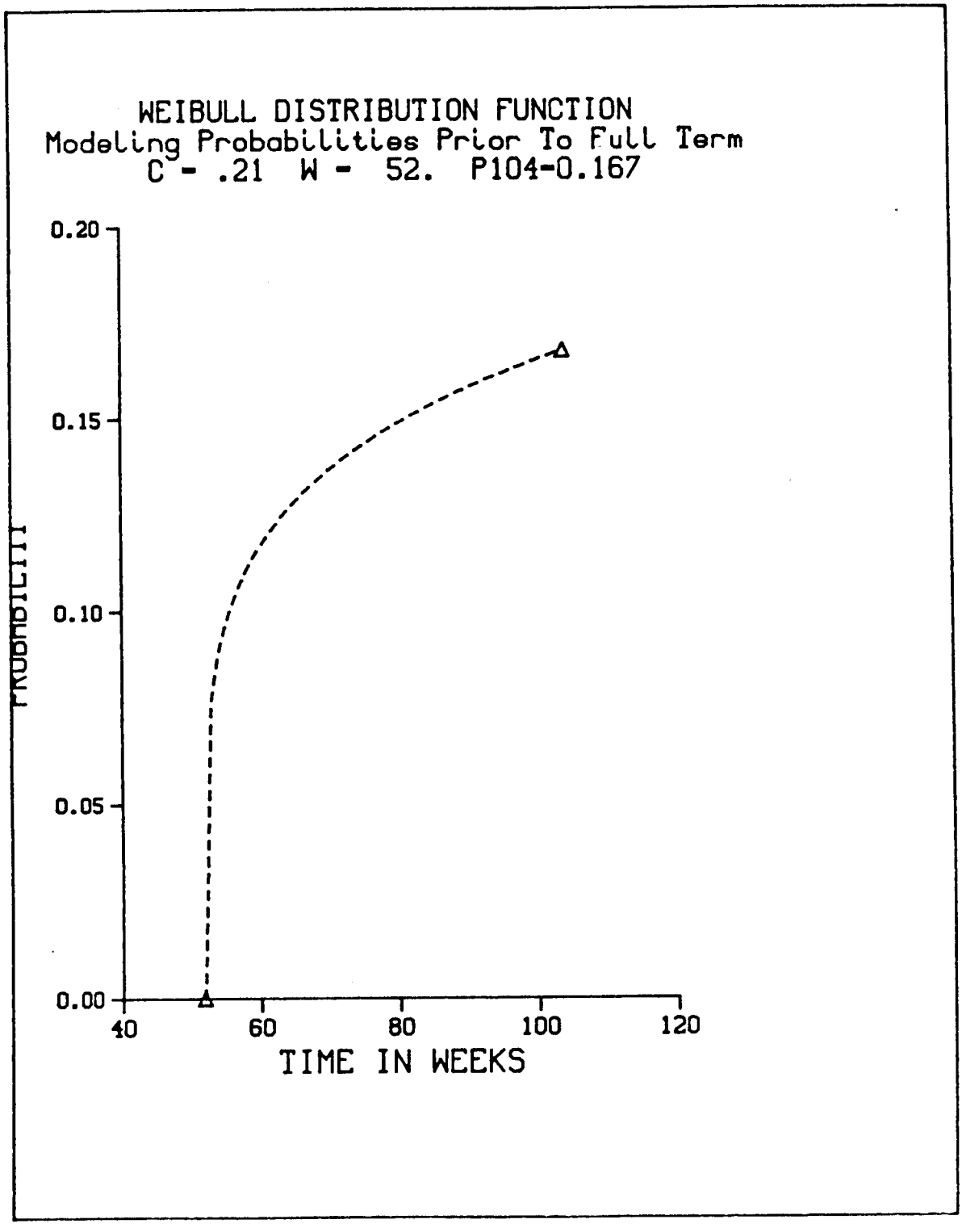

WEIBULL DISTRIBUTION FUNCTION
Modeling Probabilities Prior To Full Term
C - .21 W - 52. P104-0.167
PROBABILITY
0.20
0.15
0.10
0.05
0.00
40
60
80
100
120
TIME IN WEEKS

Fig. 41.2

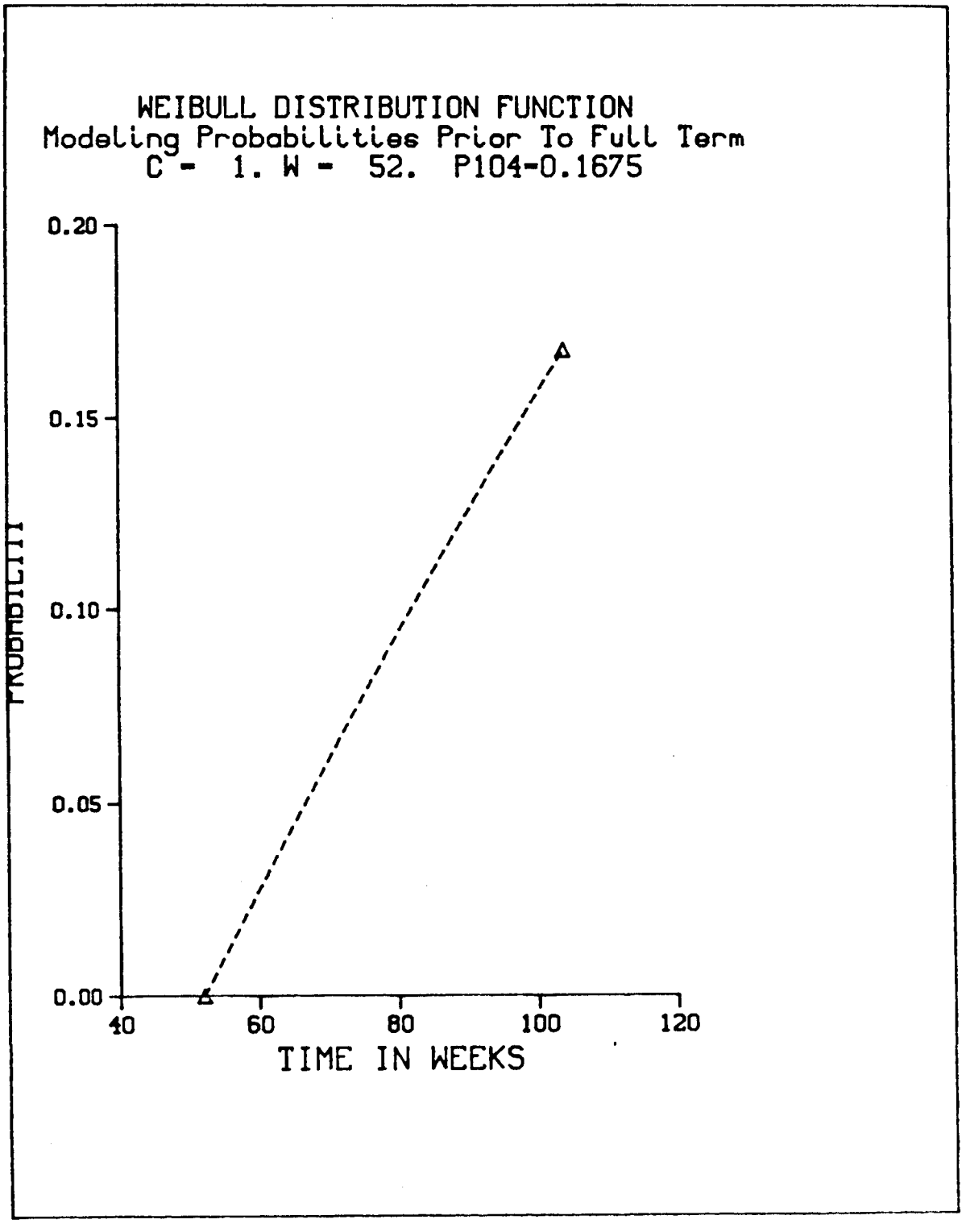

WEIBULL DISTRIBUTION FUNCTION
Modeling Probabilities Prior To Full Term
C - 1. W - 52. P104-0.1675
PROBABILITY
0.20
0.15
0.10
0.05
0.00
40
60
80
100
120
TIME IN WEEKS

Fig. 11.3

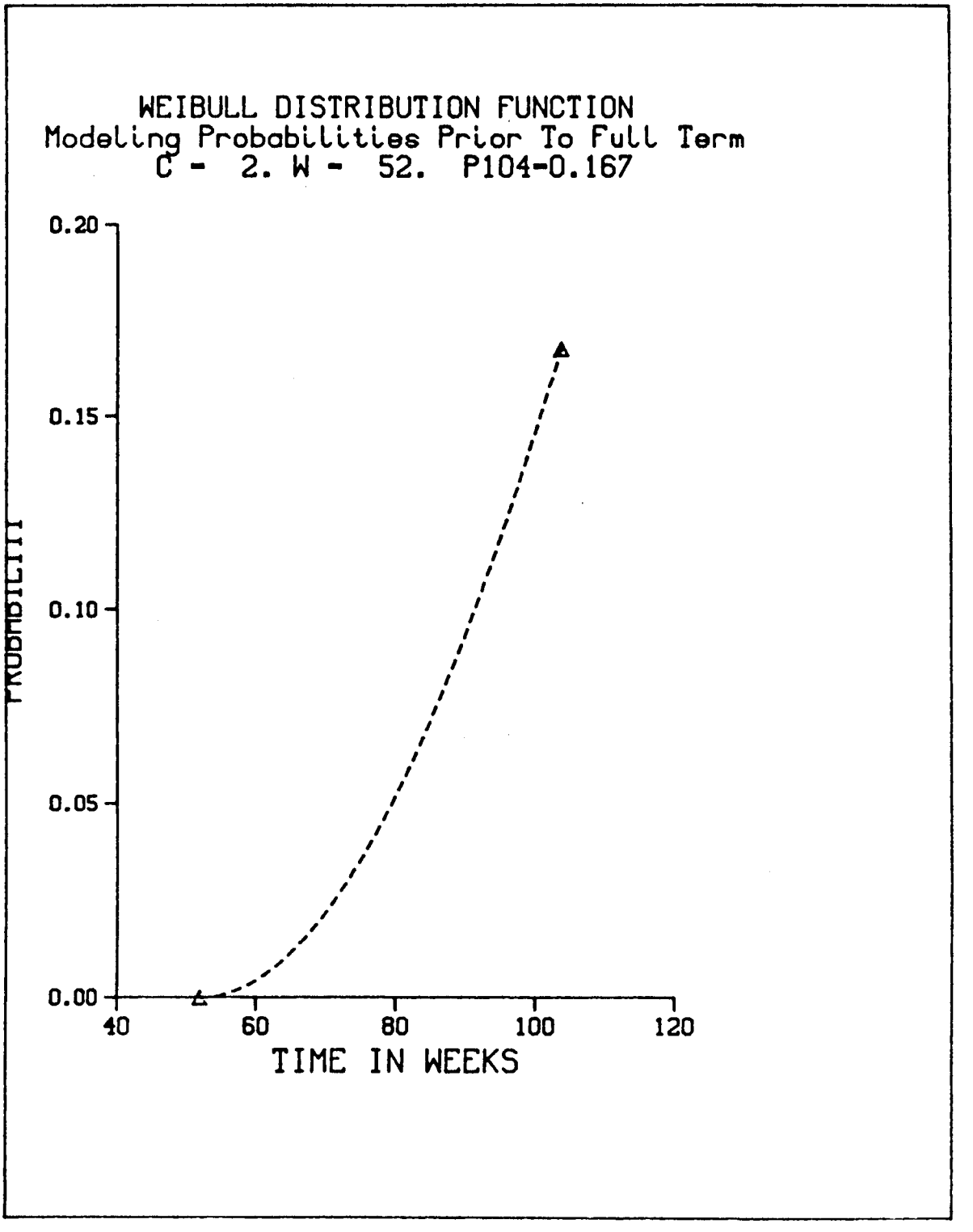
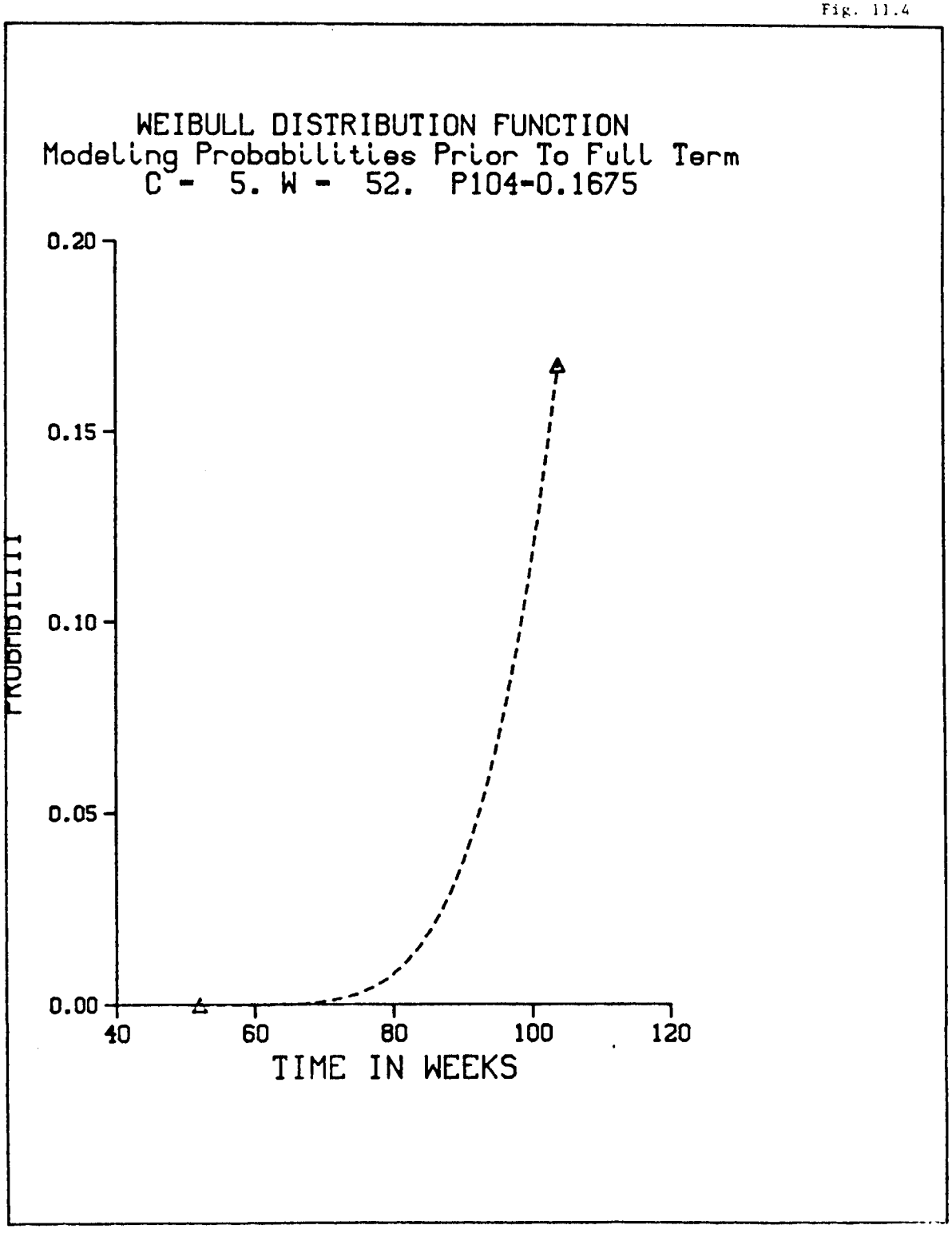

WEIBULL DISTRIBUTION FUNCTION
Modeling Probabilities Prior To Full Term
C - 2. W - 52. P104-0.167
0.20
0.15
0.10
0.05
0.00
PROBABILITY
40
60
80
100
120
TIME IN WEEKS

Fig. 11.4


WEIBULL DISTRIBUTION FUNCTION
Modeling Probabilities Prior To Full Term
C - 5. W - 52. P104-0.1675
0.20
0.15
0.10
0.05
0.00
PROBABILITY
40
60
80
100
120
TIME IN WEEKS