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A GENERALIZATION OF TARGET MODELS OF SURVIVAL

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Howard G. Parker

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Re: UCRL-3873 - Errata

Please make the following changes in your copies of UCRL-3873

page 9 Eq. (5) should read

$$a_{\substack{n+1,\ i \\ (i < n+1)}} = \frac{k_{n+1}}{k_1 - k_{n+1}} \; a_{n,\,i} \;, \qquad (5)$$

page 22 Eq. (11) should read

$$S = e^{-kT} \sum_{r=0}^{n-1} \frac{(kT)^r}{r!} \;. \qquad (11)$$

and the succeeding equation should be

$$P(r) = \frac{(kT)^r \, e^{-kT}}{r!} \;.$$

Eq. (12) should read

$$f(T) = -\frac{dS}{dT} = \frac{k^n T^{n-1} e^{-kT}}{(n-1)!} \qquad (12)$$

page 23, about 3/4 way down the page, should read — — — —

and the probability of survival of a single target is

$$q = 1-p = e^{-kT} \;.$$

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Abstract

A multistage model for the description of biological survival curves is proposed as a possible means of generalizing target and hit theories to provide for interdependence of events. The model includes single- and multiple-hit and multiple-target theories as special cases, emphasizing their similarities and their differences. Its increased flexibility points out the nonunique character of the fit of various current models to data. In addition it provides a simple scheme for holding in mind the current theories and their assumptions.

The basic model consists of a series of n discrete stages. The time in each stage is randomly determined on the basis of a frequency k_i which can be set differently for each stage. When all the k's are equal, multihit theory results. An arithmetic progression in the k's gives rise to Kiga's multitarget theory. Alternatively, other untested relationships between the k's can be examined.

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The Role of a General Model

The model for survival proposed here is an example of a multistage stochastic model. Hoffman has explained the term stochastic process as "synonymous with 'random process' and by common usage. . . associated with processes depending on time."[1]

The application of a single-stage stochastic model to the duration of generation times has been discussed by Feller.[2] A more complex stochastic model for generation time, postulating a series of successive stages, with the time spent in each stage randomly determined, has been proposed by D. G. Kendall.[3] On the other hand, a number of authors dealing with survival times have fitted data with curves derived in terms of independent "targets" or independent "hits" on a single target. This treatment has been most successful in describing survival after irradiation.[4, 5, 6] It has also been used by Wood in describing heat inactivation of unicellular organisms.[7] An article by K. G. Zimmer summarizes much of the work with hit theory and suggests a number of other potential applications.[8] Recent suggestions that radiation at low dose rates "accelerates aging"[9, 10] have prompted an examination of these different stochastic theories as models for survival of any nondividing cell or higher organism, both when subjected to injurious agents and in normal aging.

A complex stochastic model for survival can postulate "lifetimes of a series of excited states of very large molecules."[1] Or, it may postulate a sensitive volume accumulating multiple "hits" before death ensues.[4] On the other hand, it may postulate multiple "targets" being hit.[5, 7, 11] These concepts have largely been developed independently. The assumption basic to each of them, however, is that of a chain of multiple discrete steps taken by the organism and leading to its death. The following model is proposed which makes this assumption but does not require the restriction of complete independence of targets or hits that characterizes the usual model. This development introduces greater complexity into the mathematical formulae, but undoubtedly can thereby bring them more into accord with biological reality.

The General Model

A series of stages that must be passed before an organism dies is postulated, with the length of time spent in each of these stages determined by a random or accidental event. See Fig. 1. The probability of occurrence of random events is constant within each stage, but different from one stage to another. Time is used as the independent variable in this treatment, but one might substitute units of radiation dose for time in any of these equations.

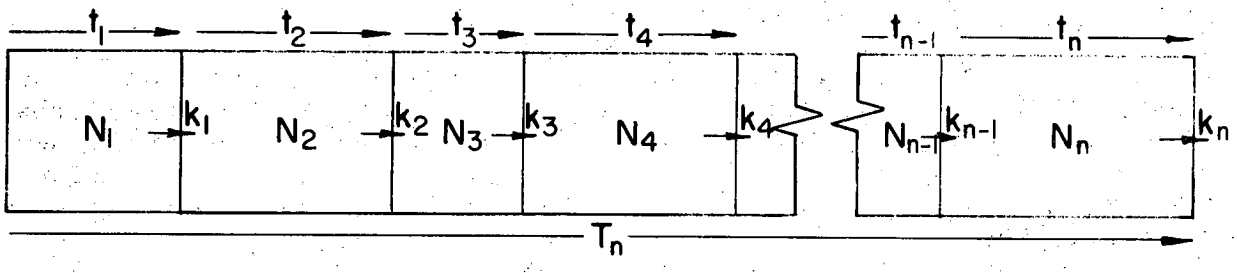

Fig. 1. Schematic representation of the general n-stage model.

A model in which retrograde movement from one compartment to another can also occur might be useful for including "recovery." Its great generality might provide a helpful conceptual framework, but in biology one cannot specify enough parameters to make explicit use of such a model at present. The model proposed in this paper is used simply as an approximation less restricted than most current ones. We shall consider what Feller refers to as a "pure death process."[2]

The assumptions and the mathematical treatment of this model correspond with those used in the differential equations of the multicompartment systems that have recently become a useful tool in biology. They also correspond with the mathematics describing chains of radioactive isotopes in transient equilibrium.

If the length of time spent by the organism in any single stage i is t_i, and the probability that a random event will terminate the organism's presence in that stage during an interval dt is the constant k_i times dt, then the lengths of time spent in that stage have a distribution of probabilities given by

$$f(t_i) = k_i e^{-k_i t_i} . \quad \text{(See Fig. 2)} \qquad (1)$$

In a two-stage inactivation process, one must work out the frequency distribution for total time spent in two such compartments (see Appendix). This distribution has quite a different form from the one-compartment case, and the difference illustrates the reason for using multistage theories for fitting bell-shaped death-rate curves or sigmoid survival curves (Figs. 3 and 4). One can obtain the solution of the equations for death-rate curves as more and more stages are added, either by considering the statistics of times spent in the whole process in relation to the time spent in each stage, or alternatively by the successive solution of first-order differential equations describing the number of individuals in each stage (see Appendix). One can then obtain a more general result through mathematical induction:

When

$$f(t_i) = k_i e^{-k_i t_i} ,$$

$$f(T_n) = a_{n,1} e^{-k_1 T_n} + a_{n,2} e^{-k_2 T_n} + a_{n,3} e^{-k_3 T_n} + \cdots\cdots$$

$$+ a_{n,n} e^{-k_n T_n} ;$$

Or,

$$f(T_n) = \sum_{i=1}^{n} a_{n,i} e^{-k_i T_n} , \qquad (2)$$

where the first subscript indicates the number of stages and the second subscript indicates the number of the term considered.

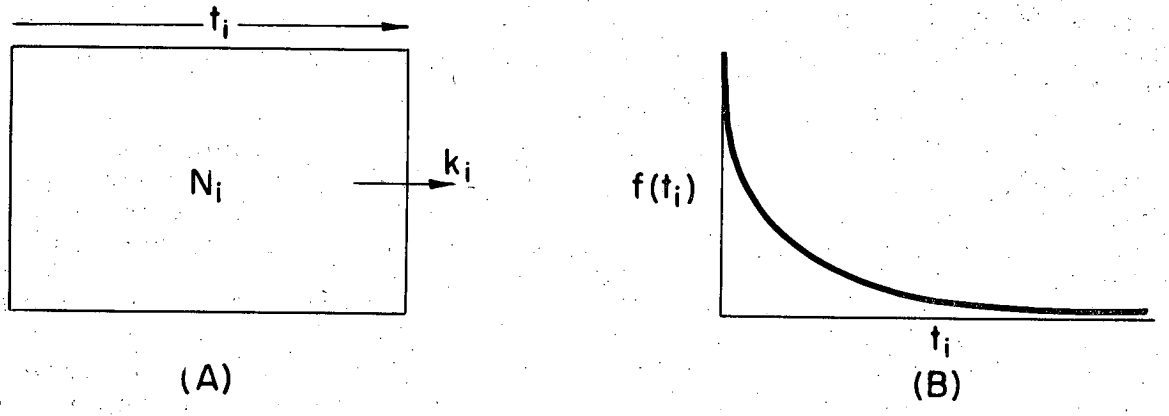

Fig. 2. (A) represents schematically the random influence k_i on the duration of time t_i spent in stage i. (B) is the linear plot of $f(t_i)$ against t_i, an exponential curve with a mean life of $1/k_i$.

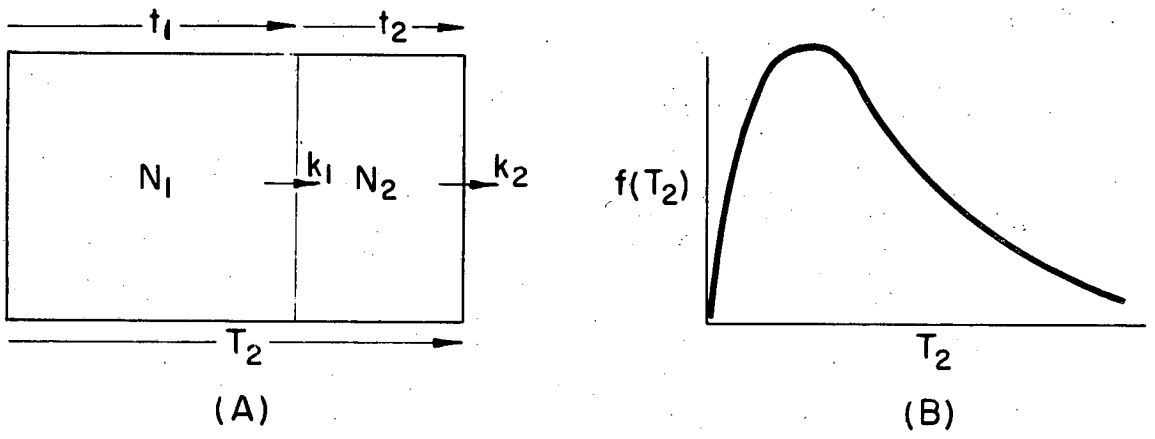

Fig. 3. (A) represents schematically the two discrete stages 1 and 2, each with its random influence, k_1 and k_2 respectively, on the duration of time (t_1 and t_2) spent in each stage. N_1 and N_2 represent the number in each stage. T_2 represents the total time for passage through the two stages. (B) is the linear spot of $f(T_2)$ against T_2.

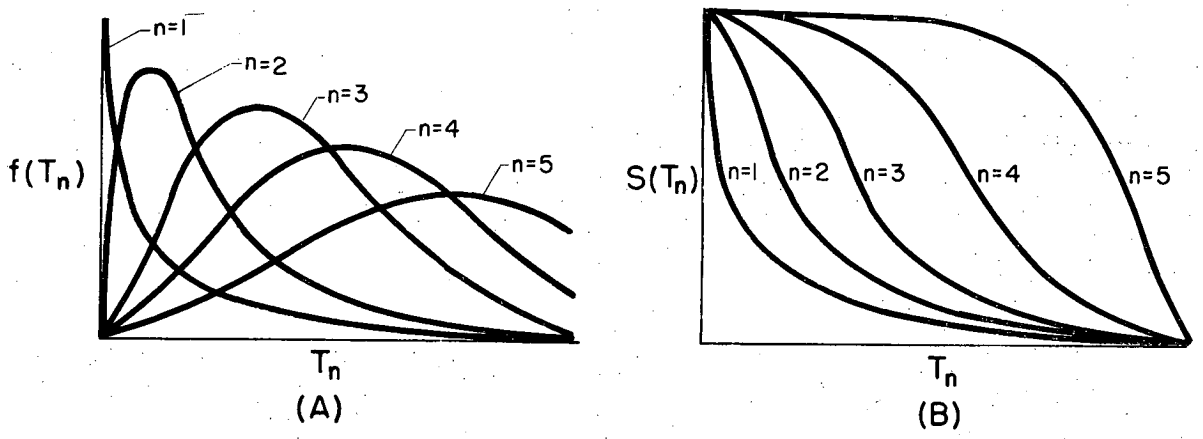

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Fig. 4. (A) illustrates the change in the death-rate function $f(T_n)$ plotted against time as n, the number of stages is increased. Note the change from exponential to a progressively more bell-shaped curve. (B) illustrates the parallel changes that take place in the survival function $S(T_n) = \int_t^{\infty} f(T_n)dt$ as n is increased.

The recursion formula

$$f(T_{n+1}) = k_{n+1} \sum_{i=1}^{n} \frac{a_{n,i}}{k_i - k_{n+1}} \left(e^{-k_{n+1} T_{n+1}} - e^{-k_i T_{n+1}}\right) \qquad (3)$$

gives rise to relationships between the coefficients $a_{1,1} = k_1$, (4)

$$a_{n+1,\, i \; (i < n+1)} = \frac{k_{n+1}}{k_i - k_{n+1}} a_{n,i} , \qquad (5)$$

and

$$a_{n+1,\, n+1} = \sum_{i=1}^{n} a_{n+1,\, i} , \qquad (6)$$

which are useful for obtaining the form and coefficients of the death-rate function. When none of the k_i are equal, this crude death-rate function is always the sum of n exponential terms in $k_i T_n$. It has coefficients, both positive and negative, of increasing complexity, but involving only the k's. The recursion formulae permit fairly rapid calculation of the coefficients in a particular case even when n is rather large. After the coefficients have been tabulated, the individual exponential terms may be added graphically on semilogarithmic paper to show the form of the death-rate curve. The formula can be integrated, term by term, and similarly plotted to give the survival curve. In some cases, to be described later, the values of the coefficients rapidly converge to limiting values regardless of further increase in the number of stages.

For the sake of generality, it is important to note that the order of occurrence of the n stages used in visualizing the process has no bearing on the form of $f(T_n)$, the death-rate function.

A Special Case

If all the k's have the same value, then in deriving the death-rate function one obtains a somewhat different result. To avoid division by zero, the general formula given above must assume $k_1 \neq k_2 \neq k_3 \neq \ldots\ldots k_n$. However, with $k_i = \text{const} = k$ and all other assumptions remaining the same, one obtains the single expression

$$f(T_n) = \frac{k^n T_n^{\,n-1} e^{-kT_n}}{(n-1)!} \qquad (7)$$

The recursion formula here is simply

$$f(T_{n+1}) = \frac{kT}{n} \; f(T_n),$$

when

$$f(T_1) = e^{-kT_1} . \qquad (8)$$

The curves derived from these expressions as n is varied are qualitatively similar to those in Fig 4A, B. It is this special case, in which the k's are all the same, that Kendall has treated.[3] He indicates that with a simple change of variable, Eq. (7) corresponds to the equation for the frequency function of the χ^2 variable with 2n degrees of freedom. This points out some interesting relationships between the χ^2 variable, the Poisson distribution, and the random processes used in the multistage derivation of Eq. (2). In addition it makes possible reference to tables of χ^2 for curve fitting in this special instance.

When some, but not all, of the k's have the same value, the formulae become more complicated, and a separate derivation becomes necessary.

The Multihit Case

The general model, when restricted to k_i = const (i.e., when all the k's are equal), gives rise to the mathematics of multihit processes, with kdt the probability of a hit in dt and n the number of hits required to inactivate. The correspondence of this model, that of Kendall for generation times, and the multihit model becomes obvious when one considers the basic assumption of successive irreversible steps taken randomly. In each of these cases, simultaneous hits are excluded from the model as having a negligibly small probability.

The correspondence of the mathematical details derived from the present model and from the usual consideration of the Poisson distribution is indicated in the Appendix.

The Multitarget Case

If one imposes, instead, the restriction

$$k_{i+1} = \frac{n-i}{n-i+1} \; k_i ,$$

an arithmetic progression in k_1/n, he obtains the equivalent of the multitarget theory developed by Kiga[11] (Appendix). In this theory there are n independent targets, any m of which, when hit, give rise to death of the organism. The mathematical work involved in applying Kiga's formula is much simplified if a table of the incomplete β function is available.[12] If the target number goes beyond these tables (or for convenience in graphical work), one can calculate the coefficients according to the recursion formulae given here (Eqs. (3), (4), (5), (6)). The correspondence between the arithmetic progression

in k's and Kiga's multitarget model can be indicated by an example (Fig. 5). In this case, if k indicates the probability of a hit on an individual target, we see that in the first stage, four targets are exposed; in the next, three targets remain, and so on. The number of stages corresponds to the number of hits necessary to kill, while the coefficient of k corresponds to the number of targets left.

In the multitarget case, k_i is the sum of the individual probabilities of a hit for each target, with the assumption that none of these probabilities is much greater than the average. If any individual target has a probability of being hit that is large in comparison with the sum of probabilities for the rest of the targets, it will have the practical effect of creating an (n-1)-hit curve from an n-hit curve. This point has been developed by Wijsman[12] in the analysis of radiation-induced mutations. Rigorous consideration of such situations, as well as the occurrence of injurious stimuli that simultaneously injure many targets, is excluded from our present model by the very nature of its assumptions. Their importance, however, would be obvious in a theory of survival that could include catastrophic events, for example the wiping out of a population, or the sudden destruction of a healthy organism.

A case of particular interest is the survival of populations that appear to have been converted from a multi-event type to a single-event type--for example, human cancer populations,[14] or a population of hypophysectomized rats.[15] In this case, one might visualize rapid inactivation of all targets but one at the time of the unknown metabolic change, or creation of a new type of interdependence of targets such that when a particular target is later hit, all the others are simultaneously inactivated. A more attractive alternative would be to visualize one or more targets as individually essential to life, and having such a low probability of being hit that they are not involved in the ordinary death mechanism. The metabolic change then might simply raise the susceptibility of one of these targets to damage to such a high level that this single-hit mechanism predominates. It might do so by removing protective factors, for example, without changing the present interpretation.

The multitarget model by Atwood and Norman[5] is particularly suited to analysis of survival curves where genetic damage and considerations of ploidy may reasonably be presupposed.[6] In its simplest applications, it is easier to use for curve-fitting than the general model given here. It rigidly restricts the relationships of the target hits necessary for death. In its present form it cannot provide for more general interdependence of genetic units.

The Generality of the Model

The n-compartment generalization given here was developed in order to allow the expression of conditional probabilities, so that, for instance, when one target is hit, the probability of the next hit can be adjusted at will. This is done by varying the values of the k's.

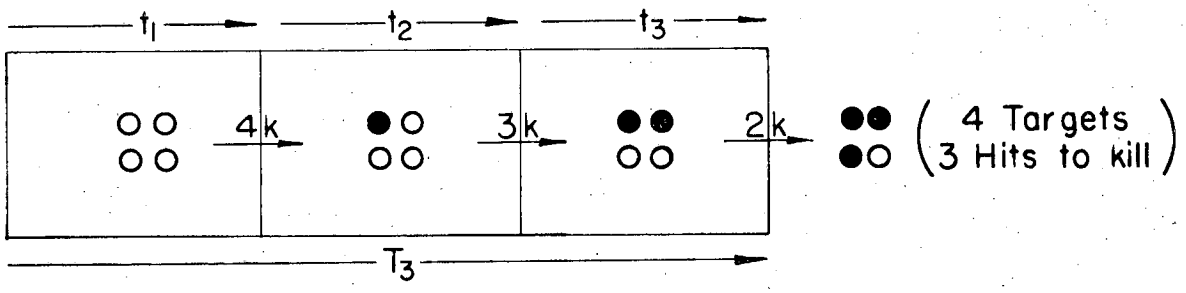

Fig. 5. The multitarget case.

New general relationships between k_i and k_{i+1} can be examined. A type of "recovery" or an increased susceptibility may be described this way. Preliminary examination of some of these relationships has been carried out to learn their effect on death-rate curves. Some interesting points raised by these studies are mentioned in the next section.

A number of techniques are already developed which might also have applicability in adjusting the k's.[2] Dependence of the outcome in a particular stage on the outcome of the directly preceding one (a Markov chain) might be incorporated in a model of survival. This might prove a worth-while technique for constructing a gross model for human survival, for example, if the change in probability of death on entering each of the major diagnostic disease catagories could be ascertained. However, this consideration of targets individually goes beyond our present model.

High Multiplicity, the Normal Curve, and the Central-Limit Theorem

The investigation reported here was begun with the idea that stochastic models of this type might be used to fit survival data (e. g., human survival data) that have been described by the Gompertz function,[9, 10] in which the logarithm of the age-specific death rate rises linearly with age. This effort has not met with complete success. However, it has led us to consider multistage processes which have very high numbers of stages, and in which the probability of the next hit rises sharply as the hits accumulate. Some interesting ideas in this regard will be mentioned:

R. A. Fisher has shown that the χ^2 variable approaches the normal distribution as $n \to \infty$, and for practical computation, more than 30° of freedom (more than 15 stages in the multihit model) can be treated as if the time of death were normally distributed.[16] This points out a very interesting possible relation of stochastic processes in biology to the normal or Gaussian distribution. The normal curve can be derived as the limiting case in a number of processes and need not be related to the concept of "true value" with a "curve of error." The interplay of genetically determined variability in a population's resistance to a lethal agent with other chance factors in resistance is not explicitly handled by target theories. This is a major weakness of present target theories. It is a less serious one, however, when genetically highly homogeneous populations are being described. One might profitably investigate the stochastic basis for a number of approximately normally distributed variables in biology, such as size or weight. Such an approach would appear warranted for crude death-rate curves for humans, or for mammalian red blood cells, for example.[14, 17]

A consideration of the Central-Limit Theorem[18] shows that a wide variety of relationships between the k's gives rise to a death-rate curve that approaches the normal curve as the number of stages is increased without bound. However, specific cases of interest such as an arithmetic progression (multitarget case) or a geometric progression in the k's give rise to nonnormal distributions when $n \to \infty$, and in fact may converge rapidly to a limiting curve that is largely determined by a small number of the slowest stages. When death rate is given by the normal curve and log age-specific death rate is plotted from it, it gives rise to the nearest approximation to the straight-line

Gompertz function that these investigations have furnished. It always has a concave downward curvature, however. Whether curves of this sort, more nearly linear when plotted against the log of time than against time, are a more or less adequate fit to human survival data than the Gompertz function remains to be settled. Multihit curves have greater downward concavity than normal curves on the semilog plot, approaching the normal curve as $n \to \infty$. Multitarget curves are still more sharply curved on this plot, and curves with a geometric progression in the k's even more so. Recalling that the order of occurrence of stages is immaterial in this result, we see that the multihit curves (k_1 = const.), and the normal curve that they approach, are as close to the straight-line Gompertz function as this sort of theory comes. Additional considerations will be necessary to fit data in which the Gompertz plot is truly linear throughout the survival of 95% or more of the population. However, in some cases, multihit theory appears to fit data at least as well as the Gompertz function (see Figs. 6 and 7). Such a circumstance can be predicted whenever the log-log plot of age-specific death rate is more linear than the semilog plot.

Some Other Models

The work of Brues and Sacher and of Jones[9, 10, 19] indicates that at low dose rates, doses of ionizing radiation are approximately additive in determining the age-specific death rate. In addition, a great deal of the material presented here is applicable to survival curves if radiation dose is substituted for time in the equations. These facts suggest that radiation and normal aging may both involve random accidents to the same targets on a macromolecular level. This idea is not new,[20] but bears re-emphasis. Further examination of hit theories in which the independent variable is (t + const. x D) may be of interest. (See Fig. 7(B).)

A number of alternative models might be proposed for the production of sigmoid survival curves (survival curves corresponding to a roughly bell-shaped crude death-rate curve--see Figs. 4A and 4B). For example, a sigmoid curve might be related to random chemical events by analogy with one of the chemical "clock reactions" that has been investigated in detail.[21] Such a theory might describe the competition between protective and destructive agents for a site in the cell.[22] The actual situation is undoubtedly a complex of competing chemical reactions of this sort.

A very interesting new stochastic theory of the origin of the mortality curve has been advanced by Sacher,[23] presenting quite a different viewpoint. It is not wholly inconsistent with target theory, however, nor is it basically any more successful. It explains the Gompertz function as the approximate result of a linear change with time in a "mean physiologic state." However, the change in mean state requires further assumptions that might well be justified by a target theory.

At the macromolecular level, the various aging theories -- accumulation of toxic products, consumption of protective agents, or accumulation of partially inactivating changes in structure -- may one day be combined into a complex but coherent picture of events. As indicated here, target or hit

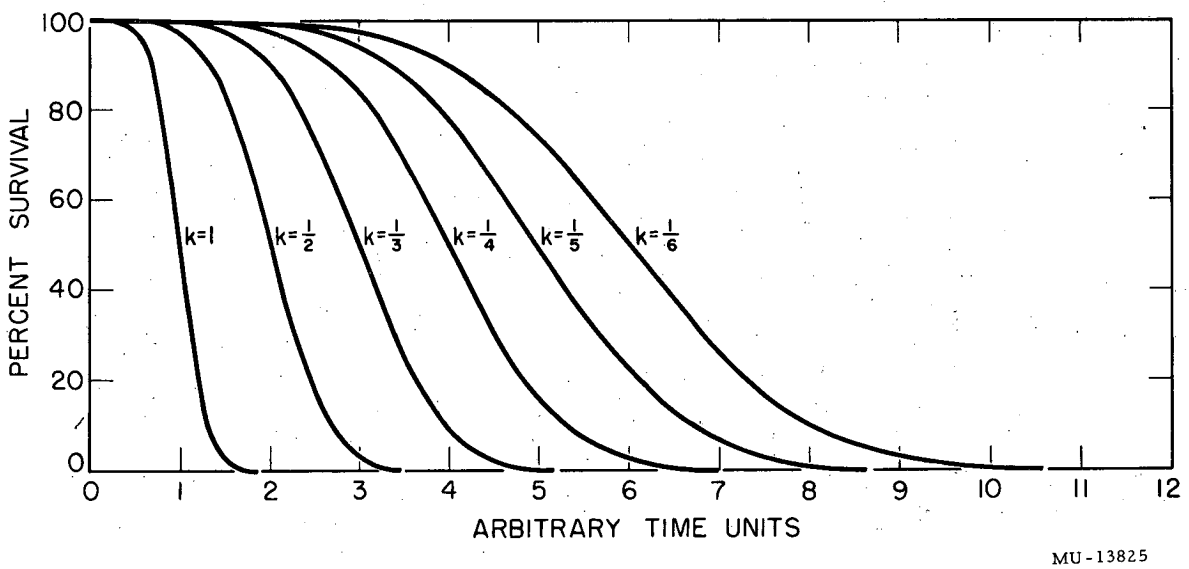

Fig. 6(A) A family of cumulative normal curves used as a good approximation to multiple-hit survival curves when n, the hit number, is 15 or greater. The parameter k (the probability of a single hit) is varied, giving rise to this family of curves as n is held constant. (Such a situation might be visualized in populations x-irradiated at constant intensity throughout life.)

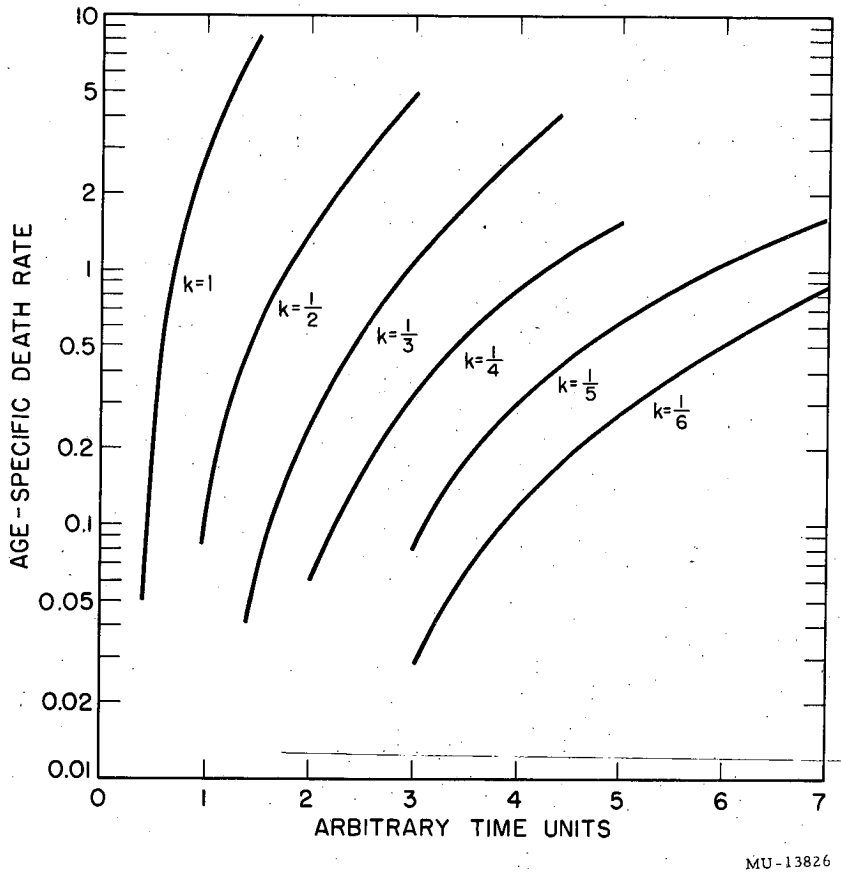

Fig. 6(B) Illustrates the properties of the family of curves shown in (A) when replotted as log of age-specific death rate against time (the Gompertz plot). A log-log plot would straighten these curves only a bit more.

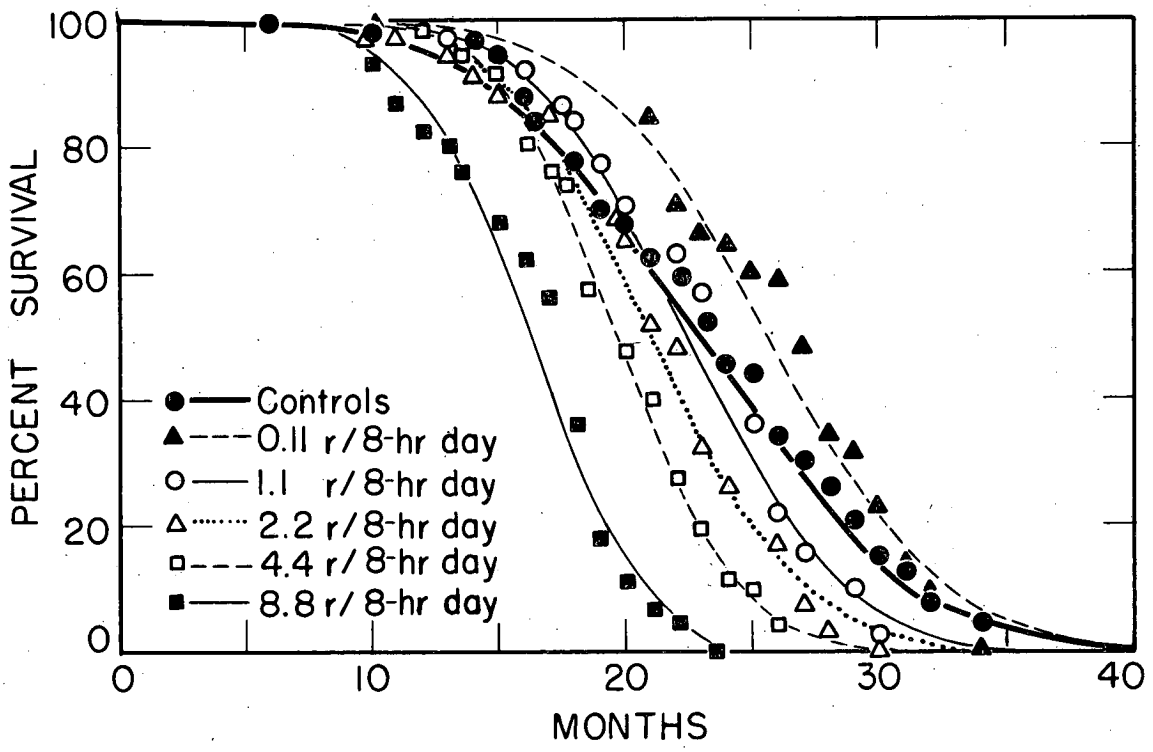

Fig. 7 (A) The data of Lorenz on LAF_1 mice irradiated at constant average intensity throughout life,[24] refitted with the cumulative normal curve appropriate to multihit theory with $n > 15$. This was done by fitting the best straight line on probit paper, which uniformly gave a good fit. It has been replotted on plain paper for greater readability. Application of more complex models suggested as possibilities in the text does not appear warranted by these data; however, such models serve to remind us of the nonunique nature of the present fit.

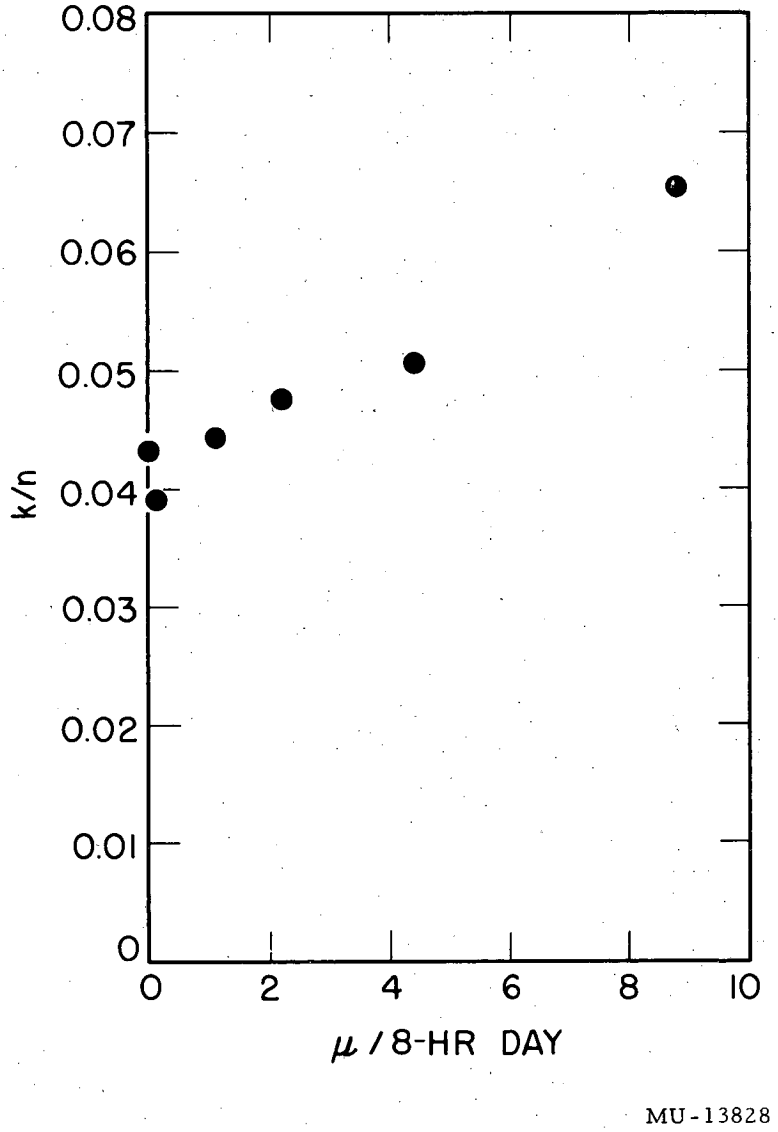

Fig. 7(B) A plot of k (the probability of a single hit) divided by n, the hit number, against dose rate in r per 8-hr day, using the data of 7(A). Here n, the hit number, is assumed constant; k = n/mean survival from hit theory. The lowest dose rate (0.11 r per 8-hr day), should be used for comparison instead of the control, in order to avoid for the present the unsettled problem of apparent increase in survival at low dose rates. Note that the increase in k is approximately linear with increase in dose rate.

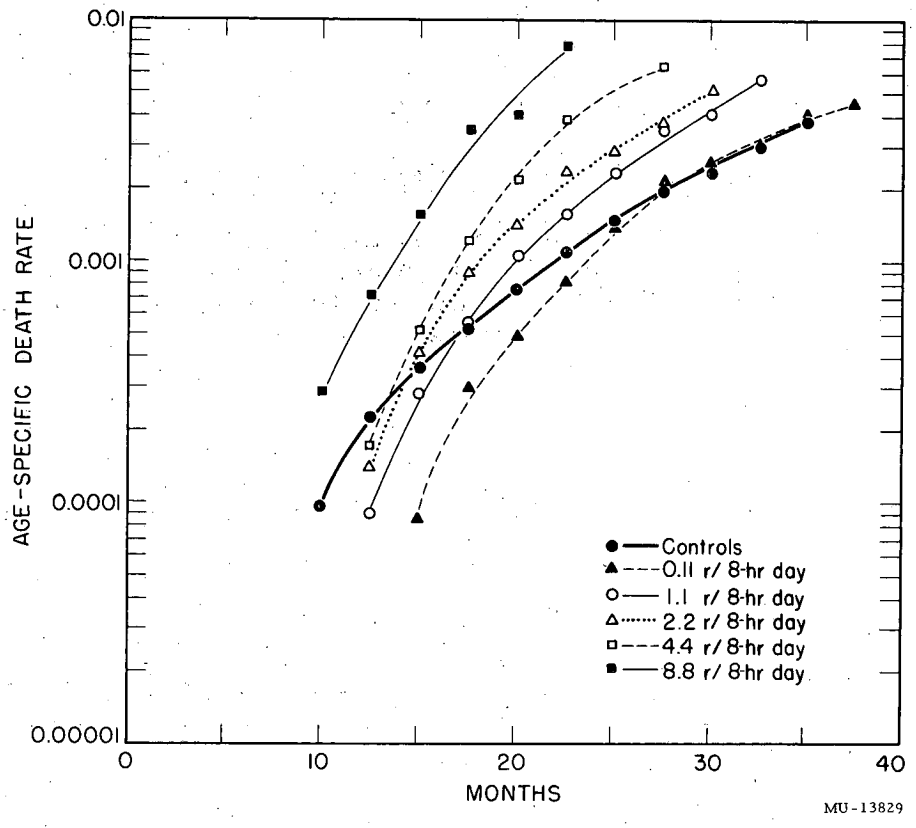

Fig. 7(C) The Gompertz plot of the cumulative normal curves of (A). Judgment of the fit to the data is more appropriately made in (A). The Gompertz plot is shown to indicate the shape and relationships of these theoretical curves for comparison with the same data fitted with straight lines in Fig. 5 of Ref. 18.

theories portray a progressive stepwise accumulation of basic cellular defects regardless of the interplay of protective and destructive agents. The model presented here emphasizes the basic assumptions in these models and the variety of sigmoid survival curves made possible by simple combinations of purely random events.

APPENDIX

Derivation of the General Model

Two alternative methods of deriving the form of the death-rate curve for the general model are outlined below (A and B). In each case, let t be a random variable denoting time of death, and $f(t)$ the frequency function of time of death. $S(t)$ can then be defined as

$$S(t) = \int_t^\infty f(t)\ dt \ .$$

$S(t)$ is then the survival-curve function and $f(t)$ the death-rate function. From Eq. (1) we have

$$-\frac{dS}{dt} = f(t) \ .$$

The age-specific death rate is defined as $-\frac{dS}{dt} / S$. Also, let N_i be the probability that an organism is present in stage i, so that we have

$$S(t) = \sum_{i=1}^{n} N_i\ (t) \ ,$$

and

$$f(t) = k_n\ N_n(t).$$

A. If the length of time spent by the organism in any single stage i is t_i, and the probability that a random event will send the organism into the next stage during any interval dt is the constant k_i times dt, then the length of time spent in stage i occurs with the frequency

$$f(t_i) = k_i\ e^{-k_i t_i} \ ,$$

while the total length of life, T_n, occurs with a frequency $f(T_n)$ that depends on n and the k_i's. The derivation of the death-rate curve for a two-stage process is used as an example. The problem is to find the frequency function for total time T_2 spent in the two stages from the frequency functions for t_1 and t_2, the time spent in each separate stage. (See Fig. 3) Similar problems can be found in Ref. 15.

Given

$$f(t) = k_1 e^{-k_1 t_1} ,$$

$$f(t_2) = k_2 e^{-k_2 t_2} ,$$

we have

$$f(t_1 t_2) = f(t_1)\, f(t_2) = k_1 k_2 e^{-(k_1 t_1 + k_2 t_2)} .$$

Let

$$T_2 = t_1 + t_2 ,$$

$V = t_2$, a change of variables preliminary to obtaining $f(T_2)$.

Then we have

$$\frac{\partial T_2}{\partial t} = 1, \quad \frac{\partial T_2}{\partial t} = 1, \quad \frac{\partial V}{\partial t} = 0, \quad \frac{\partial V}{\partial t} = 1, \qquad \text{and}$$

$$f(T_2, V) = \frac{f(t_1, t_2)}{\frac{\partial (T_2, V)}{\partial (t_1, t_2)}} = \frac{k_1 k_2 e^{-(k_1 t_1 + k_2 t_2)}}{\begin{vmatrix} 1 & 1 \\ 0 & 1 \end{vmatrix}} = k_1 k_2 e^{-[k_1 (T_2 - V) + k_2 V]}$$

Then $f(T_2)$ is obtained from $f(T_2, V)$:

$$f(T_2) = \int_0^{T_2} f(T_2, V)\, dV = \int_0^{T_2} k_1 k_2 e^{-[k_1 (T_2 - V) + k_2 V]}\, dV$$

$$= k_1 k_2 e^{-k_1 T_2} \int_0^{T_2} e^{(k_1 - k_2) V}\, dV,$$

$$f(T_2) = \frac{k_1 k_2}{k_1 - k_2} \left(e^{-k_2 T_2} - e^{-k_1 T_2}\right). \qquad (10)$$

Addition of a third stage requires that this process be repeated, using Eq. (10) and

$$f(t_3) = k_3 e^{-k_3 t_3}$$

to obtain $f(T_3)$. The general result, Eq. (2), and the recursion formula, Eq. (3), can be obtained similarly by mathematical induction.

If k_i = const and the same process is followed, repetition of the integration step in the above derivation continues to give rise to a single term; hence the simplicity of Eq. (7) compared with the general formula.

B. The same result can be obtained as follows:

In the first stage

$$\frac{-dN_1}{dt} = k_1 N_1 \text{ or } N_1 = e^{-k_1 t} .$$

If a second stage is added we obtain,

$$\frac{dN_2}{dt} = k_1 N_1 - k_2 N_2 = k_1 e^{-k_1 t} - k_2 N_2 ,$$

a first-order linear differential equation whose solution is

$$N_2 = \frac{k_1}{k_1 - k_2} \left(e^{-k_2 t} - e^{-k_1 t}\right) .$$

The rate of death is then

$$f(T_2) = k_2 N_2 = \frac{k_1 k_2}{k_1 - k_2} \left(e^{-k_2 t} - e^{-k_1 t}\right) .$$

If a third stage is added, we have

$$\frac{dN_3}{dt} = k_2 N_2 - k_3 N_3 ,$$

which, by use of the result for $k_2 N_2$, can be solved for N_3; $k_3 N_3$ is then the death rate for a three-stage process. Mathematical induction again will give the general result, Eq. (2). Solution of these differential equations involves successive solution of first-order linear equations, always yielding an answer in closed form.

The Multihit Case

The form in which the multihit survival curve is usually given[4, 5] is (in our notation)

$$S = e^{-kT} \sum_{r=0}^{n-1} \frac{(kT)^r}{r} . \qquad (11)$$

Here the number surviving at time T is given by the sum of those which have received hits of zero to n-1 where the probability of having received r hits is given by the Poisson formula

$$P(r) = \frac{(kT)^r e^{-kT}}{r} .$$

Differentiation of Eq. (11) gives

$$f(T) = -\frac{dS}{dT} = \frac{k^n T^{n-1} e^{-kT}}{(n-1)} , \qquad (12)$$

which corresponds with Eq. (7) derived by one of the methods given above. It is easier to visualize the significance of Eq. (12) if it is written

$$f(T) = k \cdot \frac{(kT)^{n-1} e^{-kT}}{(n-1)} \qquad (13)$$

The factor on the right in Eq. (13) is the probability of exactly n-1 hits' having occurred by time T according to the Poisson formula, and k times this factor gives the probability of the n^{th} hit's occurring at time T.

The Multitarget Case

The multitarget theory developed by Kiga,[11] in which there are n independent targets, any m of which when hit give rise to death of the organism, expressed in our notation is

$$S_{n,m} = \sum_{r=0}^{m-1} \binom{n}{r} (1-e^{-kt})^r (e^{-kt})^{n-r} . \qquad (14)$$

The number $S_{n,m}$ is seen to be the sum of those who have received hits of zero to m-1 where the probability of having received r hits is given by the binomial formula

$$P(r) = \binom{n}{r} p^r q^{n-r} ,$$

and where p, the probability that a single target has been hit, is given by

$$p = 1 - e^{-kt} ,$$

and the probability of survival of a single target is

$$q = i-p = e^{-kt} .$$

The correspondence of this formula for S(t) and the one derived from Eq. (2) of the general model we have shown only by an analysis of the assumption involved, which are identical, and by the checking of simple cases. Further formal demonstration has not been done.

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