

Mathematics and statistics of aging

Jayant V. Deshpande

In this article we review the various concepts of aging as they apply to ensembles or populations of individuals. We observe that these notions are extremely useful in the study of biological units and populations as well as mechanical, electronic and other types of components, systems composed of such components and their populations. It is shown how various stochastic models may be based on different qualitative aging concepts. Statistical aids for choosing between various models are also introduced. A recent report on the aging of fruitflies is critically examined in the light of these aging concepts.

EVERY new-born grows old and eventually dies. This is universally accepted as truth. So, perplexity sets in when sometimes it is reported that 'life expectancies may not always decrease as organisms grow older'. It was reported in *Science*¹ and quoted in the *Times of India* dated 30 Oct. 1992 that the results of certain experiments on fruitflies indicated that once a fly was past a certain age, its life expectancy may increase with age. Is this consistent with the universal truth stated in the first line above? Such seeming anomalies may be reconciled only through a detailed study of the phenomenon of aging.

Let us consider units which are new (just born or manufactured), which carry out their appointed functions for a time and then fail (or die) once for all. Thus, we are for the present excluding units which may be repaired and made functional again. Each such unit has certain physical or biological properties and characteristics. Besides, there is the totality of such units in a lot, say those manufactured in a batch, those born to similar parents in a given interval of time, etc. Such an ensemble is called a population in statistical language. The units in the populations, though subject to innate variability, exhibit certain regular statistical patterns. A study of these patterns from a probabilistic point of view provides useful insights about the population as a whole. Many anomalies arise out of the confusion between the properties of the individual unit and those of the whole population, particularly when the population properties are erroneously imputed to specific individuals in it.

The areas of survival analysis and reliability theory in statistics and probability deal with the life/death phenomenon. These have developed in strength since the sixties with some isolated distinguished work earlier also^{2,3}. Our emphasis in this article will be on various concepts of aging and their consequences, to indicate

carefully to the user their respective spheres and limitations and help him in resolving apparent inconsistencies. This is done in terms of the failure rate and the mean residual life functions of the random variable denoting the lifetime of a unit. The implications of various shapes of these functions for the populations of such units are discussed. We provide a couple of simple statistical procedures which help in the choice of a model according to the evidence regarding the shape of the failure rate. The last section considers critically several statements appearing in the article regarding the fruitflies experiment.

Modelling lifetime as a random variable

It is seen that the electric bulbs made by the same factory to the same specifications still have different lifetimes. This unpredictability of the lifetime makes it a random variable. Hence, its characteristics can only be described probabilistically and statistically. Let a random variable X denote the lifetime of a unit. Then it may be conveniently, and without loss of practical utility, assumed to be positive-valued and continuous, i.e. x will have a distribution function $F(x)$, a survival function $\bar{F}(x) = 1 - F(x)$ and a probability density function $f(x) = dF(x)/dx$. It should be noted that $F(x)$ denotes the probability that the unit fails not later than time x , or $P[X \leq x] = F(x)$; $\bar{F}(x)$ is the probability of the complementary event that it fails after time x , $\bar{F}(x) = P(X > x)$, and the probability that the unit fails in an interval $(t_1, t_2]$ is given by

$$F(t_2) - F(t_1) = \int_{t_1}^{t_2} f(x) dx.$$

Any of the above three functions carries all the probabilistic information regarding the random variable X . We specify various models for it taking into account the qualitative prior information which we possess. This is

Jayant V. Deshpande is in the Department of Statistics, University of Poona, Pune 411 007, India

where usually probabilistic modelling begins; but in modelling for lifetime distributions we start with certain other functions related to the above three.

The new concept which is relevant to lifetime modelling is the concept of age. It is the time lapsed since birth or since the unit was pressed into service without failure or interruption. In lifetime experiments the unit is monitored continuously since it is put into operation and hence one can talk of its age at any time until it fails. The function $r_F(t) = f(t)/\bar{F}(t)$, called the failure (or hazard) rate, is the rate at which the units fail in a very short interval at time t , given that it has not failed before, i.e.

$$r_F(t) = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} P(t < X \leq t + \Delta t | t < X) = \frac{f(t)}{\bar{F}(t)}.$$

Different populations show different behaviours in their failure rates. The difference between the probability density function $f(x)$ and the failure rate $r_F(x)$ is worth remarking upon. The former gives the rate at which electric bulbs are failing in the populations at age t , whereas the latter gives the rate at which the electric bulbs which have already attained age t are failing immediately at age t . Again, in the first case we consider the entire population and consider among them those failing at age t and in the second case our population is restricted only to those bulbs which have attained age t and consider those which fail immediately thereafter. It is well to keep this difference in mind because a confusion here could cause a misunderstanding later. It is, therefore, clear that among the two rates the failure rate reflects the effect of age on the failure patterns and the probability density function merely summarizes the failure pattern of the entire population.

Another function relevant to the probability distribution of lifetime is the mean residual life at age t , $\mu_F(t) = E[X - t | X > t]$. This is the expected further life (average further life) of a unit which has already attained age t . That is to say, $\mu(t) + t$ is the total expected life of a unit which is known to have survived up to time t . Obviously, $\mu(0)$ is the expected life of a new, as yet unused, unit. One can adduce reasons for the consideration of $\mu(t)$ as a characteristic of the aging patterns similar to those given in the case of $r_F(t)$. Either of the functions introduced above, $r_F(t)$, $\mu_F(t)$, is quite sufficient to provide the entire probabilistic information regarding the lifetimes while keeping age in mind. Any of the functions may be derived from any of the others⁴. But they do bring out different aspects of the probabilistic structure.

Aging of a population

A population is an ensemble of essentially like units, even if there are variations in their characteristics. It

could consist of fruitflies, or electric bulbs or human beings or motor cars, etc. If we say that X is the random variable representing the lifetime of the units in this population, then we also assert that $F(x)$, the distribution function of X , denotes the probability that a unit *chosen randomly* from this population will fail before or at age x . For a large population, it will approximately be equal to the proportion of units failing before or up to age x among the total number of units in the population. It is hard to impute these properties to a *specific single unit* in the population. A specified fruitfly will live its random, that is to say, initially unknown and unknowable lifetime and then perish. The probabilities can be ascribed to a single unit only if it loses its specificity and is regarded as an unmarked randomly chosen member of the population.

Let us consider a large population of fruitflies. For the sake of convenience, let us regard each member of the population as having been born at the same time. Usually this can be accomplished in an actual population by appropriately aligning the times of birth of the fruitflies.

As the time passes, the age of all the units increases and one by one they die, the population is progressively depleted and eventually exhausted. But, of course, in a real population there are births as well which combined with deaths will lead to extinction, equilibrium or explosion of the population. At this time we ignore births altogether. Such an ensemble of fruitflies or other biological entities is called a cohort.

To understand the effect of aging, we consider the deaths at any age t as a proportion of the part of the population still at risk, i.e. the residual cohort, in a unit interval of time at age t . This is approximately the probability of death in an interval of unit time, conditional on survival to age t . If the fruitflies, at least after a certain age, become more and more prone to death with advancing age, then this conditional probability should show an increase with increasing t . With biological populations, particularly the human population, the usual experience is that from birth to a certain young age t_0 , the effect of age is beneficial, meaning that the proportion of number of deaths to the population at risk shows reduction. Then there comes a period over which this proportion remains more or less constant. After a second threshold t_1 is passed, the effect of age is positively adverse and the proportion of deaths among the still-at-risk population increases till the population is exhausted. This leads to what is called a 'bathtub (BT)-shaped' failure rate $r_1(t)$, as shown in Figure 1.

In the case of human population the first phase over age $(0, t_0)$ corresponds to infant mortality, wherein deaths are due to congenital defects, postnatal complications and, in general, due to the extra vulnerability of infants to a harsh environment. The deaths during the interval (t_0, t_1) would essentially be accidental deaths,

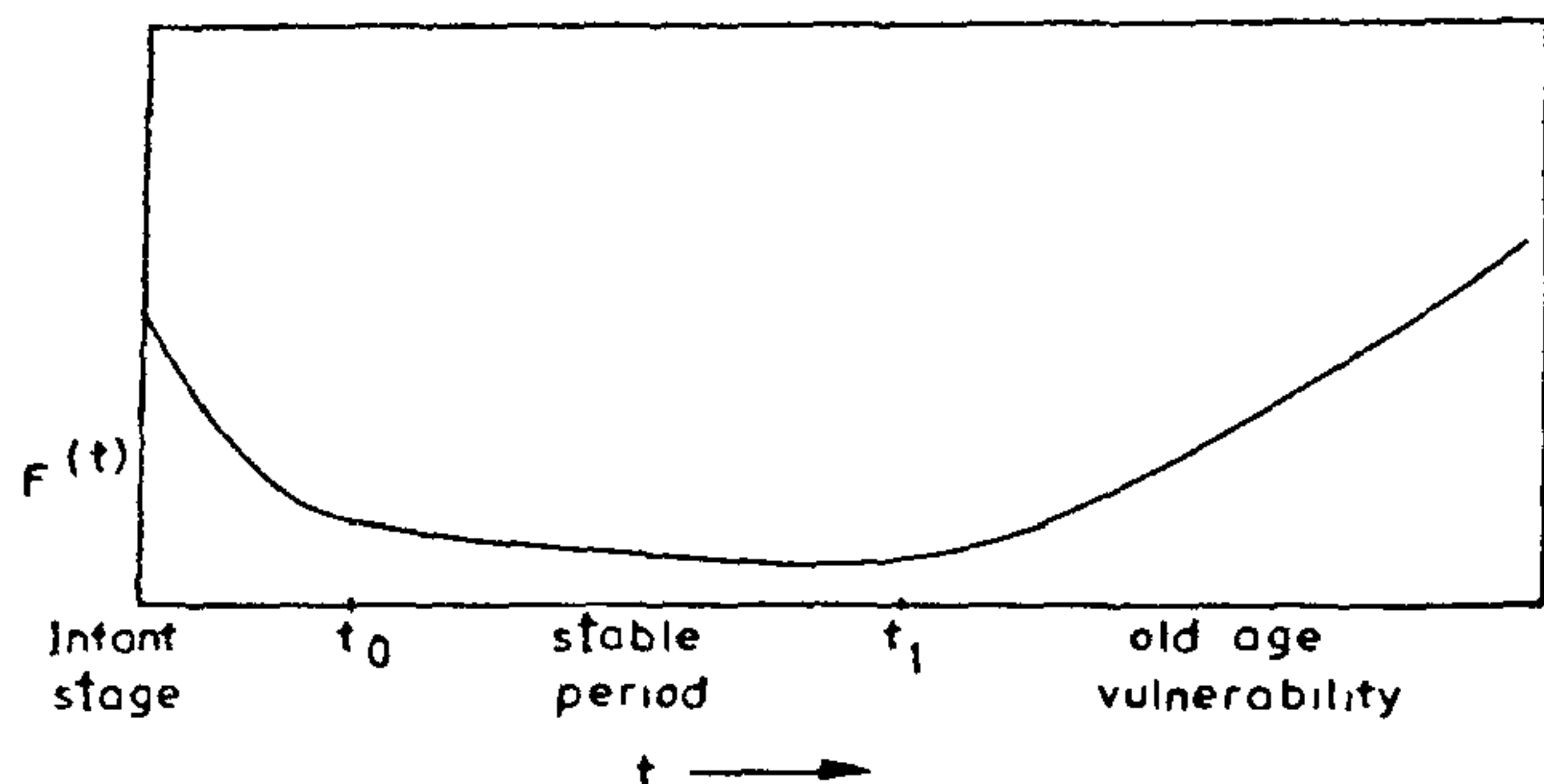


Figure 1. Bathtub-shaped failure rate

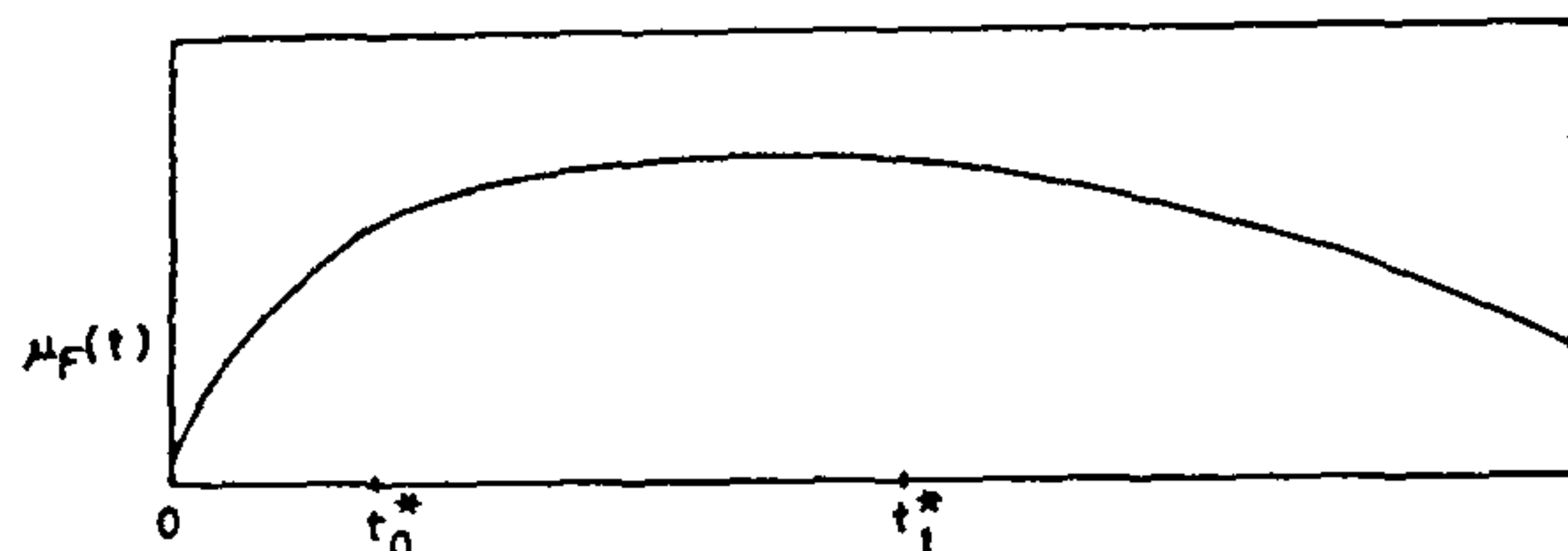


Figure 2. Upside-down bathtub-shaped mean residual life function.

those caused by an external agency like road accidents, accidental contraction of lethal viruses, predator attacks, etc. The deaths which occur beyond t_1 are attributed to what is termed, loosely speaking, as old age. The causes would be general wear and tear of tissues, hardening and narrowing of arteries, slow depositions of calcium and other materials at vital spots, wasting of muscles, etc. Automobile tyres or break linings wear out with use, thus making them more vulnerable to breakdowns with progressive age. In general, the deaths in this period are attributable to certain processes having a cumulative effect over time and which mature into conditions which become more and more favourable to death.

Instead, if we consider the above experience of aging in terms of the mean residual life function $\mu_F(t)$, then the graph will look like an 'upside-down bathtub' (UBT), as shown in Figure 2. Here t_0^* and t_1^* correspond to the two thresholds for moving from infancy to young and from young/middle age to old age, respectively. A BT shape for $r_F(t)$ will generally lead to a UBT shape for the corresponding $\mu_F(t)$ but not necessarily vice versa. Also, the thresholds t_0, t_1 for $r_F(t)$ and t_0^*, t_1^* for $\mu_F(t)$ will not necessarily be identical. This is because in $r_F(t)$ only the effect of age up to and including the time t is shown up, whereas $\mu_F(t)$ incorporates the effect of aging at ages beyond t also. See ref. 5 for details of such nonmonotonic aging patterns.

Moving away from human (or biological) populations may result in radical changes in the effect of aging. Consider electric bulbs. Those bulbs which do not have manufacturing defects would fail only when accidental

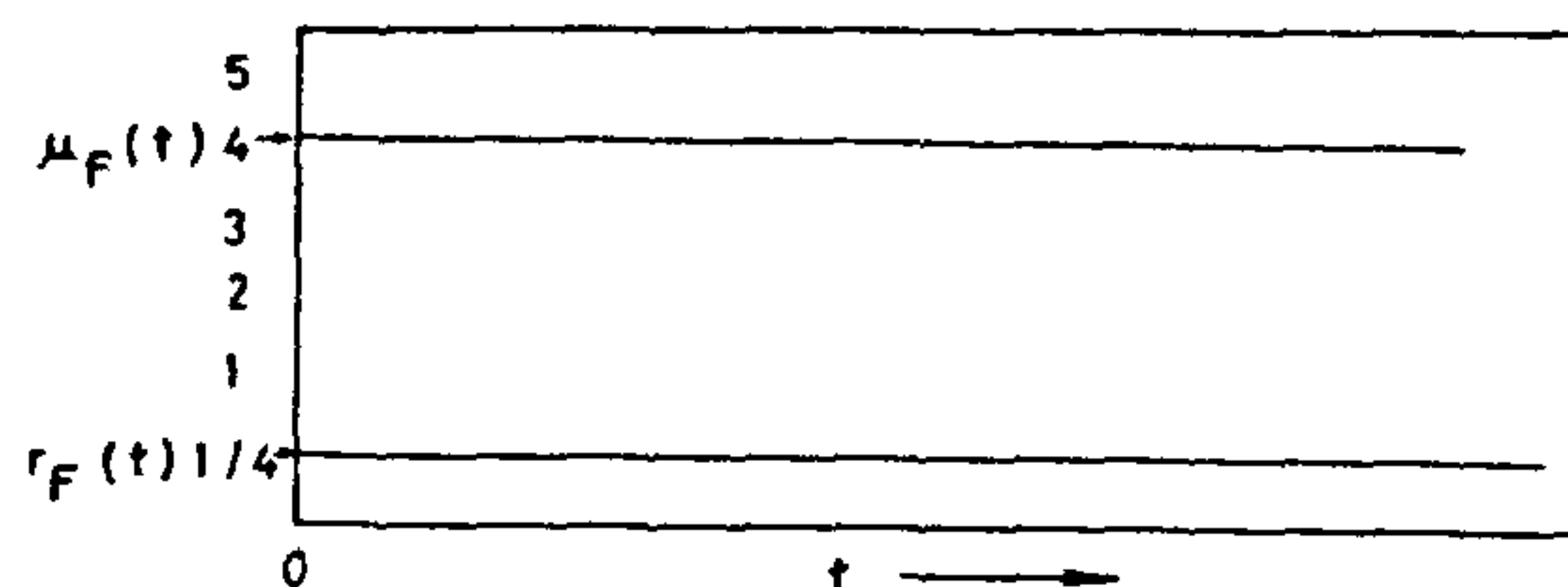


Figure 3. Constant failure rate and mean residual life function

external shocks (like a surge in the voltage, falling down from the socket, breakage of the filament, etc.) prove fatal. There is no discernible effect of age at all. Hence, the failure rate as well as the mean residual function are constant (and $r_F(t) = 1/\mu_F(t) = c$) as exhibited in Figure 3.

Besides electric bulbs, other units like electronic components, etc., show the same constant pattern of failure. This failure pattern, called constant failure rate, is a characteristic property of the exponential distribution function:

$$F(t) = 1 - e^{-\lambda t}, \text{ with } \bar{F}(t) = e^{-\lambda t},$$

$$f(t) = \lambda e^{-\lambda t}, r_F(t) = \lambda, \text{ and } \mu_F(t) = 1/\lambda \text{ for } t \geq 0.$$

The constant failure rate property is also called the lack of memory property or the no-aging property for obvious reasons. In a population it is manifested by approximately the same proportion of the population-at-risk failing in any unit interval of time, irrespective of the age. In radioactivity, the same model is found applicable under the nomenclature 'constant half-life' for electron emissions².

Models other than the exponential

In the last section we saw that the exponential distribution provides an adequate model for the distribution of the lifetime of a no-aging unit. However, we know very well that apart from electronics the no-aging phenomenon is rare. When systems are composed of statistically independent components, each having the exponential distribution, except in case of a series system, the lifetime of the system does not retain the no-aging property. Even in a simple system like the parallel system of two components, where the system lifetime is the maximum of the two component lifetimes, the distribution is not exponential; it does not even possess a monotonic failure rate. For a large class of systems called coherent systems the system lifetime possesses the IFRA (increasing failure rate average) property, which says that the failure rate $r_F(t)$ is such that the average

$$\frac{R_F(t)}{t} = \frac{1}{t} \int_0^t r_F(u) du$$

is an increasing function of t , though the failure rate itself may not be monotonic.

Next let us consider a mixture of several exponential populations. That is to say, our population is composed of several subpopulations, each of which possesses the no-aging property with different constant failure rates. Then the overall population, surprisingly enough, theoretically possesses a decreasing failure rate. In other words, the proportion of deaths to the number of still-at-risk per unit time interval will tend to show a *decreasing* trend as age increases. This is what we call the beneficial effect of age.

The third commonly occurring situation is the one in which a unit upon failure is replaced by another statistically independent unit from the same population. Then often the experimenter is interested in the total life of two or more units. Again, it is easily seen that even if each of the units has the same exponential life distribution, the total life length of two or more units exhibits an IFR (increasing failure rate) distribution, meaning a probability distribution which possesses an increasing $r_F(t)$ (as t increases). Thus, in practice we would find that, if we look upon the ensemble of the sums of two (or a larger fixed number) lifetimes as our population, then the proportion of failures to the number of still-at-risk for such entities shows an increasing trend.

In passing it should be noted that all IFR distributions possess the IFRA property also and the only distribution common to the DFR and the IFR (or the IFRA) class is the exponential distribution, since the constant failure rate is the only failure rate which is simultaneously non-decreasing and nonincreasing. These classes (DFR, IFR, etc.) are called monotone aging classes of distributions². A UBT failure rate distribution defined above cannot be in the IFR or DFR class though it could be in the IFRA class. Similarly, a BT failure rate distribution may be a member of the DFRA class (to be defined in analogy with the IFRA class)⁵.

Appropriate models belonging to these classes may be chosen to match the specific conditions of the experiment. The following families, besides the exponential distribution, are quite popular as models:

(i) *The Weibull family*: The failure rate is specified by

$$r_F(t) = \lambda \beta t^{\beta-1}, \quad t > 0, \lambda, \beta > 0.$$

It is seen that $\beta = 1$ leads to the constant failure rate (exponential distribution), $\beta > 1$ leads to distributions with the IFR property and $\beta < 1$ to the DFR family.

(ii) *The gamma family*: The probability density function is given by

$$f(t) = \frac{t^{\beta-1} e^{-t/\alpha}}{\Gamma(\beta) \alpha^\beta}, \quad t > 0, \alpha, \beta > 0.$$

Here also $\beta = 1$ leads to the exponential distribution. The IFR and DFR case is obtained with $\beta > 1$ and $\beta < 1$, respectively.

(iii) *The Pareto family*: The failure rate is given by

$$r_F(t) = \frac{1}{(t_0 + t)^\beta}; \quad t > 0, \beta > 0.$$

Here each member is DFR. This arises as a limit of mixtures of increasing number of nonidentical exponential families.

(iv) *The lognormal family*: The probability density function is given by

$$f(t) = \frac{1}{\sqrt{2\pi\sigma t}} \exp\left\{-\frac{(\log t - \mu)^2}{\sigma^2}\right\},$$

$$t > 0, -\infty < \mu < \infty, \sigma > 0.$$

The failure rate is known to be nonmonotonic, first increasing and then decreasing. This distribution is actually such that the log of the random variable has the normal distribution. The shapes of the failure rates of the above families are indicated in Figure 4.

Choosing a model statistically

To choose the appropriate family, one may follow the simple graphical procedure given below.

Let the lifetimes of n randomly chosen units from the population be available. This number n should be reasonably large (say 100 or more). Divide the positive axis $(0, \infty)$ into equal intervals (called unit intervals) $(0, 1)$, $(1, 2)$, ..., etc. Let r_i be the number of units still alive at the beginning of the i th interval. Obviously, $n = r_1$. Also, let d_i be the number of deaths in the i th interval. Calculate d_i/r_i for each i until the deaths of all the units are recorded. Plot these numbers d_i/r_i against i . Ignore the

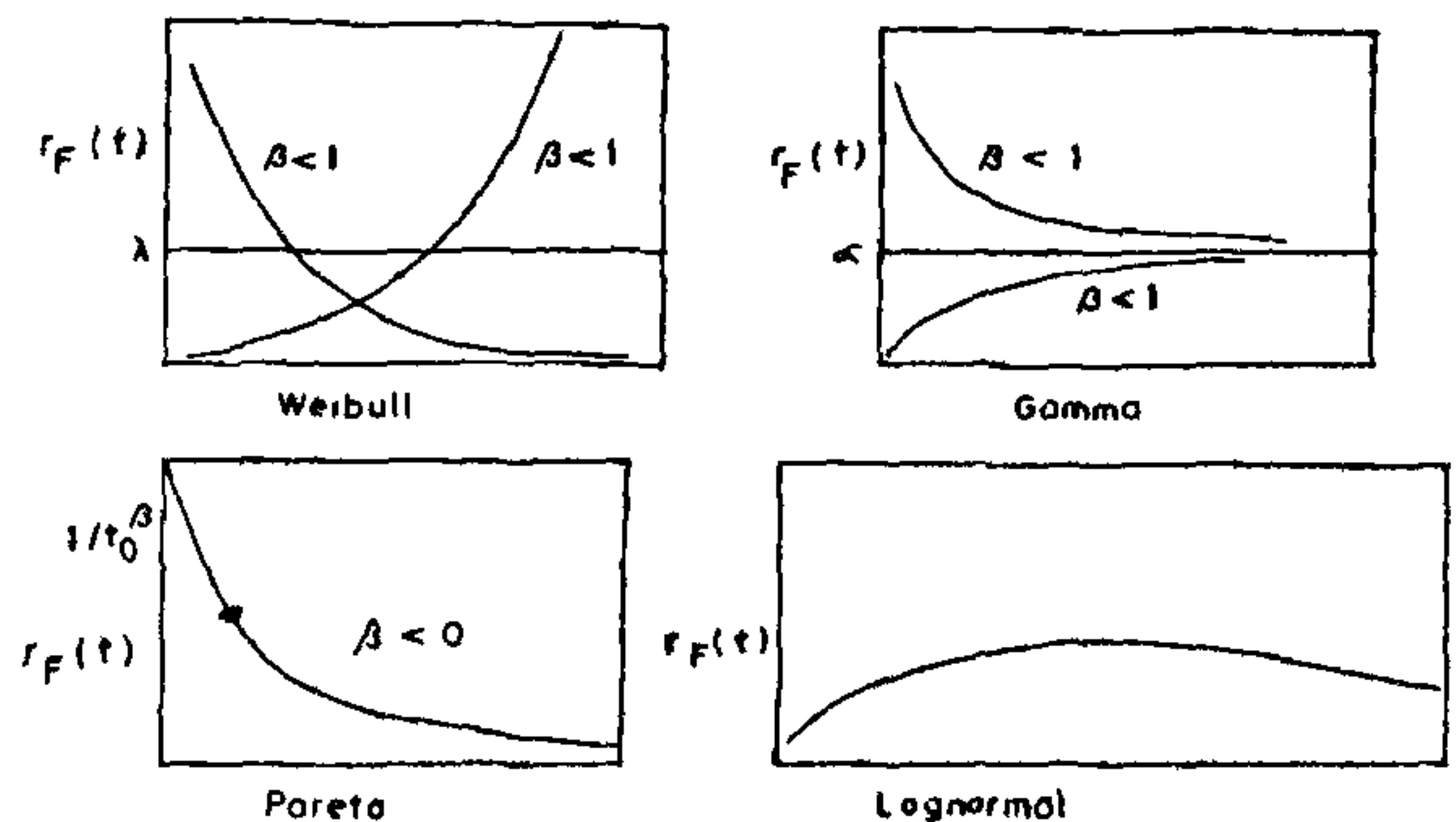


Figure 4. Failure rates of selected life distributions

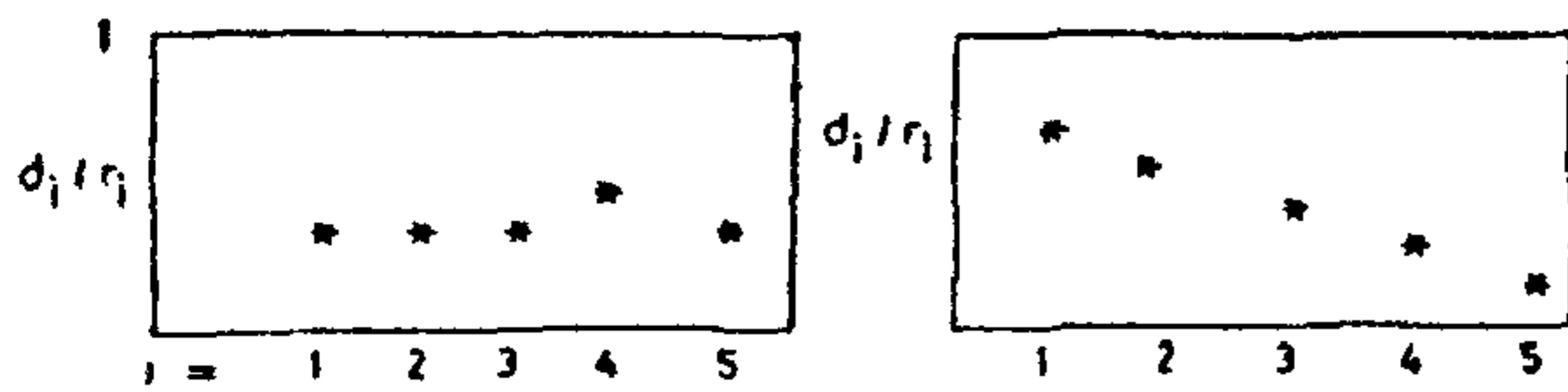


Figure 5. Graphs of the observed ratio of deaths to the number of units still at risk

ratio in the last nonempty interval, which is bound to be 1. The locations of these points would mimic the theoretical failure rate to some extent. For example, the points, as seen in the first graph of Figure 5, probably indicate the constant failure rate or the exponential distribution, whereas those in the second graph seem to indicate a decreasing failure rate starting at some finite level. This procedure was adopted for the fruitfly cohort by Carey *et al.*¹

If n is a rather small number, say 10 or 20, then the following alternative procedure may be used for recognizing the shape of the failure rate. Let $x_1 \leq x_2 \leq \dots \leq x_n$ be the observed lifetimes in increasing order of magnitude. Calculate the normalized spacings

$$\begin{aligned}
 y_1 &= x_1, \\
 y_2 &= 2(x_2 - x_1), \\
 y_3 &= 3(x_3 - x_2), \\
 &\vdots \\
 y_n &= n(x_n - x_{n-1}),
 \end{aligned}$$

and the sum

$$s_n = x_1 + x_2 + \dots + x_n.$$

Calculate further the ratio t_i , called the scaled total time on test up to the i th failure,

$$\begin{aligned}
 t_1 &= y_1/s_1, \\
 t_2 &= (y_1 + y_2)/s_2, \\
 &\vdots \\
 t_n &= (y_1 + y_2 + \dots + y_n)/s_n = 1.
 \end{aligned}$$

It can also be seen that $0 \leq t_1 \leq \dots \leq t_{n-1} \leq t_n = 1$. Plot these values on the x axis against $0, 1/n, 2/n, \dots, (n-1)/n$ and $n/n = 1$ on the y axis, respectively, to get the graph $(t_i, i/n)$, $i = 0, 1, 2, \dots, n$, which is called the graph of the scaled total time on test.

The shape of the graph $(t_i, i/n)$ indicates many things about the aging prevalent in the population from which this random sample is obtained. If it lies very near the diagonal joining $(0, 0)$ with $(1, 1)$ except for small random fluctuations on both sides, then no aging

(exponential distribution) is indicated. If, on the other hand, it lies entirely below (above) the diagonal then adverse (beneficial) aging of some kind or the other is indicated. A concave (convex) graph entirely above (below) the diagonal, as seen in Figure 6, makes a strong case for DFR (IFR) type. If the values

$$\left(z_i = \frac{n-i}{n(1-t_i)}, \frac{i}{n} \right)$$

form a graph with a convex shape, even though the total time on test is not convex, the decreasing residual life expectancy is indicated without having strictly IFR property.

A bathtub-shaped failure rate is indicated by a graph in which points first fall below the diagonal and then above it, as indicated in Figure 7.

Many more sophisticated methods like probability paper graphing, goodness of fit tests, etc., are also available for the choice of the family⁷⁻⁹.

After the choice of the family of distributions is made, one must estimate the values of the unknown parameters in these distributions, viz. α, β, γ , etc. Standard statistical procedures like maximum-likelihood estimation may then be followed on the basis of random samples. We shall not discuss these technical procedures here; many standard books on statistical theory and methodology relating to life distributions will provide the necessary details.^{3, 10}



Figure 6. A concave-shaped scaled total time on test graph

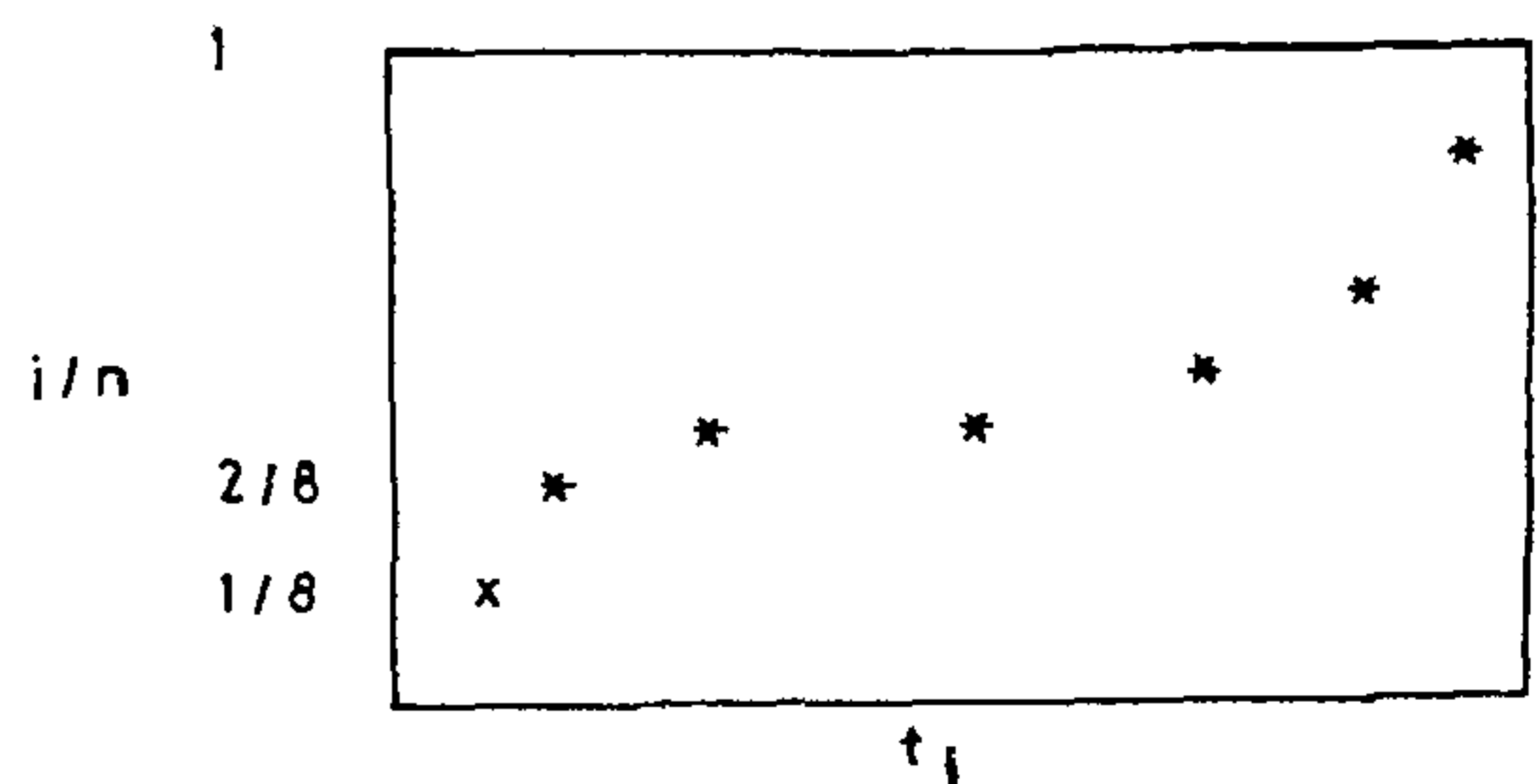


Figure 7. The scaled total time on test graph of a bathtub-shaped failure rate

All the models proposed in this section give positive probability to all intervals on the entire positive part of the real line, i.e. $(0, \infty)$. This means that indefinitely large values of age are not ruled out. This may look like a handicap of these models. However, it is extremely difficult for biologists or engineers to put an absolute limit on the age of the units that they deal with. In practice, they would only assert that very large ages are extremely unlikely. In any of the above models, this feature can be built by requiring it to give a very low probability (say, less than 10^{-12} or even 10^{-20}) for the occurrence of ages larger than a specified large value, without ruling out absolutely the possibility of even larger ages. The low order of the probabilities quoted above will mean that, in practice, one may not at all observe any age above the limit. The possibility of infinitely large age is present only in infinite populations, which do not exist in reality. Naturally, among the models suggested above, the DFR models will be long-tailed compared to the IFR models.

The chosen model may then be used to estimate and predict the various constants and variables associated with the population.

The fruitfly experiment and report

One of the aims of this article has been to comment on the several statements appearing in the news report carried by the *Times of India* dated 30 Oct. 1992 which seem to have emerged out of some misunderstanding of fundamental notions regarding aging as well as of the original article of Carey *et al.*¹. We quote from the report below:

(i) 'The new findings, however, indicate that some Methuselahs among fruitflies at least, can live at least twice as long as is normal for their species.'

The model well-accepted for the no-aging electronic or electric components, i.e. the exponential models, lays down the following approximate frequencies of failures:

Failures before half the average (normal) life	40%
Failures between half and average (normal) life	25%
Failures between average and twice average life	15%
Failures after twice average life	20%

So in this model late deaths (or for that matter early deaths) are not at all rare. In DFR distribution, which will be comparatively long-tailed, the frequency of late failures will be even more. So it should not cause any surprise that some Methuselahs live to at least twice the normal age. In human beings (for India) the average life at birth is 57 years or so. Living to 114 years, though extremely rare, is not unheard of. This aspect has been noted by Curtsinger *et al.*⁶

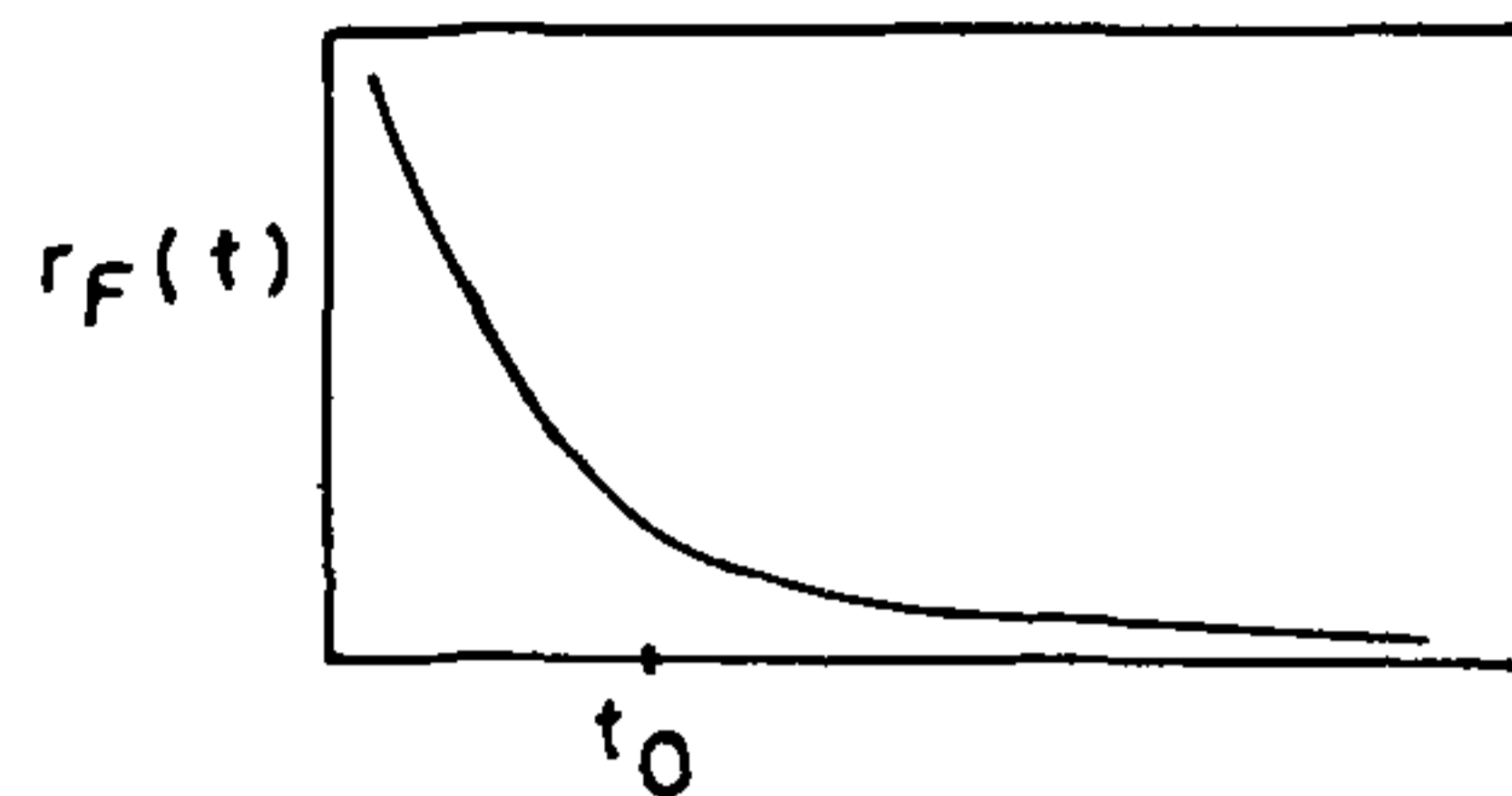


Figure 8. Monotonic decreasing failure rate

(ii) 'With just a few individuals once a fly was past a certain age, its life expectancy increases'.

We would expect this phenomenon to hold right from the birth of the fruitfly, not only after a certain age was past. In birds, animals in the wild and such species who do not have medical help available, the common experience is as given in the graph of the failure rate (Figure 8). What happens is that in the infant stage there is very high mortality because of congenital defects and also the inability of the very young to take care of themselves. After a certain age, when the young become fully mobile and are able to gather their food effectively, they die of accidents – a broken leg leading to starvation, falling prey to a predator, etc., so much so that in the wild it is extremely rare that an animal will die of old age causes as most adult humans do. Hence, the failure rate never goes beyond the middle constant part, thus giving an overall experience of decreasing failure rate. And, of course, increase in the mean residual life function is inherent in decreasing failure rate.

Another possible explanation for the observed increase in mean residual life could be that the population of fruitflies is composed of several subpopulations with different failure rates. The totality, which is a mixture of the various subpopulations, would show a decreasing failure rate and thus an increasing mean residual life. This observation may be intuitively justified in the following way. If a population consists of several subpopulations with different failure rates then in the initial stages there will be comparatively more failures in the subpopulations with higher failure rates, leaving the subpopulations with lower failure rates unscathed. Thus, the population as a whole keeps improving in the sense that the remainder of the population at any stage is stronger than the entire population at the beginning.

In the actual data provided by Carey *et al.*¹, it is seen that the estimated failure rate steadily increases until the 29th day of the life of the fruitflies. By this time about 80% of the cohort is dead. For the next 40 days the failure rate remains more or less constant. At this stage more than 99.9% of the cohort is dead. The values in these two stages are for highly selective groups of individuals and may be said to belong to identifiable subpopulations obeying different laws.

(iii) 'The traditional model of aging is the time bomb model. When you attain a certain age, you self-destruct.'

This seems to be a highly unrealistic model. The deaths due to old age (leaving out infant mortality and accidental deaths in young to middle ages) are due to the cumulative effects of certain processes, e.g. arteriosclerosis, calcification, degeneration of tissues, growth of cells, etc. The total threshold levels of these disorders differ from individual to individual. Also, the rates at which the accumulation takes place differ according to the individual, according to environmental factors as well as according to the interventions carried out. So it does not sound at all likely that everyone carries one's own time bomb which explodes at an unknown but pre-set time. In fact, as our discussion in the preceding section shows, it is fruitless to talk of the time of death of an individual prior to the event and try to devise a model and set rules for it. One can only view an individual as a member of a large ensemble and have laws of statistical nature for the ensemble as a whole. This aspect has been recognized by Curtisinger *et al.*⁶ when they quote that the maximum human life time may be described by a normal distribution with a mean of 85 years and a standard deviation of 7 years.

(iv) 'He said that the new findings supported the "spaceship model" that there is no fixed age at which everybody must be dead.'

Given a large population of like individuals, it is certainly possible to find appropriate models for the distribution of the lifetimes in the population. The model could then provide a number T beyond which age life is extremely improbable: to any degree. It will not be possible to guess accurately the life of any single individual

at birth itself even if we have information on a large number of covariates.

Concluding remarks

Survival analysis and reliability are flourishing areas of statistics. They deal with statistical laws and procedures for deaths and lifetimes. An interplay between the mathematical models developed here and those developed by biologists and engineers should lead to many more insights into the phenomena of life and death. However, accurate guessing of individual lifetimes would remain a mirage, outside scientific enquiry.

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