See Letter to Editor for preliminary comments.

LIFE TABLE TECHNIQUES APPLIED TO EXPERIMENTS IN CARCINOGENESIS, AND OTHER INVESTIGATIONS *

by

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The purpose of this paper is to explain several actuarial-demographic-statistical techniques and show their application in medical investigations. The techniques which will be explained (briefly) are:

(1) measurement of mortality, and morbidity;

(2) life table analysis, including multiple-decrement life tables;

(3) expectation of life; and

(4) force of mortality.

Although this paper draws mainly from actuarial and statistical references, techniques (1), (2), (3), and (4) are much used in demography-see [14], and [21].

Section 1. A Simple Exposed to Risk Technique

Consider an arthritis study designed to compare Treatment A with aspirin. The study has investigators in Minneapolis, DesMoines, Houston, and Cincinnati. There will be 100 patients per center. For simplicity, we will assume that 50 of each 100 receive Treatment A, and 50 receive aspirin. There are several sampling designs to affect this, but they will not be discussed here. See Wei [22], for example.

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The patients range in age from 50 to 80. Because of the sequential nature of the arrival of patients, the study at each center may last from 6 months to 1 year.

One of the problems in analyzing the data is the loss of some patients from observation over the testing period. Common sense might suggest that investigators ignore those patients who fail to ever return to the centers. But serious loss of data occurs when patients who have been observed for most of the study disappear.

One solution to this problem is to use techniques which actuaries use in measuring mortality. These are explained in Batten [3], and Gershenson, [11]. Essentially they allow investigators to measure exposure to risk of non-stationary populations during any period of observation. Let us agree that the risk in the arthritis study is that the medicine is non-effective. We will record a "1" for each patient for each week (or suitable sub-unit of the observation period) during which the medicine is non-effective. The sums of these ones for the two categories will be the numerators of two rates. The denominators will be the exposed-to-risk figures. The exposed-to-risk figure for one patient consists of the number of completed weeks of observation. The sums of these figures provides the respective denominators. These seriatim procedures can be replaced by more sophisticated procedures when thousands of patients are involved.

The next page shows sample data for Minneapolis. Similar pages would reflect the studies at the other three centers. Over-all rates could be obtained by adding comparable figures for the four centers before divisions.

Center: Minneapolis

Treatment A

Number N of week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total
Number of patients completing week N	49	48	47	46	44	41	41	41	39	39	38	38	37	34	33	32	31	27	27	27	26	26	26	26	26	26	915
Number reporting non-effectiveness in week N	11	9	13	12	9	10	11	11	11	9	8	8	8	7	7	8	6	6	6	6	7	8	6	5	6	6	214
Rate of non-effectiveness	$\frac{\text{Sum of Row 3}}{\text{Sum of Row 2}} = \frac{214}{915} = .234$																										

Aspirin

Number N of week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total
Number of patients completing week N	49	47	46	45	43	40	39	38	38	37	37	36	34	32	30	28	28	27	27	26	26	26	25	25	24	24	877
Number reporting non-effectiveness in week N	13	12	12	13	12	11	11	10	10	10	9	10	9	10	8	7	6	7	7	8	6	5	6	6	6	6	230
Rate of non-effectiveness	.262																										

For some studies it would be appropriate to compute a time series of rates, but that seems unnecessary in this example. In reference [2], such time series are portrayed very effectively in Figure 2. The two parts of that figure show the results of clinical trials where approximately equal numbers of cancer patients were treated with neutrons or photons. The figures portray the multiple risks of death, incomplete regression, and recurrence, as well as complete regression as the eighteen month period evolves, and as the number of patients under each treatment declines. Four colored areas reveal the progressions of the time series.

Numerous recent statistical papers have been concerned with sample designs for clinical trials of treatments for cancer, coronary heart disease, or other serious disease. A central theme is the ethical one of minimizing the number of apparently inferior treatments. References Flehinger-Louis [9], Zelen [23], and Wei [22], are examples of such papers.

A paper which was studied carefully in the preparation of this paper was "Statistical Aspects of Clinical Trials" by B. W. Brown, [6]. The 64 references in that paper proved useful in several ways. The reference to Gehan [10], led to a helpful version of a life table which will be pursued in Section 2. The reference to The University Group Diabetes Program, [16], [18], revealed a wealth of material on cooperative clinical trials.

Section 2. Life Table Analysis

The techniques in Section 1 produced over-all rates, but not duration dependent rates. Moreover, no attempt was made to keep separate counts of those people who were either lost to follow-up, or withdrew from the study.

In the next example, 100 people are observed fro 24 months beyond an initial time. Following Gehan, [10], page 633, the initial time could refer to the time of start of treatment, time of diagnosis, or time of first symptoms. The life table format is based on page 632 of [10], and the column headings are self-explanatory, except for the last one. That column has a starting value of 1.00000. Each subsequent value is obtained by multiplying the preceding entry by the comparable value in the column headed: Conditional Proportion Surviving. For example, .94902 = .96965 (.97872), approximately. The first column requires a little explanation. The initial month is given, followed by a dash to indicate that the period ends just short of the next initial number. Thus 9 - refers to the period from the beginning of the 9^{th} month through the end of the 11^{th} month. The two columns whose labels start with the word "conditional" assume survival to the beginning of the various intervals.

In a cooperative clinical trial, such as UGDP ([16], [18]), it might be possible to prepare such a life table for each group of ages (e.g. < 45, 45-64, ≥ 65), or perhaps for each age group, by sex. The present table is for all ages and both sexes combined.

A LIFE TABLE

INTERVAL	MID-POINT	NO. ENTERING INTERVAL	NO. LOST TO FOLLOW-UP	NO. WITHDRAWN ALIVE	NO. EXPOSED TO RISK	NO. DYING	CONDITIONAL PROPORTION DYING	CONDITIONAL PROPORTION SURVIVING	CUMULATIVE PROPORTION SURVIVING
0-	1.5	100	0	1	99.5	1	.01005	.98995	1.00000
3-	4.5	98	0	1	97.5	2	.02051	.97949	.98995
6-	7.5	95	1	1	94.0	2	.02128	.97872	.96965
9-	10.5	91	1	1	90.0	3	.03333	.96667	.94901
12-	13.5	86	2	2	84.0	3	.03571	.96429	.91739
15-	16.5	79	2	1	77.5	2	.02581	.97419	.88463
18-	19.5	74	4	2	71.0	4	.05634	.94366	.86180
21-	22.5	64	6	2	60.0	5	.08333	.91667	.81325

Let us next consider a toxicology study on rats in which the competing risks are: (1) cancer (induced by drugs), (2) old age, (3) pneumonia, and (4) influenza.

How do you separate (2), (3), (4) deaths from treatment effects deaths from cancer induced by drugs?

All die within 3 or 4 years.

Solution. With the data we will build a multiple-decrement table. According to Jordan [13],p. 271, "A multiple-decrement table is a mathematical model which assumes a large body of lives subject to several independent causes of decrement which are operating continuously. The body of lives forms a closed group, there being no new entrants and no re-entrants after the operation of the various decrements."

We will introduce the standard notation [13],pages 271-280 in the terms of this example,

$d_x^{(1)}$ = number of decrements from cancer between ages x and x + 1.

$d_x^{(2)}$ = number of decrements from old age between ages x and x + 1.

$d_x^{(3)}$ = number of decrements from pneumonia between ages x and x + 1.

$d_x^{(4)}$ = number of decrements from influenza between ages x and x + 1.

$d_x^{(T)}$ = total number of decrements from all causes between ages x and x + 1

$= \sum_{k=1}^{4} d_x^{(k)}$.

$l_x^{(T)}$ = number of lives attaining age x in a body of lives subject to the operation of causes of decrement (1), (2), (3), (4).

$l_x^{(T)} - d_x^{(T)} = l_{x+1}^{(T)}$.

$q_x^{(k)}$ = probability that (x) will leave the body of lives within one year as a result of cause (k):

$$q_x^{(k)} = \frac{d_x^{(k)}}{l_x^{(T)}}.$$

$q_x^{(T)}$ = probability that (x) will leave the body of lives within one year regardless of cause:

$$q_x^{(T)} = \frac{d_x^{(T)}}{l_x^{(T)}} = \sum_{k=1}^{4} q_x^{(k)} .$$

$p_x^{(T)}$ = probability that (x) will remain in the body of lives for at least one year:

$$p_x^{(T)} = 1 - q_x^{(T)} = \frac{l_{x+1}^{(T)}}{l_x^{(T)}} .$$

Similarly, ${}_np_x^{(T)} = \frac{l_{x+n}^{(T)}}{l_x^{(T)}}$, and ${}_nq_x^{(T)} = 1 - {}_np_x^{(T)}$.

Let us assume that 1000 rats are observed, with the resulting multiple-decrement table:

x	$l_x^{(T)}$	$d_x^{(1)}$	$d_x^{(2)}$	$d_x^{(3)}$	$d_x^{(4)}$
0	1000	22	0	17	24
1	937	43	0	26	33
2	835	84	0	39	47
3	665	174	42	69	82
4	298	103	87	47	61

Various probability statements can be answered from this table. For example:

$q_2^{(1)} = \frac{84}{835}$ = probability of death from cancer between ages 2 and 3.

$q_3^{(T)} = \frac{174 + 42 + 69 + 82}{665}$ = probability of death from any of the 4 causes between ages 3 and 4.

${}_2p_0^{(T)}$ = probability of survival 2 years from age 0 = $\frac{835}{1000}$

${}_2q_0^{(1)}$ = probability of death from cancer in first 2 years = $\frac{22 + 43}{1000}$

${}_{3|}q_1^{(1)}$ = probability of death from cancer between ages 4 and 5 = $\frac{103}{937}$

We now wish to determine total decremental rates which would operate if all cancer deaths were eliminated. We will use a technique explained on pages 137-9, of Spiegelman [21], the demography text for actuarial students. A principal reference for that technique is Greville [12], a paper which will also be referred to later.

Let $p_x^{(-i)}$ = probability that (x) will survive in a life table from which cause i has been eliminated.

Let $q_x^{(-i)} = 1 - p_x^{(-i)}$.

The quantity $d_x^{(i)}$ who are now saved from cause i would be exposed to deaths from all other causes for one half year, on the average. Hence the extra deaths due to other causes are

$$\frac{1}{2} d_x^{(i)} \cdot q_x^{(-i)}.$$

The new mortality rate for all causes except (i) is

$$q_x^{(-i)} = \frac{d_x^{(T)} - d_x^{(i)} + \frac{1}{2} d_x^{(i)} \cdot q_x^{(-i)}}{l_x^{(T)}}.$$

Upon solving for $q_x^{(-i)}$, and then $p_x^{(-i)}$, one obtains

$$p_x^{(-i)} = \frac{l_{x+1}^{(T)} + \frac{1}{2} d_x^{(i)}}{l_x^{(T)} - \frac{1}{2} d_x^{(i)}}$$

Applying these rates to $l_0^{(T)} = 1000$ yields:

x	0	1	2	3	4
$l_x^{(T)}$	1000	959	897	705	470

This table is based on the rates:

$$p_0^{(-1)} = \frac{937 + 11}{1000 - 11} = \frac{948}{989} = .95854$$

$$p_1^{(-1)} = \frac{835 + 21.5}{937 - 21.5} = \frac{856.5}{915.5} = .93555$$

$$p_2^{(-1)} = \frac{665 + 42}{835 - 42} = \frac{623}{793} = .78562$$

$$p_3^{(-1)} = \frac{298 + 87}{665 - 87} = \frac{385}{578} = .66609$$

A comparison of the vectors of $l_x^{(T)}$ values gives one indication of the improvement of mortality. Another indication is to compare expectations of life. The curtate and complete expectations of life are defined by:

$$e_x^{(T)} = \frac{1}{l_x^{(T)}} \sum_{t=1}^{\infty} l_{x+t}^{(T)}$$

$$\mathring{e}_x^{(T)} = \frac{1}{l_x^{(T)}} \int_0^{\infty} l_{x+t}^{(T)} \, dt$$

As Jordan, [13] says on p. 173: "On the average, the complete future lifetime exceeds by half a year the number of integral years in the future lifetime, and hence

$$\mathring{e}_x^{(T)} \doteq e_x^{(T)} + \frac{1}{2} ."$$

Before applying these formulas, the second table must be extended because it is very doubtful that all 470 lives in $l_4^{(T)}$ would die in the next year. Four different extension methods are described on page 23 of Miller's monograph, [19]

We will use the fourth method, restricted as follows:

$$1_x^{(T)} = A + Bx + Cx^2 + Dx^3, \quad x = 2, 3, 4, 5, 6$$

$$q_6^{(T)} = 1.000, \text{ or } 1_7^{(T)} = 0.$$

This produces the following four equations:

$$897 = A + 2B + 4C + 8D$$
$$705 = A + 3B + 9C + 27D$$
$$470 = A + 4B + 16C + 64D$$
$$0 = A + 7B + 49C + 343D.$$

The solution of this system of equations is:

$A = 954.792$; $B = 129.142$; $C = -95.453$; $D = 8.217$.

The extrapolated values are therefore $1_5^{(T)} = 241$, and $1_6^{(T)} = 68$.

The following tables portray the respective life expectancies, and hence the gains in expected life by the elimination of cancer from this closed population of 1000.

x	0	1	2	3	4
$e_x^{(T)}$	2.735	1.919	1.153	0.448	0.000
$\overset{o}{e}_x^{(T)}$	3.235	2.419	1.653	0.948	0.500

x	0	1	2	3	4	5	6
$e_x^{(T)}$	3.340	2.483	1.654	1.105	0.657	0.282	0.000
$\overset{o}{e}_x^{(T)}$	3.840	2.983	2.154	1.605	1.157	0.782	0.500

The associated single-decrement tables can be constructed from a multiple-decrement table as discussed in pages 277-280 of [13]. Let $q_x'^{(k)}$ represent the probability of decrement from cause k between ages x and x + 1. This rate will not apply to $l_x^{(T)}$ since some of those lives are not exposed to cause k for a full year since they leave due to one of the other causes. If we assume that those lives are exposed to cause k for one-half year before leaving, the $l_x^{(T)}$ figure should be reduced by $\frac{1}{2}(d_x^{(T)} - d_x^{(k)}) = \frac{1}{2} d_x^{(-k)}$. Therefore,

$$q_x'^{(k)} \doteq \frac{d_x^{(k)}}{l_x^{(T)} - \frac{1}{2} d_x^{(-k)}} .$$

This was the method followed by Pike and Roe [20] in their analysis of an experiment in carcinogenesis. The Appendix of Lee [17] used this method. Lee also presents another method which will be discussed in Section 3. Both methods are concerned with obtaining comparable cancer rates. The Introduction to Lee's paper explains the problem on page 777. "In many comparative carcinogenesis experiments in animals the non-tumour mortality experience of the different groups of animals varies considerably. Allowing for this differing non-tumour mortality is a major problem in the analysis of such experiments."

A valuable and early paper using life table analysis and data from the Mayo Clinic is [4] by Berkson and Gage. Table 1 on page 509 of [4] compares expectations of life at durations 0, 1, 2,..., 15 years after treatment for cured and not cured patients treated for cancer of the breast. Table 3 on page 512 of [4] utilized the formula for $q_x'^{(k)}$ for death from cancer.

Section 3. Force of Mortality

A function representing force of mortality can be used to construct a life table. Thus, this section is a continuation of life table analysis. This brief explanation is based on pages 12-24 of Jordan [13]. Typically a life table portrays the numbers of lives alive at the beginnings of integral ages. However, the intensity of mortality is changing at each instant of time. This could be measured by the simple derivative of the life function, i.e. $\frac{dl(x)}{dx}$. However, these derivatives would be subject to the exposed to risk l(x). To avoid that problem, to have positive values, the force of mortality is defined as

$$\mu_x = -\frac{dl(x)}{dx} \cdot \frac{1}{l(x)}.$$

An alternative expression for μ_x is

$$\mu_x = -\frac{d}{dx} \ln_e l(x).$$

This easily produces the result $l(x) = l(0) \exp\{-\int_0^x \mu_y dy\}$. Therefore, given the radix l(0) and μ_x, one can produce the l(x) column, and hence the d(x) column. Also note that

$$ {}_nP_x = \exp\{-\int_x^{x+n} \mu_y dy\}$$

$$= \exp\{-\int_0^n \mu_{x+t} dt\}; \text{ and}$$

$$ {}_nq_x = 1 - \exp\{-\int_0^n \mu_{x+t} dt\}.$$

Let us again consider the life table in the beginning of Section 2. As discussed on pages 629, 631, and 634 of Gehan [10], the force of mortality is also referred to as the hazard function. On page 634, [10], an estimate of the hazard function during the i^{th} time period is given as

$$\lambda_i = d_i / \{h_i(n_i - d_i / 2)\}$$

where h_i is the length of the i^{th} time period, and n_i is the number exposed to risk. This actuarial estimate of the hazard function is described in Kimball [15]. For our table, $h_i = 0.25$.

Utilizing our life table, we obtain the following approximate values for the forces of mortality.

INTERVAL	n_i	d_i	$h_i (n_i - d_i / 2)$	λ_i
0-	99.5	1	24.750	.04040
3-	97.5	2	24.125	.08290
6-	94.0	2	23.250	.08602
9-	90.0	3	22.125	.13559
12-	84.0	3	20.625	.14545
15-	77.5	2	19.125	.10458
18-	71.0	4	17.250	.23188
21-	60.0	5	14.375	.34783

Actuaries developed two far-reaching laws of mortality. Gompertz developed the law: $\mu_x = Bc^x$.

Makeham's law accounts for accidental deaths by adding a constant to the above geometric progression. Thus,

$$\mu_x = A + Bc^x.$$

These laws have been very useful in modelling human mortality, and have also been used for other types of life For example, Berry and Wagner [5] in a carcinogenesis experiment assumed that the natural death rate of a group of rats followed the Gompertz distribution in the absence of exposure to the carcinogen.

Actuaries have used these laws in mortality studies involving millions of lives, and thousands of deaths. Over the years special techniques have been developed to estimate A, B, and c. These are explained in detail in pages 44-47 of Miller, [19]. The simplest method applies when the data is smooth, as judged (Miller [19], p.8) by the progression and size of some order or orders of the finite differences of the data. In that case, one chooses four equidistant values of l(x) and solves the set of simultaneous equations resulting from equating the observed values to the function values. For Makeham's μ_x, $l(x) = ks^x g^{c^x}$ where $k = l(0)/g$, $\ln_e s = -A$, and $\ln_e g = -B/\ln_e c$. These constants may be obtained by solving equation (6.31), page 44 of [19].

$$\ln_e l(x) = \ln_e k + x \ln_e s + c^x \ln_e g$$

$$\ln_e l(x+t) = \ln_e k + (x+t)\ln_e s + c^{x+t} \ln_e g$$

$$\ln_e l(x+2t) = \ln_e k + (x+2t)\ln_e s + c^{x+2t} \ln_e g$$

$$\ln_e l(x+3t) = \ln_e k + (x+3t)\ln_e s + c^{x+3t} \ln_e g.$$

When the observed data is not regular, methods explained on pages 45-47 of [19] are used.

An important multiple-decrement paper is [12] by T.N.E. Greville. One of its sections is concerned with calculating net from crude death rates, when competing risks are involved. This was accomplished by assuming that the forces of mortality were constant for short periods of time. The paper cited earlier, [4] by Berkson and Gage, utilized this assumption in deriving its key equation (3).

In Lee [17], the force of mortality was assumed constant for a short period of time. The three carcinogenesis experiments involved 27, 20, and 16 constant forces of mortality, respectively. Returning to our earlier equations, if $\mu_y = \mu_0$ for the interval $0 \le y \le x$, and $\mu_y = \mu_x$ for $x \le y \le x + n$, we obtain:

$$l(x) = l(0)e^{-\mu_0 x} ;$$

$$_np_x = e^{-\mu_x n} ; \text{ and}$$

$$_nq_x = 1 - e^{-\mu_x n} .$$

Let us now use the notation of Lee on page 778. Let P_{ik} represent the probability of surviving the kth risk from time t_i to t_{i+1}. In Lee's paper, risk 1 was diagnosis of a tumor, and risk 2 was death from any other cause. The symbol N_i represented the number of animals alive at time t_i (alive without ever having had a tumor), D_{ik} represented decrements from risk k for k = 1, 2, between times t_i and t_{i+1}, and $D_{i\cdot} = D_{i1} + D_{i2}$. It was assumed that in (t_i, t_{i+1}) there were constant forces of mortality v_{ik} from risk k, k = 1, 2. Thus $P_{ik} = e^{-v_{ik}(t_{i+1} - t_i)}$, k = 1, 2. The paper Chiang [7] demonstrated that P_{ik} could be estimated by

$$\hat{P}_{ik} = [1 - D_{i\cdot}/N_i]^{D_{ik}/D_{i\cdot}}$$

Populations were simulated with tumor rates of the actual population, and non-tumor death rates of suitable standard populations. Lee states that the

assumption of constant forces of mortality can be improved to the weaker restriction that the decremental rates remain in constant proportion during (t_i, t_{i+1}), and cites the book by Chiang [8]. The reader is referred to pages 244-247 of [8].

The variable in Makeham's law is typically age. In a recent paper [1], R. Bailey used the model

$$h(t) = \delta + \alpha \exp(-\gamma t)$$

as the force of mortality to describe survival after certain medical procedures. The variable t is elapsed time from the procedure. As Bailey states on page 1 of [1], "... the parameter δ is the long-term risk, α is an initial excess risk, and γ is a rate constant for the disappearance of the initial excess risk". Let T be the random variable representing survival. If $F(t) = P[T \leq t]$, then the above h(t) yields $1 - F(t) = \exp\{-\delta t - (\alpha/\gamma)(1 - \exp(-\gamma t))\}$. The paper develops a computationally useful expression for the moments

$$\mu'_v = \int_0^\infty t^v dF(t).$$

The first four moments were computed in a trial data set. Also, maximum likelihood estimates for that set provided the estimates:

$$\hat{\alpha} = 1.388, \quad \hat{\gamma} = 3.506, \quad \text{and } \hat{\delta} = 0.120.$$

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