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Statistics for Clinical Research

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The purpose of this paper is to make understandable the use of statistics in the field of medicine, and to introduce to the clinician some new methods of statistics for drawing some reasonable conclusions based on the meager data usually available. There is, after all, only one valid use of statistics: to enable oneself to make a personal decision based on the information available.

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BEFORE introducing new methods of statistics, it is appropriate to explain why the old methods are not satisfactory for use in clinical medical research. Most of the statistical procedures currently used rely on a mathematical model called a "normal distribution function". This function is best described by its moments of which the mean and variance are the more common and useful. A number of methods of statistical inference or hypothesis testing are based on the use of these parameters. Furthermore, these methods have been widely used and have been given great credence in clinical research. Unfortunately, both in theory and in practical application, these methods have little or no validity when used on clinical data.

It must be remembered that, when statistical inference is used, inductive reasoning matches a "real life" situation to a formalized abstract mathematical model. The validity of the statistical inference, then, is only as good as the match between the "real" and the "abstract". This matching is at best an intuitive judgment by the individual who gathers the data. This in turn requires that the investigator accept a number of assumptions about the source of data. These assumptions are most difficult to accept from a realistic viewpoint. They require that the charac-

teristics under study have *a priori* and repeated probabilities in the total population. To be true the characteristic under observation must be completely independent of any other characteristic that is not under observation. For example, if some physiologic function is observed for a control sample and a treated sample of people, then either of two requirements must be met: 1) An assumption must be made that the physiologic function has no relation to age, weight, sex, etc. of the total population, or 2) the exact relationship of this function to these characteristics must be known. Even more difficult to accept is a necessary assumption that the sample be a random one as defined mathematically. In a more simple statement, the distribution function of the sample must be the same as the distribution function of the population. By observation it is known that a sample of less than 30 data points never has a normal distribution. The question that always arises with small samples is whether the sample, despite its non normality, does indeed come from a normally distributed population.

The simplest way to avoid the preceding question is to use "distribution free" statistics. A method of this kind will be discussed later. Another method is to assume that the population has the same distribution as the sample and use that as the mathematical model. This does not permit the use of conventional parametric statistics when the samples are less than 30 data points.

When studying events in living systems it should not be expected that the distribution functions would have normality. Normality requires that the biologic process remain stationary; that is, it must not change with time. Living systems are not stationary; they have a birth, a growth period, a maturation period, and a decay period. Some systems are characterized by an infant mor-

tality distribution, others by an old age survival function and still others by a simple random decay process. None of these are normal distributions. But, they can be described by other distribution functions such as the exponential, the gamma, the log-normal, the extreme value, and others.

Statistical methods are a very personal thing. Regardless of what methods are used in statistical analysis or inference, they are only as valid as the user's belief in them. The only purpose of statistical inference is to enable the user to make a decision when the outcome has some doubt. Two tools are available to make that decision: 1) An intuitive belief based on past personal experience and 2) a statistical evaluation of some specific data. The final decision will be based on a blending of these two tools. This blending into a decision process can best be accomplished by a "statistical design" of the experiment. This design is really only a formalized state of the steps to be taken in collecting data and arriving at a decision.

Statistical Design

The most important requirement for the statistical design of an experiment is good common sense. The entire experiment must be looked at with proper perspective. What is the purpose of the research? What will it cost in time and money? Are the possible rewards worth the effort? What is the methodology to be used? The questions must first be answered in an informal yet orderly and common sense fashion. Then a more rigorous approach to the design must be established. *What is the purpose of the research?* Here, we assume that with today's costs in time and money, a research project does have a real purpose, at least as far as the investigator is concerned. For a realistic pursuit of the research problem, he must state that problem in a concise, consistent

and somewhat rigid manner. Here we meet the concept of personal probability. The investigator has met some problem that challenges him and on which he has some personal views. He wishes to establish whether his ideas are right or wrong. The second requirement in a statistical design then, is a concise and proper statement of the problem.

The third requirement is the formulation of a plan of action based on the results of the solution of the problem. This requirement is seldom met in medical research and, if it is considered, it is usually only haphazardly. With today's economy and cost consciousness about research, a project has little or nothing to merit its undertaking if, when completed, it does not provide a definite decision about further activity based on the results of the research. The pursuant action may be a simple decision to desist from further concern about the problem. It may be a decision to continue activity in a different direction. Or, it may be a decision to implement a new clinical procedure or treatment. In any case, the rules for arriving at these decisions must be established before the research takes place. Unfortunately, this is not a simple step.

In the current practice of classical biostatistics, emphasis is placed on preventing the investigator from rejecting a hypothesis when it is true, but little is done to protect him from accepting the hypothesis when it is false. This "significance" testing plays a major role in the current practice of statistical inference. This practice has many pitfalls, both in the use of "significance levels" as a basis of hypothesis testing and in the acceptance of several "assumptions" in applying the statistical models to the data available. It is in this area that the investigator has failed the most in his responsibility to the deci-

sion process. He must assign a "utility" to a correct decision and a "risk" to a wrong decision. Only he can do that and again we meet the reality of a personal probability, a personal feeling of how useful is the utility and how risky is the risk. This becomes much less of a problem if we consider hypothesis in the light of "confidence" rather than "significance". By doing this we consider at the time not only the risk of accepting as wrong what is right, but also the risk of accepting as right what is wrong.

Order statistics can be very powerful in establishing these "confidences". Further, use of the Weibull distribution can give added latitude in their applications.

The next requirement for a statistical design is the method of collecting data or information to be used in solving the problem. It must be remembered that data collection devices are not, in the real world, "noise free." In other words, when you collect data from an experiment, that data represents both the information that is generated by experiment and the noise generated by the data collector. This data collector may be instruments, people or a combination of both. In any case, it will have some noise. The statistical design then will have a data collection device that is as simple as it can be made to eliminate sources of noise.

Also, the investigator must know the system so that he can best appraise the noise that is present.

It follows that the next stage is a method of separating the information from the noise in the data. We call this "statistical analysis". From this operation we expect to have some insight into the character of the information. The noise should be filtered out. To

establish some order to the data, different modes should be identified, if they are present, and, hopefully, some knowledge of the distribution functions underlying the samples could be suggested.

The final step in the statistical design we shall call "statistical inference". With this step we come to conclusions about comparisons of our samples of information concerning the problem as it was stated. At this stage, we relate our data samples to statistical mathematical models and, by inductive reasoning, come to some conclusions, with a stated amount of certainty or uncertainty about the real world that these samples represent.

Order Statistics

Before discussing order statistics, we should generalize on statistics as used in analysis and inference. Statistics are used to make inferences about populations that are so large as to be practically immeasurable. Therefore, we take samples from these populations, measure the samples and by statistics refer the sample measurements to the total population. With classical statistics, this is at best a risky business. For example, we assume that the population does not change with time. What's true today is true tomorrow. We identify these populations by one or more characteristics that attract our interest. We measure these characteristics in the sample and we assume that they are independent of any characteristics other than the ones that are measured in the sample. In other words, if we find that a certain measurement taken from the sample is independent of all other measurements of the sample, then we assume the same holds true of the entire population; ie, that our sample is truly representative of the population in all respects. It takes courage to make this assumption.

We assume that the total population has a set of measurements similar to our sample. These have certain identifying features that we call parameters. This set of population measurements we will call the distribution function. Thus we have the parameters of the distribution function, and these are used to identify one distribution function from another. Since the populations are so large as to be immeasurable, we cannot know the exact values of these parameters. We can estimate them, however, from the parameters of our samples. Whether or not these estimates are realistic, we will never know. However, to use classical statistics we say they are and let it go at that.

These parameters are named *mean, variance, skewness* and *kurtosis*. The *mean* represents a balance point in the distribution function, a fulcrum about which all the measurements of the population are balanced as to weight. If this fulcrum happens to coincide with a point in the distribution that equals half the total members of the population, we say that we have a symetrical distribution. If it does not, we say the distribution is *skewed* (another parameter).

Since members of a population differ or vary from one another, the amount of this difference, or *variance*, is characteristic for a given population. So, their distribution functions can be characterized by this *variance* (another parameter).

Classical statistics assumes that these parameters are known or correctly estimated and also that they are the best descriptors of the population. If the investigator truly believes this, then classical statistical inference will provide him with more assurance of certainty or uncertainty about his problem, based on his data. If he is in doubt about these

assumptions, either because of past experience (personal probability again) or just plain reluctance to accept so many assumptions about a large unknown population, the classical statistical inference is of little assistance.

In the classical approach to statistics, we define some population and we assign to this population a set of descriptors or parameters (mean, variance, etc.). Then we try to select a representative sample from this population so that we can estimate its parameters from the sample. As has been pointed out, this can be risky business.

In using order statistics we approach the problem from a different direction. We first collect a sample, any set of values of some unknown population. If we have such a sample, we assume only that the sample itself is not the total population but has been drawn from some population. No further assumptions are made about the population, except that it can be made countable.

Having done this, the population thus must have percentiles. It can be divided into fractions of a fourth of the population, a half, three quarters, etc. Since this population is too large to count, we must estimate its percentiles from the sample. We can count the sample and divide it into percentiles. It is not realistic to believe that a percentile of the sample would exactly or even closely represent a corresponding percentile of the population. Since we assumed nothing about the population, our first approximation of what percentile of the population is represented by a percentile of the sample must be pure chance (a 50% probability).

The operation for achieving this is quite simple. First, each member of the sample must be ordered according to its

value with its neighbor, the smallest being first, etc. Hence, we have a set of order statistics. A note should be made here concerning the value of each ordered statistic. Since we are dealing with percentiles of the population, the exact value of each member of the sample does not have to be known exactly. We need only know whether it is larger or smaller than its neighbor. This consideration can be most useful in clinical medicine where numerical values are sometimes difficult to establish, such as in grading of reflexes, amount of pain, etc.

To return to the problem at hand, we have ordered the data set. For computational purpose we will label each member j, so we have a set of j order statistics and we will call the order number of each j, k. We can rank each member of the sample then by simply computing:

$$\text{sample rank} = \frac{j_k}{n}$$

where n = sample size

We have said, however, that this would not be a very realistic guess as to where the sample number j_k would rank in the total population.

A simple calculation

$$\text{median rank} = \frac{j_k - .3}{n + .4}$$

where n = sample size

yields the median rank of j_k in the total population. This establishes what percentile of the total population the sample member represents, with a 50% probability of its actual rank being either higher or lower. The calculation of the actual median rank and its mathematical derivation is quite complicated.[1]

Empirically, it has been determined that when a sample thus ranked is plotted on Weibull probability paper (the abscissa is log and the ordinate is log log) and it produces a straight line, the population has a Weibull distribution function. When this occurs, it enables the use of the Weibull function in many techniques of statistical inference. We shall discuss these methods later.

To return to order statistics, we have thus far determined the pure chance ranking of our sample. Let us proceed to other probability levels for ranking the sample into the total population. For example, we shall take the 5% and 95% ranks (in clinical research a ranking of 1% and 99% may be preferred). For the 5% rank we shall determine at what percentile of the population a sample member has only a 5% probability of being less. For the 95% rank, we shall determine the percentile of the population that the sample has a 95% probability of being less.

Now we have drawn "confidence bands" for the population from which our sample was drawn. We have established, with a 90% probability, the range of the population from which our sample was drawn. This gives us a tool for making statistical inference about other samples we may have and their relation to the original sample. In the process, we have no assumptions about the population other than it does exist and that it is countable.

The calculation of population ranks other than the median rank is not simple but is mathematically sound. Computer programs are available that will calculate any rank for any size sample.[2]

This becomes a powerful statistical tool for medicine because it makes no requirements about stationarity, *a priori* and repeatable probabilities, or functional dependence of the assumed population.

The Weibull Distribution

In 1939 Waloddi Weibull postulated a very general cumulative distribution function whose only requirements were that it be non-zero and non-decreasing. In other words, the probability of accounting for the total population was ever increasing as you "added up" your total sample. This is done very simply by first ordering the sample, just as in order statistics and then determining the median rank of each member of the sample. A Weibull function exists when a linear relationship holds between the logarithm of the values of the order statistics and the logarithm of the logarithm of the cumulative percent of the population.

Experience has shown that data collected from experiments in industry and biology do fit a Weibull distribution.[3-5]

Weibull has called this distribution a function of broad applicability for it is, in reality, a whole family of distribution functions. The "normal" distribution function is a Weibull distribution function, and so is the exponential, the Chi Square and the gamma. Thus, it is not only a very useful model for statistical inference but it also is useful in determining whether or not your data fits a more well-known distribution function.

The Weibull distribution also has parameters or characteristics which describe it exactly. The first of these is the location parameter. The location parameter (alpha, α) describes the point of origin of the probability density function. The second Weibull parameter (beta, β) is the shape parameter. This parameter gives a numerical value which equates to the general shape of the probability density function. The

third parameter is the scale parameter, (theta ϕ) which defines the value of your sample (x) at which 63.2 percent of your density function has been accounted.

Since the shape parameter, beta, describes the shape of the probability density function, it is the slope of the linear function of the cumulative distribution function. It then becomes a simple procedure to estimate all three Weibull parameters. The best alpha will give the best linear fit of the data. This determines the beta, and the theta is then self defined. From these parameters, the more familiar parameters of your distribution can be evaluated such as mean (mu), variance (sigma squared) and skewness.The Weibull distribution function is of considerable use in evaluating the data and separating the information from the noise, particularly when we use its graphical properties. If we have a sample set of data that represents a single function, it will plot on Weibull probability paper (abscissa-log, ordinate log-log) as a straight line. If, however, the data represents more than one function, the Weibull plot will be a mixture of straight lines.[3] By trial and error, the sample points can be separated and replotted until each is identified with its particular function. This is a simple yet proven method of separating a mixed signal. This method can also be used to determine whether or not extreme values in a sample really belong to the population under study, or, if they should be discarded from further consideration.

For statistical inference, a large set of procedures using the Weibull parameters can be used in hypothesis testing, comparison of samples and predictions about sampling. There is no need to assume a normal distribution for the data. Whether or not it is normal can be determined by using the Weibull

parameters. The techniques of "classical" statistical inference, as well as many others, can be used when the classical techniques are inappropriate.

Bayesian Statistics

There are many arguments concerning the Bayesian approach to statistics and the concept of "personal probability" even among the Bayesians themselves.[6] However, in the realm of clinical investigation, the idea and use of personal probability should not be avoided. The use of a statistical evaluation of a clinical experiment is simply an extension of a physician's intuition about some problem based upon some defined observations. Institution of the research, organizing of the problem and the method of data collection are unavoidably influenced by the clinician's intuition. It is proper that this intuition should be properly utilized in following through on the project. Indeed, in the final utilization of the results of such experimentation, the experiment will only prove useful if in fact the results can be made compatible or acceptable to the clinician's prior probability (intuition) of these results.

Summary

The foregoing summary of ideas concerning the use of statistics in medical research suggests that statistics should be simple, easily understood and based on common sense. The investigator's own feelings should be the basis for the design of the experiment and the evaluation of the results (Bayesian statistics). The simplest approach is order statistics, where it is not required that we make any assumptions about the character of the population that is being investigated. If a more complicated model is desired or necessary, the Weibull distribution function is the most appropriate, both from its

simplicity of use and its broad character that encompasses most of the distribution functions with which we are familiar.

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Appendix I

The Random Sample

If there is some population of elements that has some characteristic X that we wish to investigate, and the population has some distribution function $F_0(x)$, we suppose that for $k = 1,2,\ldots$, and for an arbitrary $x_1, x_2, \ldots, x_k$ there exists the conditional distribution function

$$F_k(x|x_1, x_2, \ldots x_k) = P(X'_{k+1} < x | X'_1 = x_1, \ldots X'_k = x_k)$$

If this supposition is true then we may choose some elements of a sample of the population by a random method if:

(1) for every x we have $P(X < x) = F_0(x)$
(2) for $k = 1, 2, \ldots, n-1$ and for arbitrary $x_1, x_2, \ldots, x_k$ we have the equalities

$$P(X_{k+1} < x \cdot X_1 = x_1, \ldots, X_k = x_k) = F_k(x \cdot x_1 \ldots, xk)$$

It must be noted that this equality is conditional:

$$F_k(x \text{ if } x_1, \ldots, x_k \text{ exists}) = P(X_{k+1} < x \text{ if }$$
$$X_1 = x_1, X_2 = x_2, \ldots, X_k = x_k)$$

In classical statistical inference an assumption is made that indeed for X being a member of the population and x being a member of the sample population, $X_1 = x_1, \ldots X_k = x_k$ or that $P(X_1 = x_1, \ldots, X_k = x_k) \geq 0.99$ (almost certainty). In real life problems this is of necessity an intuitive or personal probability since it cannot be established by observation.

Further assumptions are required for most classical tests of statistical significance. One such assumption is that

$$X_1, X_2, \ldots X_k \rightarrow F_0(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp -\left[\frac{(x-\mu)^2}{2\sigma^2}\right]$$

or that the characteristic X is normally distributed in the population. Again since this cannot be observed we assume that since $X_1 = X_1, \ldots X_k = x_k$ (intuition) then

$$x_1, \ldots x_k = F_0(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left[\frac{(x-\mu)^2}{2\sigma^2}\right]$$

It has been observed that when $k<30$, the sample $x_1, \ldots x_k$ is not normally distributed. Therefore when small random samples are used as a basis for classical inference several intuitive assumptions must be accepted before beginning the testing of the samples.

It can be further observed that samples, regardless of how large, when drawn from biological populations are also not normally distributed. This should not be expected since many biological populations display infant mortality, random decay, or old age survival. In such cases the characteristic X of the population or a sample x drawn from such a population could not be normally distributed.

Appendix II

Parameters of the Distribution of a Random Variable

There are four kinds of parameters of a distribution of a random variable:
    (1) moments
    (2) functions of moments
    (3) order parameters
    (4) functions of order parameters

Moments
    The moment of order k of the random variable X is:
$$m_k = E(X^k)$$
For the discrete distribution
$$E(X^k) = \sum_1 x_1{}^k p_1$$

For the continuous distribution
$$E(X^k) = \int_{-\infty}^{\infty} x^k f(x)\,dx$$

If $m_k = E[X-c]^k$, and $c = m_1 = E(x)$, then

$\mu_k = E[X-E(X)]^k$ are central moments when

$c = m_1 = E(X) = 0$

Then $\mu_1 = E[X-E(X)] = E[X-m_1] =$

$$E[X] - m_1 = m_1 - m_1 = 0$$

The central moment of the first order, μ_1, is called the mean of the distribution function of X (the population). It follows that
$$\mu_2 = E[X - E(X)]^2 = E[(X-m_1)^2]$$
$$= E[X]^2 - 2m_1 E(X) + m_1{}^2$$

The central moment of the second order, μ_2 is called the variance of X and is denoted by σ^2.

The central moment of the third order, μ_3 is the third power of μ_1.

$$\mu_3 = E[X-E(X)]^3 = E[(X-m_1)^3]$$
$$= E(X^3) - 3m_1 E(X^2) + 3m_1{}^2 E[X] - m_1{}^3$$
$$= m_3 - 3m_1 m_2 + 3m_1{}^3 - m_1{}^3$$
$$= m_3 - 3m_1 m_2 + 2m_1{}^3$$

If the distribution of X is symmetrical then all odd moments are zero, but if this is not the case then a function of the third central moment, μ_3, is defined as $\alpha = \frac{\mu_3}{\sigma^3}$ and is called the coefficient of skewness.

Order Parameters

The value x satisfying the inequalities
$$P(X \leq x) \geq 1/2, \quad P(X \geq x) \geq 1/2$$
is called the median of the distribution of the random variable X.

The value x satisfying the inequalities
$$P(X \leq x) \geq p, \quad P(X \geq x) \geq 1-p, \quad (0<p<1)$$
is called the quantile of order p.

The value of x satisfying the equality
$$P(X \leq x) = 0$$
is called the point of origin of the distribution of X. This is called the parameter α of a Weibull distribution function.

The value x satisfying the equality
$$P(X=x) = 0.623$$
is called the location parameter of a Weibull distribution.

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Appendix III

Order Statistics

Let $X_1, X_2, \ldots X_n$ be an n dimensional random variable.

Let $x_1, x_2, \ldots x_n$ be a sample of values drawn from $X_1, X_2, \ldots X_n$.

Arrange the sample $x_1, \ldots x_n$ in such a way that $x_{r_1}, x_{r_2}, \ldots x_{r_n}$ satisfies the inequalities $x_{r_1} \leq x_{r_2} \leq \ldots \leq x_{r_n}$

Then $f[x(-\infty < x < \infty)] = 0$ for $x < x_{r_1}$
and $f[x(-\infty < x^\infty)] = \frac{m}{n}$ (m=1,2, ... n) for $x > x_{r_1}$.

By definition $x_{r_n} < x = S_n(x)$ and is called the "empirical distribution function" of x.

From these assumptions it follows that $P(X_r < x) = F(x) = p = $ constant (r = 1,2, ... n)

Hence, for a fixed value of x, $S_n(x)$ is the frequency of successes in the Bernoulli scheme. Thus

$$P\left[S_n(x) = \frac{m}{n}\right] = \frac{n!}{m!(n-m)!} [F(x)]^m [1-F(x)]^{n-m}$$

Let the function of $(X_1, X_2, \ldots X_n)$ which takes the value x_{rk} in each possible sequence $x_1, x_2, \ldots x_n$ be called an "order statistic" and be noted by $\zeta_k^{(n)}$. The number k is called the "rank" of $\zeta_k^{(n)}$.

Let $\phi_{kn}(x) = F(\zeta_k^{(n)}) = P(\zeta_k^{(n)} < x) =$

$$P\left[S_n(x) \geq \frac{k}{n}\right] = \sum_{m=k}^{n} P\left[S_n(x) = \frac{m}{n}\right]$$

then $\phi_{kn}(x) = \sum_{m=k}^{n} \frac{n!}{m!(n-m)!} [F(x)]^m [1-F(x)]^{n-m}$

assume f(x) = F'(x) exists

then $f_{kn}(x)$ of $\zeta_k^{(n)}$ exists

therefore $f_{kn}(x) = \frac{n!}{(k-1)!\,(n-k)!}$

$[F(x)]^{k-1} [1-F(x)]^{n-k} f(x)$

Appendix IV

The Weibull Distribution

If $P(X \leq x) = F(x)$
then $F(x) = 1 - e^{-\phi(x)}$

The probability of the occurrence of some event x from a set of events $x_1, x_2, \ldots x_n$ is defined by:

$P_n = 1 - e^{-n\phi(x)}$

The function $\phi(x)$ must be specified with the necessary conditions that it be a positive, non-decreasing function, vanishing at some point $\geq$ zero.

$\phi(x) = -\left(\frac{x-\alpha}{\theta-\alpha}\right)^\beta$ satisfies these requirements.

Then $F(x) = 1 - e^{-\left(\frac{x-\alpha}{\theta-\alpha}\right)^\beta}$ is a three

parameter Weibull distribution function.

If alpha is assumed to be zero then F(x)=

$1 - e^{-\left(\frac{x}{\theta}\right)^\beta}$ is a two parameter Weibull distribution function.

For the two parameter Weibull distribution we may show that the shape parameter beta is the slope of the linear function Y = BX+A when plotted on Weibull probability paper (ordinate-log log and abscissa-log) as follows:

$$F(x) = 1 - e^{-\left(\frac{x}{\theta}\right)^\beta}$$

$$1 - F(x) = e^{-\left(\frac{x}{\theta}\right)^\beta}$$

$$\frac{1}{1-F(x)} = e^{+\left(\frac{x}{\theta}\right)^\beta}$$

$$\ln \frac{1}{1-F(x)} = \left(\frac{x}{\theta}\right)^\beta$$

$\ln\ln \frac{1}{1-F(x)} = \beta \ln x - \beta \ln \theta$

let $Y = \ln\ln \frac{1}{1-F(x)}$
let $X = \ln x$
let $A = -\beta \ln \theta$
let $B = \beta$
then Y = BX+A

The probability density function of the two parameter Weibull Function is:

$$f(x) = \frac{\beta x^{\beta-1}}{\theta^\beta} e^{-\left(\frac{x}{\theta}\right)^\beta}$$