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A deterministic approach to survival statistics

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Abstract. Survival functions of the form $p(t) = \exp[-(\lambda t)^{\gamma}]$, $\gamma > 0$ can be generated by deterministic nonlinear, asymptotically stable (chaotic) dynamical systems. These systems thus provide an alternative to stochastic interpretations of failure time data. We use this approach to analyze cancer patient survival statistics. In this manner we are able to obtain fresh insights into the implications of negative and positive clinical trials.

Key words: Survival times — Clinical trials — Cancer — Asymptotic stability — Fractal distributions

1. Introduction

An important index for describing the progression of a disease and its response to therapy is the patient survivorship function, $S(t)$ (Lee 1980). As shown in Fig. 1, this function can be determined by plotting the fraction of the number of patients surviving longer than a time t as a function of t. For many patients, including those with cancer, both exponential (Fig. 1a) and non-exponential (Fig. 1b,c) forms for $S(t)$ have been observed (Burch 1976). $S(t)$ is used to determine the 50th percentile (i.e., the median) and other percentiles of survival time and to compare survival data from two or more patient groups.

The interpretation of data obtained from clinical trials intimately depends on the interpretation given to quantities such as $S(t)$. It is typically assumed that $S(t)$ reflects the operation of underlying stochastic processes (Kalbfleish and Prentice 1980; Lee 1980). From this assumption it follows that inferences drawn from clinical trials involving large groups of patients can be directly extrapolated to therapeutic decisions made at the bedside on individuals. It is quite surprising, given the enormous implications of these 'life and death' decisions, that the stochastic origin of $S(t)$ has been so rarely questioned.

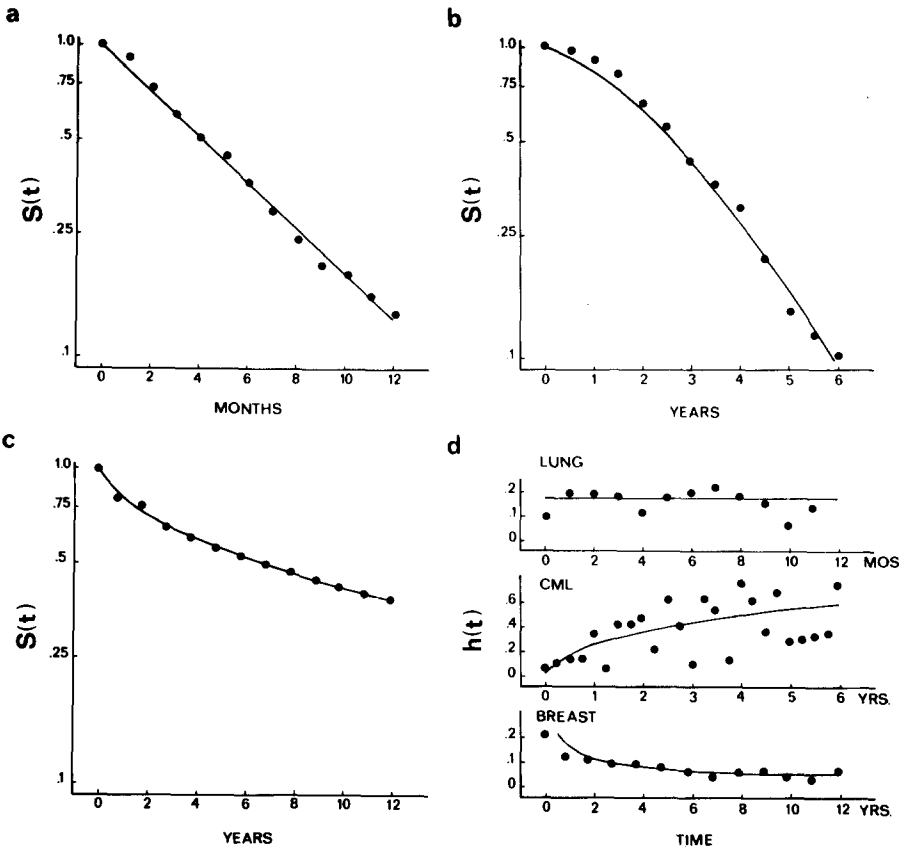

Fig. 1a–d. Patient survival for **a** lung cancer (Roswit et al. 1968), **b** chronic myelogenous leukemia (CML) (Wintrobe, 1976), and **c** breast cancer (1963 California Tumor Registry from Burch 1976). The survivorship functions, $S(t)$, were calculated from (2.6) and the hazard functions, $h(T)$, in **d** were calculated from (2.7) and are represented by the *solid lines*. Values of γ in **a–c** were, respectively, 1.0, 1.5 and 0.6 and of λ were, respectively, 0.17 month^{-1}, 0.3 year^{-1} and 0.09 year^{-1}

Over the last two decades it has become recognized that simple, nonlinear deterministic equations can produce complex, aperiodic solutions often referred to as *chaotic* (Devaney 1986). These observations have blurred the traditional distinctions made between stochastic and deterministic processes. Indeed for any given one-dimensional probability density it is possible to construct an infinite number of deterministic dynamical systems whose iterates are chaotic and which have the prescribed density (Lasota and Mackey 1985). Thus, for example, the observation of an exponential survivorship function (e.g., Fig. 1a) is not sufficient to identify its origin as an underlying Poisson process.

Deterministic models for population survival provide an alternative to stochastic interpretations (Lasota and Mackey 1980). With these models it is possible to directly compare the effect of treatment on an individual to that of a

population and to examine the efficacy of treatment strategies. Thus *in principle* it is possible to gain analytical insight into the results of clinical trials.

Here we show that deterministic finite difference equation models can be constructed to reproduce all of the types of survivorship functions $S(t)$ shown in Fig. 1. We then use these models to examine the effects of various treatment strategies on patient survival. Our observations provide a number of new insights into the nature of clinical trials.

2. Survival statistics: basic considerations

Survival times, T, are usually considered to be random variables and hence to have a distribution (Kalbfleish and Prentice 1980; Lee 1980). It is customary to define the *cumulative distribution function*, $\Phi(t)$, as the probability that an individual dies before time t,

$$\Phi(t) = \text{Prob}(T < t), \tag{2.1}$$

and the *density function*, $\phi(t)$, as the probability of death in a small time interval, where

$$\phi(t) = \frac{d\Phi(t)}{dt}. \tag{2.2}$$

The *survivorship function*, $S(t)$, cf. Fig. 1, provides an estimate of the probability, $p(t) = 1 - \Phi(t)$, that an individual survives longer than a time t, i.e.

$$p(t) = \text{Prob}(T > t), \tag{2.3}$$

and thus can be used to estimate $\Phi(t)$ and thus $\phi(t)$. Having $p(t)$ and $\phi(t)$ it is possible to evaluate the probability of death per unit time, or *hazard function* $h(t)$,

$$h(t) = \frac{\phi(t)}{p(t)}. \tag{2.4}$$

The hazard function plays an important role in survival data analysis since it gives the risk of dying per unit time.

For diseases that display exponential survival statistics (a typical example is that of lung cancer in Fig. 1a), the probability $p(t)$ that an individual survives longer than a time t can be simply expressed by the equation

$$p(t) = \exp(-\lambda t), \tag{2.5}$$

where λ is a constant with the dimensions of $time^{-1}$ that is characteristic of the progress of the disease, and $t = 0$ is taken to be the time of diagnosis. (Alternately one can interpret $p(t)$ as given by (2.5) as the fraction of a large population surviving longer than time t.) In this case it is easy to show that $\phi(t) = \lambda \exp(-\lambda t)$. Furthermore, $h(t) = \lambda$ and the risk of dying remains constant throughout the course of the disease.

However, it is often the case that survival statistics do not obey the simple exponential behaviour of (2.5). Two typical examples are shown in Fig. 1b,c.

In Fig. 1b we show the survival statistics for chronic myelogenous leukemia (CML), while Fig. 1c illustrates the survival from breast cancer. As the statistics are plotted in a semilogarithmic manner, it is manifestly obvious that neither are described by simple exponential decay functions of the form given by (2.5). A convenient way in which to describe non-exponential forms of $S(t)$ is to use the expression

$$p(t) = \exp[-(\lambda t)^{\gamma}], \tag{2.6}$$

where γ is a positive constant. For the data of Fig. 1b,c, the solid line that is drawn in each of the figures is the graph of the best fit of the function given by (2.6). For breast cancer, $\gamma \simeq 0.6$, while for CML $\gamma \simeq 1.5$. Clearly, when $\gamma = 1$, (2.6) coincides with (2.5).

The choice (2.6) for $p(t)$ yields the Weibull probability density which has an interesting interpretation. Namely, the evolution of the disease is governed by a stochastic process in which the probability of dying per unit of time is a *function of the length of time that the disease has been in operation*; in particular

$$h(t) \equiv \text{probability of dying per unit time} = \lambda\gamma(\lambda t)^{\gamma-1}. \tag{2.7}$$

Thus, for $\gamma = 1$ the probability of dying is constant per unti time. For $\gamma > 1$ the probability of dying per unit time is an increasing function of the length of time the disease has been present (CML in Fig. 1d), and when $0 < \gamma < 1$ the probability of dying per unit time is a decreasing function of the length of time the patient has had the disease (breast cancer in Fig. 1d).

Alternately a non-exponential $p(t)$ can be considered to represent the sum of n exponential processes, i.e. $p(t) = \sum_{i=1}^{n} a_i \exp(-\lambda_i t)$ where $\sum_{i=1}^{n} a_i = 1$. Multiple exponentials arise in models in which there exists distinct sub-populations (Burch 1976) or in which disease progression occurs through the operation of multiple Markov processes, e.g. multiple hit theories of disease (Kalbfleish and Prentice 1980). While such a procedure will surely given an adequate fit to data like those shown in Fig. 1b,c if n is sufficiently large, it is at the expense of introducing many more parameters since, for n exponential processes, $2n - 1$ parameters must be determined.

For all of the situations we have considered above, the interpretations of the survivorship function $S(t)$ have been predicated on the fundamental assumption that the evolution of the disease of interest proceeds as a stochastic process. However, recent results from the application of ergodic theory to the behaviour of nonlinear dynamical systems (Lasota and Mackey 1985) gives the possibility of a totally different and *deterministic* interpretation of a variety of patient survival statistics. In Sects. 3 and 4 we develop this new interpretation.

If this new approach gave nothing more than a different interpretation of existing data, then one might question its usefulness. However, in Sect. 5 we use this new interpretation of the statistics of patient survival to: (1) show how two very different classes of treatment may show profound differences for patient survival; and (2) give new insight into the results of clinical trials of disease treatment protocols.

3. Deterministic treatment of survival

In developing the concepts necessary to understand our deterministic point of view, we start by first placing our ideas within the general context of aging.

We assume that, given a level of investigative skill far in excess of that currently available, each individual could, at any given point in time, be characterized by a battery of anatomical, biochemical, cytochemical, physiological, and psychological tests. If we assume that there are M such tests, that every one is administered at each of the equally spaced times $t_0, t_1, t_2, \ldots$, and that the ith test yields a value $z_i(t_j)$ at time t_j, then the evolution of a given individual from birth will be described by the sequence of M vectors $z(t_j) = (z_1(t_j), \ldots, z_M(t_j))$ for $j = 0, 1, \ldots$. The vector $z(t_j)$ evolves in an M dimensional space as life proceeds, and we assume that this evolution is completely deterministic in that the state of an individual at time t_j completely determines the state at the next time, t_{j+1} through a rule U that may be written in the form

$$z_{j+1} = U(z_j), \tag{3.1}$$

where we have set $z(t_j) = z_j$ to simplify the notation. The set of values $\{z_j\}_{j>0}$ defines the *life trajectory* of an individual.

Furthermore, we assume that the death of an individual occurs whenever the trajectory $\{z_j\}_{j>0}$ enters certain regions of the M dimensional space. For concreteness, one might visualize this process as in Fig. 2 where we show a representative trajectory winding its way in a complex manner through a block of Swiss cheese. At any point in time, if the trajectory exits from the cheese into one of the holes, we associate this event with the death of the individual whose trajectory we are following. Conceptually, one would expect that these holes are

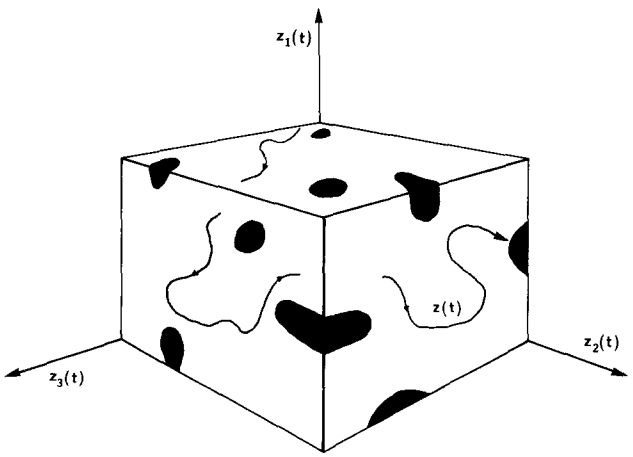

Fig. 2. Representation of the course of a life trajectory, $z(t)$, through a three-dimensional space whose axes represent the results of three tests $z_1(t)$, $z_2(t)$ and $z_3(t)$. The *black regions* ("holes") represent values of $z(t)$ which are associated with the death of an individual

functions of the age of the individual, some or all of them being relatively large at birth, and then decreasing as the individual approaches maturity only to again gradually increase in size as middle age is approached. Since the likelihood of death is, to a rough approximation, proportional to the volume of the space occupied by the holes, we would expect that the hazard function would initially decrease and then again increase as an individual ages (the so-called "bathtub" type of hazard function, cf. Lee 1980). The acquisition of a disease within this conceptual framework could be viewed in one of two ways. Either the disease increases the size of one or more preexisting holes, or it creates a new hole(s). The time T at which the trajectory $\{z_j\}_{j>0}$ enters one of the holes is defined as the survival time.

The multidimensional model for survival given by (3.1) and illustrated in Fig. 2 can be simplified to a one-dimensional model as follows. The results of each clinical test, $z_i(t_j)$ can be assigned a numerical value and the results of all M tests summed (with appropriate weighting) to give a number or score x_j. For heuristic reasons, we assume that this single statistic is available at equally spaced times $t_0, t_1, \ldots$ (or $t_j = j\delta$, where δ is the sampling interval), that it is normalized so it always takes on values between 0 and 1, and that its evolution is governed by the equation

$$x_{j+1} = V(x_j). \tag{3.2}$$

In writing (3.2), as was the case with (3.1), we are explicitly assuming that the state x_j of the individual at a time t_j completely determines the state x_{j+1} at time t_{j+1}.

Prediction of survival from either (3.1) or (3.2) will, in general, be very difficult since the course of the trajectory will typically be quite complex and may show many erratic fluctuations (cf. Fig. 2). These fluctuations arise because many of the quantities which comprise either z_j or x_j can vary in a seemingly unpredictable manner, e.g., tumor growth (Speer et al. 1984; Steele 1977). Here we will show that when either (3.1) or (3.2) has a property called *asymptotic stability* (Lasota and Mackey 1985), then it is possible to analytically calculate the fraction of individuals $p(t)$ surviving to time t.

The concept of asymptotic stability is illustrated in Fig. 3 by two numerical experiments. In the first experiment (Fig. 3a) we imagine that we have identified a "typical" individual whose index x has a value of x_0 at time t_0. We use the rule given by (3.2) to calculate successive values $x_1, x_2, \ldots, x_n, \ldots$ of the index x and then construct a histogram of all the values obtained through this procedure. This histogram, $\tilde{f}(x)$, simply approximates the density of the distribution of the index values for an individual during the course of their life. The result that we obtain will be totally independent of the individual we selected to follow, i.e., independent of the initial value x_0. However, the resulting histogram $\tilde{f}(x)$ will be quite dependent on the specific form of the rule V. In Fig. 3a we illustrate the resulting $\tilde{f}(x)$ obtained by using this procedure for the quadratic rule $V(x) = rx(1-x)$ with $r = 4$, i.e. (3.2) becomes

$$x_{j+1} = 4x_j(1 - x_j). \tag{3.3}$$

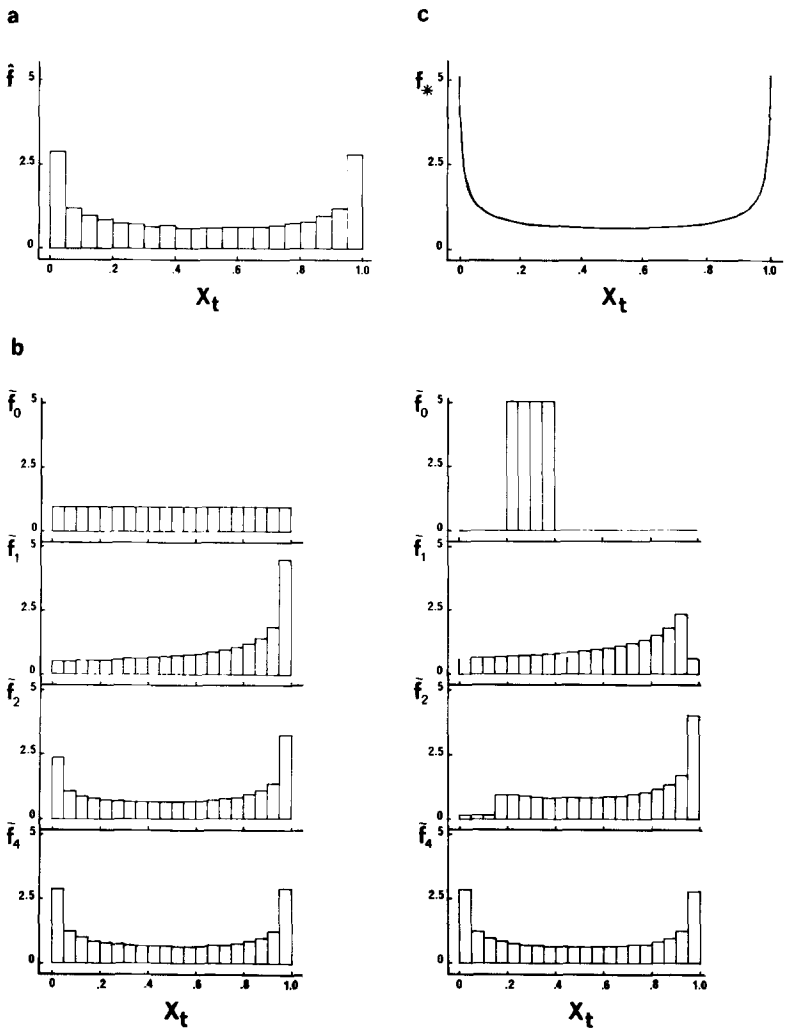

Fig. 3a–c. A graphic illustration of the property of asymptotic stability. **a** Iterate map; **b** iterate density; **c** limiting density. See the text for further details

In the second type of experiment (Fig. 3b) we identify a large number (say N_0) of individuals, and assume that at time $t = 0$ each has a slightly different value of the index. We can label these different index values by $x_0^1, \ldots, x_0^{N_0}$, and a histogram constructed from these initial values as $\hat{f}_0(x)$. One time step later, these N_0 individuals will have N_0 new x values given by $x_1^1 = V(x_0^2), \ldots, x_1^{N_0} = V(x_0^{N_0})$, with a corresponding histogram given by $\hat{f}_1(x)$. Repeating this n times we finally have the set of N_0 values given by $x_n^1, \ldots, x_n^{N_0}$ with the corresponding histogram $\hat{f}_n(x)$. As before, the histogram $\hat{f}_n(x)$ approximates the density of the distribution of the index values for our entire population

at the nth time we collected our data. In Fig. 3b we show $\hat{f}_n(x)$ determined using (3.3) for two initial densities, $\hat{f}_0(x)$.

Two comments are in order. First note that the histogram of Fig. 3a and the final histograms of Fig. 3b are approximately the same. This is because they were constructed using a rule [i.e., (3.3)] that is *ergodic*. Thus averages across a large population and long time averages along the trajectory of a single patient are the same. All asymptotically stable rules U (3.1) or V (3.2) are ergodic, but not all ergodic rules are asymptotically stable (Lasota and Mackey 1985).

Secondly, the essence of asymptotic stability is illustrated in Fig. 3b, i.e., the rule produces the same density of the distribution of population index values after n steps, $\hat{f}_n(x)$, regardless of the initial density $\hat{f}_0(x)$ of index values. We use $f_*(x)$ to denote this limiting density of asymptotically stable systems.

The limiting density $f_*(x)$ can be determined analytically by solving the equation

$$P_{\mathrm{FP}} f_*(x) = f_*(x), \tag{3.4}$$

for $f_*(x)$ where

$$P_{\mathrm{FP}} f(x) = \frac{d}{dx} \int_{V^{-1}([a,x])} f(u)\, du \tag{3.5}$$

is the Frobenius–Perron operator (Lasota and Mackey 1985) and $V^{-1}([a, x])$ is the counterimage of the interval $[a, x]$ under the operation of V. In the case that $V(x)$ is given by (3.3)

$$f_*(x) = \frac{1}{\pi\sqrt{x(1-x)}}. \tag{3.6}$$

In Fig. 3c we have plotted $f_*(x)$ given by (3.6). As can be seen there is a close correspondence between the form of $f_*(x)$, $\hat{f}(x)$ (Fig. 3a) and $\tilde{f}(x)$ (Fig. 3b). In the discussion which follows we assume that $U(x)$ or $V(x)$ are asymptotically stable systems as illustrated by the observations in Fig. 3.

4. A one-dimensional, single hole model of survival

To illustrate how the property of asymptotic stability allows us to calculate the survival fraction, $p(t)$, we choose a simple one-dimensional system with a single hole. This is not restrictive since the analysis carries through in an entirely analogous fashion for the multidimensional model with multiple holes. The mathematical background for our considerations is partially developed in Pianigiani and Yorke (1979), Lasota and Mackey (1980), Pianigiani (1981), Lasota and Yorke (1981), and Jablonski (1983a,b).

For the case of the single index x evolving according to the rule V of (3.2), we assume that death occurs when the index x_j falls in some subinterval $[a, b]$ of the interval [0, 1], i.e., when

$$0 < a \leqslant x_j \leqslant b < 1,$$

then we take

$$x_{j+1} = 0, \tag{4.1}$$

and associate this situation with the occurrence of death. Combining (3.2) and (4.1), the full evolution of the dynamics of an individual is given by

$$x_{j+1} = \begin{cases} 0, & \text{for } x \in D \\ V(x_j), & \text{otherwise,} \end{cases} \tag{4.2}$$

where D denotes the inteval $[a, b]$. Our task is to use the asymptotic stability of V to calculate the density of the distribution of the survival times T at which individuals die under the assumption that individuals evolve according to (4.2).

Assume that we have N_0 individuals at time t_0, and that the dynamics of each evolves according to (4.2). Let N_j be the number still alive at time t_j so it is clear that

$$\text{the number dying between } t_j \text{ and } t_{j+1} = N_j - N_{j+1}. \tag{4.3}$$

However, from the way in which death occurs as described by (4.2) it is also clear that

$$\text{the number dying between } t_j \text{ and } t_{j+1} = N_j \int_a^b \hat{f}_j(x)\, dx = N_j \int_D \hat{f}_j(x)\, dx, \tag{4.4}$$

since it is only by the index x_j satisfying $a \leqslant x_j \leqslant b$ that a patient may die. Equating (4.3) and (4.4) gives

$$N_j - N_{j+1} = N_j \int_D \hat{f}_j(x)\, dx. \tag{4.5}$$

If we set

$$g_j = \int_D \hat{f}_j(x)\, dx, \tag{4.6}$$

for convenience, then (4.5) may be written as a finite difference equation

$$N_{j+1} = N_j[1 - g_j], \tag{4.7}$$

which may be solved iteratively to give

$$N_j = N_0 \prod_{i=0}^{j-1} [1 - g_i]. \tag{4.8}$$

From this last equation we immediately have that the fraction of the original N_0 patients surviving to a time greater than t_j, $p(t_j)$ is given by

$$p(t_j) = \prod_{i=0}^{j-1} [1 - g_i]. \tag{4.9}$$

An approximation to the surviving fraction $p(t_j)$ given by (4.9) serves to illustrate the types of survival statistics that our approach is able to accommo-

date. First note that if the g_i are small, $g_i \ll 1$, then to a good approximation (4.9) can be replaced by

$$p(t_j) = \exp\left\{-\sum_{i=0}^{j-1} g_i\right\}. \tag{4.10}$$

Secondly, realize that for any asymptotically stable system, as shown by the quadratic rule used to obtain the densities $\tilde{f}(x)$ and $\hat{f}_n(x)$ of Fig. 3, it is always the case that $\hat{f}_n(x) \to f_*(x)$ very rapidly. Thus g_i as defined by (4.6) can be approximated by

$$g_i \simeq \int_D f_*(x)\, dx. \tag{4.11}$$

From the mean value theorem of calculus this can be further approximated by

$$g_i \simeq f_*(x_c)\mu(D), \tag{4.12}$$

where x_c is some point in $D = [a, b]$ and $\mu(D) = b - a$ simply denotes the length of the interval D.

With these approximations, substituting (4.12) into (4.10) immediately gives

$$p(t_j) = \exp(-\lambda t_j), \tag{4.13}$$

where $\lambda = f_*(x_c)\mu(D) +$ higher order terms. Thus, (4.2) predicts that the surviving fraction of a large population of N_0 patients is an exponentially decreasing function of the time from diagnosis.

A slight modification of this model gives even more interesting survival statistics. Thus, if we assume that the death interval D is not constant with respect to time, but is a function of the length of time that the disease has been in operation, then (4.2) becomes

$$x_{j+1} = \begin{cases} 0, & \text{for } x \in D_j \\ S(x_j), & \text{otherwise.} \end{cases} \tag{4.14}$$

All of the above calculations carry through in precisely the same fashion, with the end result that (4.12) is replaced by

$$g_i \simeq f_*(x_c)\mu(D_i). \tag{4.15}$$

Suppose we write

$$\mu(D_i) = \mu_{\text{init}}(D)h(i), \tag{4.16}$$

where $\mu_{\text{init}}(D)$ is the initial size of the interval D and $h(i)$ is a monotone function of i with $h(0) = 1$. As a concrete example we pick

$$h(i) = (\epsilon i + 1)^{\alpha}, \tag{4.17}$$

where $\alpha > 0$ when D is expanding and $-1 < \alpha < 0$ for D shrinking, and ϵ controls the rate of expansion or contraction of the set D. Then it is a

straightforward exercise to show that for a large number N_0 of individuals, the fraction surviving at time t is given by

$$p(t) = \exp[-(\lambda t)^\gamma], \tag{4.18}$$

where $\gamma = 1 + \alpha$ and $\lambda^\gamma = f_*(x_c)\mu_{\text{init}}(D)\epsilon^{\gamma-1}/\gamma +$ higher order terms. It is clear that the exponential survival predicted by (4.13) for a constant interval D is simply a special case of (4.19) when $\alpha = 0$. Distributions of the form (4.18) when $\gamma \neq 1$ are often called *fractal* (Liebovitch et al. 1987; Shlesinger 1987).

5. Results

To illustrate the concepts of the previous section, we combine (3.3) and (4.14) to give

$$x_{j+1} = \begin{cases} 0, & \text{for } x \in D_j \\ V(x_j) = 4x_j(1 - x_j), & \text{otherwise,} \end{cases} \tag{5.1}$$

where D_j is a single subinterval of $[0, 1]$ with $D_0 = [a, b]$ whose boundaries may change with time. For simplicity we take D to be centered at $x_j = 0.5$ as shown in Fig. 4. We consider three cases:

Case 1

$$\mu(D_j) = b - a, \quad \text{for all } j, \quad (D_j \text{ constant}),$$

Case 2

$$\mu(D_j) = (b - a)(\epsilon j + 1)^\alpha, \quad \alpha > 0, \quad (D_j \text{ increasing}), \tag{5.2}$$

Case 3

$$\mu(D_j) = (b - a)(\epsilon j + 1)^\alpha, \quad -1 < \alpha < 0, \quad (D_j \text{ decreasing}).$$

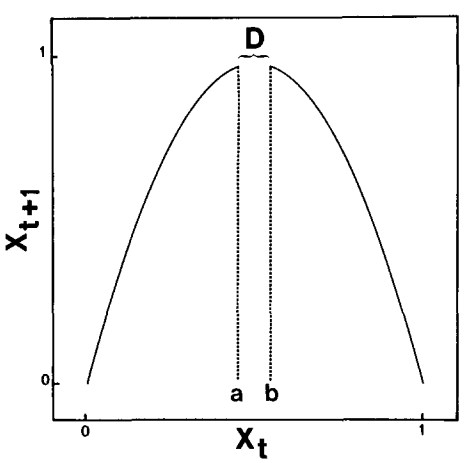

Fig. 4. Graphical representation of the model for population survival given by (5.1) when D is constant (5.2). The subinterval D is centered at $x_t = 0.5$ and from (3.6), $f_*(0.5) = 2/\pi$

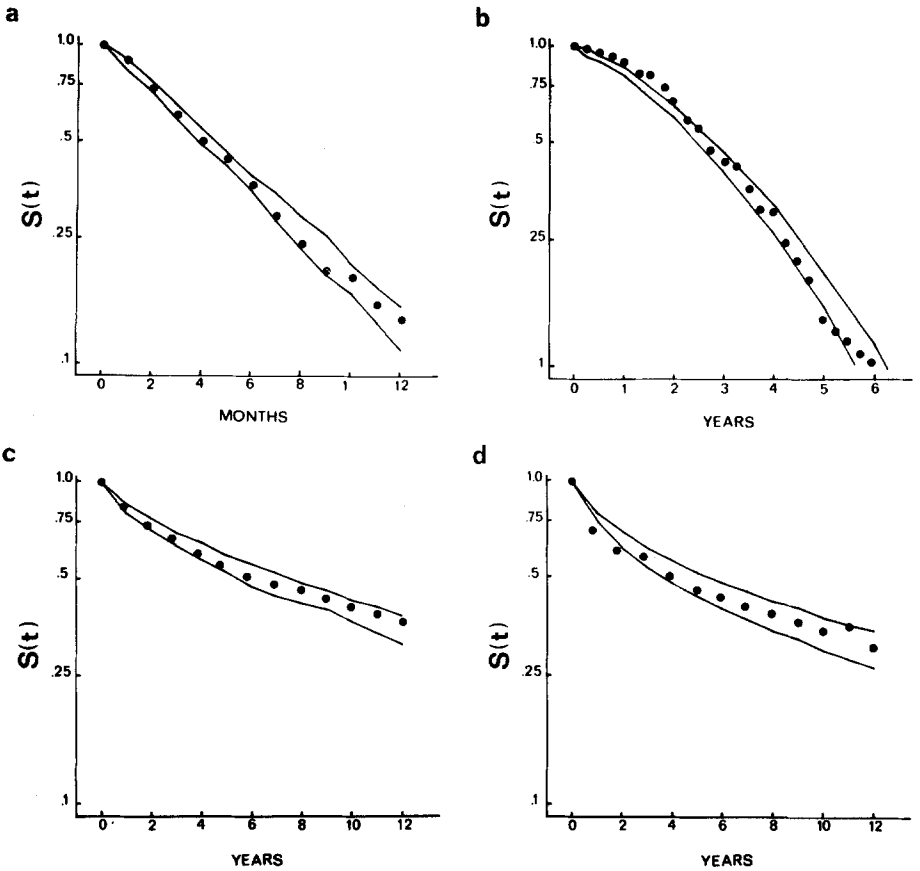

Fig. 5a–d. Comparison of computer simulations (*solid lines*) of $S(t)$ for a population of 1000 subjects whose evolution is governed by (5.1) and (5.2) to $S(t)$ (●) measured for **a** lung cancer, **b** CML, **c** breast cancer and **d** bladder cancer ($\gamma = 0.5$). Data in **a–c** is the same as in Fig. 1 and in **d** is taken from the 1963 California Tumor Registry (cited by Burch 1976). The results of these simulations are represented as the mean plus/minus two standard deviations of 11 trials. The value of $\mu_{\text{init}}(D)$ was estimated from the initial slope of the measured $S(t)$ and were, respectively, 0.16, 0.04, 0.069 and 0.13. The value of ϵ was determined so that (5.1) and (5.2) gave the observed λ and were, respectively, 0, 0.551, 0.395 and 0.847

Figure 5 compares the results of computer simulations for survival of a population of 1000 subjects whose evolution is governed by (5.1) and (5.2) to patient survival measured for four types of cancer. In these simulations the evolution of each subject is given by (5.1), a different subject corresponds to a different initial value, x_0, chosen randomly on the interval (0, 1) excluding values in D_j, and the values of α and $\mu_{\text{init}}(D_j)$ were estimated from the clinical observations (see legend). The results of the computer simulations have been represented as the mean plus/minus two standard deviations of 11 trials (solid lines in Fig. 5). As can be seen, $\gamma = 1$ occurs when D is given by Case 1 of (5.2) (Fig. 5a), $\gamma \sim 1.5$ occurs when D_j is given by Case 2 with $\alpha = 0.5$ (Fig. 5b),

$\gamma = 0.6$ occurs for case 3 when $\alpha = -0.4$ (Fig. 5c), and $\gamma = 0.5$ occurs for Case 3 with $\alpha = -0.5$ (Fig. 5d). Moreover, in all cases there is good agreement between the results of the computer simulations and clinical observations.

The model for population survival given by (5.1) and (5.2) can be used to assess the effect of different treatment strategies on patient survival. Specifically, we consider two possibilities: (1) the treatment alters x_j but not D_j; and (2) the treatment alters D_j but not x_j. The effects of these two treatments are qualitatively similar for all of the choices of D_j given by (5.2). Therefore we illustrate our results here only for the case when D is time independent (Case 1).

Figure 6a,b shows the effect of a treatment which alters x_j but not D, which we take to be $D = [0.45, 0.55]$. In this simulated clinical trial, the control group corresponds to 1000 initial points chosen randomly on the interval [0.9, 1) and the treatment group to 1000 points chosen randomly on (0, 0.1]. In Fig. 6a we show that treatments (i.e., initial conditions) which differ by as little as 1 part in 10^5 can have dramatic effects of a patient's survival, *either prolonging or*

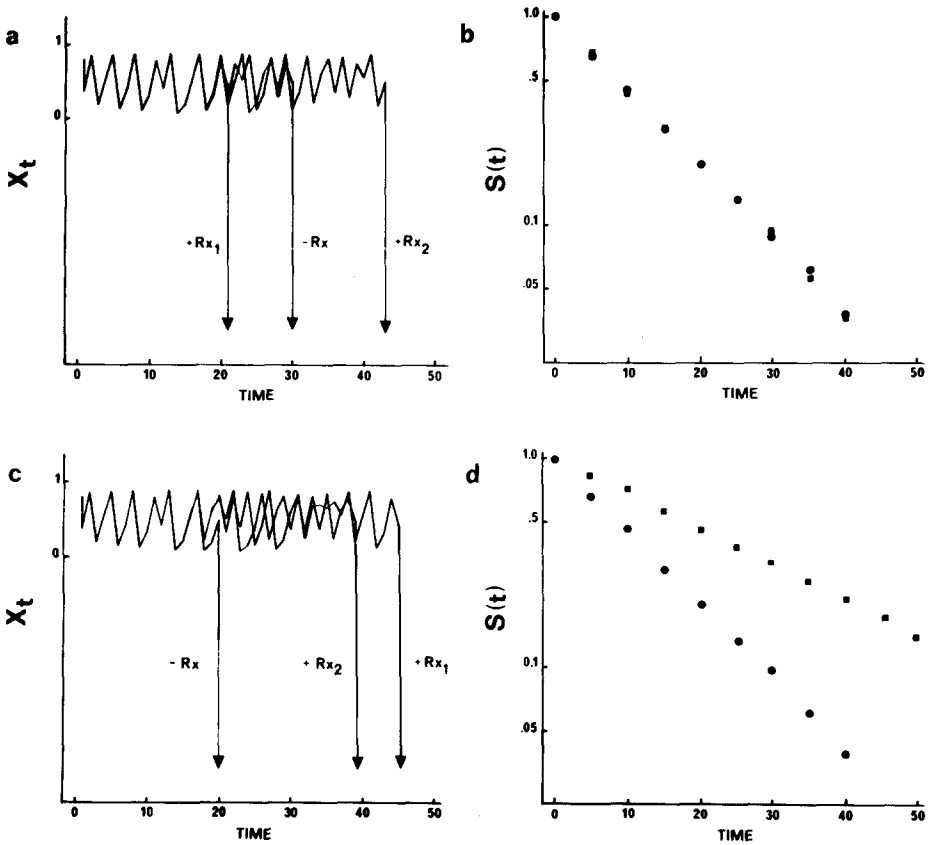

Fig. 6a–d. An illustration of individual life trajectories and population responses to treatments (Rx) resulting in a negative clinical trial (**a,b**) and a positive clinical trial (**c,d**); ■, treated; ●, untreated. See the text for a detailed explanation and discussion

shortening the survival compared to no treatment! In contrast, the population survival is not significantly altered by this treatment strategy (Fig. 6b). Thus it is not possible from the results of a negative clinical trial to infer whether or not a given treatment of this type would be of benefit.

Figure 6c,d shows the effect of a treatment strategy which alters D, but not x_j. In this case we assumed that therapy reduced the size of D by one-half so $D = [0.475, 0.525]$, and used the same initial conditions for the control and treatment groups. This treatment strategy has profound consequences for the population survival statistics, but the amount of benefit varies significantly between patients. The median survival of the treated population is longer than the untreated population. Thus it is possible from the results of a positive clinical trial to infer that a patient will benefit from a given treatment; however, it is not possible to predict how much benefit the individual can expect.

6. Discussion

In the analysis of clinical trials, survival times are traditionally considered to have a stochastic origin. This assumption has yielded a large number of analytical tools which form the cornerstone for interpreting the outcomes of clinical trials (cf. Lee 1980). Indeed there would be little point of conducting these trials without mathematical methods to test, for example, the significance of difference between treatment and control groups. The main disadvantage of this approach is that little insight is offered prior to the onset of the trial as to its probable outcome. It would clearly be advantagous to be able to utilize information about, for example, tumor biology to predict outcomes. In this way needless clinical trials could be avoided, resulting in a saving of both time and money.

Here we have shown that it is possible to construct a completely deterministic model for patient survival consistent with the measured patient survivorship functions (compare Figs. 1 and 5). Thus the observation of either exponential or non-exponential survivorship functions does not distinguish whether the underlying process(es) is (are) stochastic or deterministic. An advantage of a deterministic approach to patient survival is that it is possible, at least in principle, to directly incorporate information about tumor biology by appropriate choice of U (3.1) or V (3.2) and then to obtain some insight into the effects of different types of treatment strategies on the outcome of a clinical trial.

The efficacy of a proposed treatment for cancer is typically evaluated by undertaking a clinical trial. A prolongation of median survival of the treated group indicates a favorable, or positive outcome, whereas no change in median survival indicates an unfavorable, or negative outcome. We have shown that a negative clinical trial would occur when a treatment changes only the life trajectory (i.e., alter x_j but not D_j), whereas a positive outcome occurs when the treatment alters the risk of dying (i.e., alters D_j but not x_j).

A major objective of a clinical trial is to obtain results which can be applied to the treatment of individual patients at the bedside. There are numerous

anecdotal reports of patients who appear to benefit from treatments of questionable value (i.e., negative clinical trials), and of patients who die unexpectedly while taking beneficial medications (i.e., positive clinical trials). We suggest that results of this type are related to the chaotic nature of the life trajectory. Moreover, our results emphasize the problematic nature of attempts to extrapolate results from a clinical trial. In the case of a negative clinical trial, we cannot advise an individual patient whether a treatment will be harmful, beneficial, or neither. Furthermore, having received this treatment it is not known whether it had an effect. On the other hand, a positive clinical trial indicates that at worst a patient can expect no benefit (Fig. 6b).

In our model for patient survival we assumed that the life trajectory for a patient moved chaotically through a multidimensional space and furthermore that it was asymptotically stable (Sect. 3). These two assumptions permit the determination of a stable density function from which all of our results follow. There an infinite number of discrete maps which are chaotic and asymptotically stable (Lasota and Mackey 1985). Moreover, trajectories which meet these conditions can also be generated by continuous time models (e.g., the metastable chaos exhibited by the Lorentz equations (Yorke and Yorke 1979)). Thus we expect that the conclusions we have drawn will be generally applicable. In addition, the analysis of failure times arises in a number of other clinical contexts, e.g., seizure recurrence (Milton et al. 1987), graft and transplant rejection (Kalbfleish and Prentice 1980), as well as in a variety of industrial and engineering applications. It is quite likely that a deterministic approach to the analysis of failure times as advocated here may also yield useful insights into these situations as well.

Our observations suggest that the identification of treatments which alter D_j would be advantageous. However, not enough is presently known about the mechanisms of anti-cancer drugs to be able to determine the nature of such agents. As more becomes known about tumor cell biology and the progression of cancer, it should be possible to better determine the functional forms of the maps, U (or V) which determine the life trajectory. In this way we expect that deterministic models for patient survival will come to play a greater role in the design and evaluation of clinical trials.

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