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Relatives' Risks: Frailty Models of Life History Data

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INTRODUCTION

Population scientists frequently study the dynamics of mortality, fertility, and other life-history traits in populations that are heterogeneous along a theoretically important dimension that is not directly observed. Geneticists and genetic epidemiologists, for instance, emphasize genotypic variability. Although every individual has a genome and although great progress is being made in mapping genes, in most studies an individual's specific genetic makeup is unknown. Similarly, demographers assume that there are persistent differences among women in their fecundity: some women, at any specific age and controlling for all observed covariates, are more likely to conceive than others (Sheps and Menken, 1973). More generally, demographers, labor economists, epidemiologists, ecologists, and other population scientists assume that there are persistent differences among individuals in their susceptibility, propensity, or relative risk with regard, say, to death, disease, divorce, unemployment, migration, etc. Although some explanatory covariates may be observed, there is often an unmeasured "frailty" component of this relative risk (Vaupel, Manton, and Stallard, 1979).

Theoretical studies of the aggregate dynamics of heterogeneous populations start with an assumed distribution of subpopulations and an assumed life-history pattern for each of these subpopulations and then derive the life-history pattern for the entire population. Such studies have been very important in developing genetic theory (e.g., Ewens, 1979, or Falconer, 1981) and some progress has recently been made in developing a similarly detailed understanding of the fertility and mortality dynamics of heterogeneous cohorts of individuals who differ in their fecundity or frailty (e.g., Sheps and Menken, 1973; Vaupel, Manton, and Stallard, 1979;

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Keyfitz, 1985; Vaupel and Yashin, 1985a, b; and Vaupel, Yashin, and Manton, 1988).

The converse endeavor of trying to decompose observed population dynamics into two components—a distribution of subpopulations and the dynamics of the subpopulations—has been more difficult and problematic (Trussell and Rodriguez, 1989). As in the development of theory, geneticists have achieved far more in their empirical work than demographers and econometricians, although brave attempts by, e.g., Manton, Stallard, and Vaupel (1981, 1986), Heckman and Singer (1984), Trussell and Richards (1985), and Aalen (1987) might be noted.

Geneticists have been relatively productive and successful in their empirical studies of hidden heterogeneity because they ground their models in cogent theories of how genes are transmitted and then apply these models to data sets on related individuals. Demographers and econometricians have not, by and large, developed comparably powerful theories and have, in nearly all frailty analyses, used data on unrelated individuals and events.

Demographers and econometricians, however, may have something to contribute because they have developed methods that are based on modern statistical techniques of survival analysis and frailty modeling. Geneticists, in contrast, usually rely on classical methods of the decomposition of variance, a much less rich and multifaceted approach that may encourage unrealistic assumptions and invite misinterpretation (Feldman and Lewontin, 1975; Vaupel, 1988). Life history traits can usually be viewed as durations—time to death, to onset of illness, to divorce, to next birth, to reemployment, etc. Instead of analyzing such traits using the same method of decomposition of variance used to analyze such static phenotypic characteristics as birth weight, number of vertebrae, or thorax length, geneticists and genetic epidemiologists may gain some deeper insights by exploiting the additional information provided by survival data.

A hybrid approach to life-history analysis that combines biological theory, data on related individuals and events, and methods of survival analysis and frailty modeling thus seems to be a logical step forward. It turns out that some relevant spade work toward developing such an approach has been done by Weiss (1989), Heckman and Walker (1987), Vaupel (1988), and a group of biostatisticians, including Holt and Prentice (1974), Clayton (1978), Oakes (1982), Wild (1983), Clayton and Cuzick (1985), and Hougaard (1986b, 1988), whose research on methods for multivariate survival analysis is reviewed by Hougaard (1987).

This article builds on this body of research to develop a method for applying frailty models based on biological theory to life-history data on related individuals and events. A companion article (Vaupel, 1989) focuses on applying this method to mortality patterns by using data on twins, parents and children, and other related individuals. A second companion

article (Larsen and Vaupel, 1989) applies the method to a repeated event—a woman's successive births—in an analysis of Hutterite fertility patterns.

This article, in contrast, is terser, broader, and more abstract. It concisely summarizes the essence of the proposed method and then adumbrates some illustrative applications. The article concludes with a brief discussion of the three general purposes of frailty modeling of life history data.

General Results

Let T_{ij} be the duration of individual i in group j, $i = 1, ..., I_j$, $j = 1, ..., J$, let the indicator δ_{ij} equal 1 if T_{ij} is a death time and 0 if T_{ij} is an uninformative right censoring time, and let x_{ij} be a vector of observed covariates that may vary over time (Kalbfleisch and Prentice, 1980, Cox and Oakes, 1984). Further suppose that the hazard of death at duration t is $z_j\lambda_{ij}(t)$, where z_j is the frailty of group j and λ_{ij} is a function of x_{ij} (Vaupel, Manton, and Stallard, 1979; Hougaard, 1984). Let $g_j^0(z)$ be the prior probability density function (p.d.f.) of z_j when no survival data are available; in many applications the same g^0 will hold for all the groups. Let

$$s(t) = e^{-\int_0^t \lambda(u)\,du}$$

denote the survivorship function. Note that, as here, the indices i and j will often be suppressed.

In addition to these customary functions and variables, it will be convenient to:

— let S denote the survival data for a group, i.e., the set of survival times $T_1, ..., T_I$ and corresponding δ's and x's,

— let m denote the number of deaths in a group,

$$m = \sum_{i=1}^{I} \delta_i, \tag{1}$$

— let M denote the total cumulative hazard for a group,

$$M = \sum_{i=1}^{I} \int_0^{T_i} \lambda_i(t)\,dt, \tag{2}$$

— let h denote the total log hazard at observed death times for a group

$$h = \sum_{i=1}^{I} \delta_i \log \lambda_i(T_i), \tag{3}$$

and

— let $g^{\dagger}(M, m)$ denote the integral transform

$$g^{\dagger}(M, m) = \int_0^{\infty} z^m e^{-Mz} g^0(z)\, dz. \tag{4}$$

The likelihood of the survival data for all the groups combined is simply the product of the likelihoods for the various groups. It turns out that a simple formula gives these likelihoods.

LEMMA 1. *The likelihood of the survival data S for a frailty group is*

$$\mathcal{L} = e^h \cdot g^{\dagger}(M, m). \tag{5}$$

Proof. It follows from, e.g., Kalbfleisch and Prentice (1980) or Cox and Oakes (1984), that the probability of the survival data given z is

$$\mathcal{L}_z = \prod_{i=1}^{I} (z \cdot \lambda_i(T_i))^{\delta_i} \cdot e^{-\int_0^{T_i} z \cdot \lambda_i(t)\, dt}. \tag{6}$$

Furthermore,

$$\mathcal{L} = \int_0^{\infty} \mathcal{L}_z g^0(z)\, dz.$$

Rearranging terms and substituting (1), (2), (3), and (4) yields (5). ∎

The likelihood in (5) can be viewed as a generalization of ordinary survival analysis and frailty modeling. If a single frailty group comprises the entire population, (5) can be interpreted as a Bayesian approach to estimating the level of the hazard function. If, further, there is no heterogeneity in frailty, z can be set equal to one for everyone and $g^{\dagger}$ collapses to e^{-M}: the likelihood in (5) is then equivalent to the standard survival analysis formula. If there is heterogeneity in frailty but observations are on unrelated individuals or events, then each frailty group consists of a single individual; (5) is still valid, with m being either 0 or 1.

Another simple formula describes how g^0 should be updated based on the available set of survival data.

LEMMA 2. *The* p.d.f. *of z conditional on S is given by the two-dimensional family of distributions*

$$g(z; M, m) = z^m e^{-Mz} g^0(z)/g^{\dagger}(M, m). \tag{7}$$

Proof. Starting with Bayes' Theorem,

$$\Pr(z \mid S) = \Pr(S \mid z) \cdot \Pr(z)/\Pr(S),$$

and substituting (6) for $\Pr(S|z)$, $g^0(z)$ for $\Pr(z)$, and (5) for $\Pr(S)$ yields (7). ∎

Using this lemma it is easily shown that the mean and higher moments about the origin of $g(z; M, m)$ are given by

$$E(z^r) = g^{\dagger}(M, m + r)/g^{\dagger}(M, m).$$

Let $\bar{s}(t)$ denote the survivorship function for some frailty group with survival data summarized by M and m,

$$\bar{s}(t) = \int_0^{\infty} s(t|z)\, g(z; M, m)\, dz,$$

where the multiplicative relationship $z\lambda$ implies that

$$s(t|z) = s(t)^z.$$

Then it follows from Lemma 2 that

$$\bar{s}(t) = \frac{g^{\dagger}(M - \log s(t), m)}{g^{\dagger}(M, m)}.$$

Let $\bar{\lambda}(t)$ be the hazard function for this frailty group,

$$\bar{\lambda}(t) = -\frac{d\bar{s}(t)}{dt} \Big/ \bar{s}(t).$$

Then

$$\bar{\lambda}(t) = \frac{g^{\dagger}(M - \log s(t), m + 1)}{g^{\dagger}(M, m)} \cdot \lambda(t).$$

This is equivalent to Vaupel, Manton, and Stallard's (1979) result that

$$\bar{\lambda}(t) = \bar{z}(t)\, \lambda(t),$$

where $\bar{z}(t)$ is the mean value of frailty among survivors alive at age t.

Two other useful results are proven in Vaupel (1989). The first gives the likelihood of kindred frailty models with independent competing risks: as in ordinary survival analysis, any particular risk can be analyzed as if it were the only risk, with deaths or attrition from other causes being treated as censored cases. The second formula gives the likelihood of kindred

frailty models with competing risks when the cause of death is not observed. Such models, which add a third layer of obscurity to censoring and hidden frailty, turn out to be useful in studies of relatives who share some but not all of their genes and in situations where frailty may be changing with age.

Frailty Distributions and Transforms

Following Hougaard (1984), $g(z; M, m)$ will be called a frailty distribution. It can be viewed as a two parameter exponential family, in z and $\log z$, of distributions $g^0(z)$. The integral transform $g^\dagger(M, m)$, "g dagger," might be called a frailty transform. When m is zero $g^\dagger$ is equivalent to a Laplace transform (and closely related to moment generating functions); when M is zero, $g^\dagger$ is equivalent to a Mellin or z transform. The transform can also be viewed as a two dimensional Laplace transform in z and $\log z$. Note that

$$g^\dagger(M, m) = (-1)^m \partial^m g^\dagger(M, 0)/\partial M^m.$$

Frailty distributions and transforms can also be generated when g^0 is discrete, with the integral in (4) being replaced by a summation. The two lemmas still hold. Furthermore, the results can be extended to some distributions defined on the entire real line (e.g., the normal distribution) although such distributions can only be used as approximations in frailty models since frailty cannot be negative. Finally, the results are readily extended to the more general proportional hazards model $f_i(z_i)\lambda_{i_0}(t)$, where, e.g., $f_i(z_i)$ could be e^{z_i} or z_i^2.

Using numerical methods, g and $g^\dagger$ can be approximated for any initial distribution g^0. Exact expression can be derived for a variety of continuous and discrete forms.

Suppose, for instance, that g^0 follows a gamma distribution, as assumed by Beard (1963), Vaupel, Manton, and Stallard (1979), Clayton (1978), Oakes (1982), Wild (1983), Clayton and Cuzick (1985), and others:

$$g^0(z; \alpha, k) = \alpha^k z^{k-1} e^{-\alpha z}/\Gamma(k). \tag{8}$$

Then it is readily shown that

$$g(z; M, m) = g^0(z; \alpha + M, k + m) \tag{9}$$

and

$$g^\dagger(M, m) = \frac{\Gamma(k+m)}{\Gamma(k)} \frac{\alpha^k}{(\alpha + M)^{k+m}}.$$

In some Bayesian analyses it may be appropriate to assume that g^0 is a flat, continuous prior such that $g^0(z_1) = g^0(z_2)$, all $z_1, z_2 > 0$. Then it is clear from (7) and (8) that $g(z; M, m)$ is a gamma distribution with shape parameter $k = m + 1$ and scale parameter $\alpha = M$. Because k is an integer, this gamma distribution is equivalent to an Erlang distribution (Hastings and Peacock, 1974). The mean value of z is $(m+1)/M$; the most likely value of z is m/M; and the variance of z is $(m+1)/M^2$.

Hougaard (1986a) introduced a family of distributions derived from the stable distributions that includes the gamma distribution as a special case. It is convenient to describe this family by its Laplace transform:

$$g^\dagger(M, 0) = \begin{cases} e^{\{1 - [1 + c\sigma^2 M/\bar{z}]^{(c-1)/c}\}/[(c-1)\sigma^2/\bar{z}^2]} & \text{if } c \neq 0, 1, \\ e^{(\bar{z}^2/\sigma^2)[e^{-(\sigma^2/\bar{z})M} - 1]} & \text{if } c = 0, \\ [1 + (\sigma^2/\bar{z})M]^{-\bar{z}^2/\sigma^2} & \text{if } c = 1, \end{cases}$$

where $\bar{z}$ is the mean, σ^2 is the variance, and c is a third parameter. Hougaard (1986a) focused attention on values of c greater than or equal to one and noted that when c is one the distribution is gamma and when c is two the distribution is inverse Gaussian. Aalen (1988) showed that when c is between zero and one, the distribution is compound Poisson. Other values of c may also be of interest: e.g., when c is zero the distribution is Poisson and when c is minus one the distribution is normal. In any case, it can be shown that $g^\dagger(M, m)$ is given by

$$g^\dagger(M, m) = g^\dagger(M, 0) \cdot \left(\sum_{i=1}^{m} k_{im} \cdot \zeta(M)^{i + (m-i)c} \right),$$

where the coefficients k can be recursively calculated using the relationship

$$k_{im} = k_{i-1,m-1} + (\sigma^2/\bar{z}^{1+c}) \cdot (i + (m - 1 - i)c) \cdot k_{i,m-1}, \qquad i = 1, \ldots, m,$$

with the convention that $k_{0,m} = 0$ and $k_{m+1,m} = 0$, all m, and starting condition $k_{11} = 1$, and where $\zeta(M)$, which is equal to the mean of the distribution $g(z; M, 0)$, is given by

$$\zeta(M) = \begin{cases} \bar{z} \cdot [1 + c\sigma^2 M/\bar{z}]^{-1/c} & \text{if } c \neq 0, \\ \bar{z} e^{-(\sigma^2/\bar{z}) \cdot M} & \text{if } c = 0. \end{cases}$$

Hougaard (1986a) derived his family of distributions from the stable distribution, the use of which is discussed by Hougaard (1986b, 1987) and Aalen (1987, 1988). The $g^\dagger$ transform is readily calculated for the stable distribution, as well as for such other continuous distributions as the uniform distribution and the noncentral χ^2 distribution.

For some applications it may be appropriate to assume that g^0 is discrete. For instance, suppose g^0 follows a 2-point distribution, as assumed by Blumen, Kogan, and McCarthy (1955), Shepard ad Zeckhauser (1980), Trussell and Richards (1985), Vaupel and Yashin (1985b), and others; where

$$g^0(z_n) = p_n, \qquad 0 < p_n < 1, n = 1, 2,$$

with $\sum_{n=1}^{2} p_n = 1$. Then

$$g(z_n; M, m) = p_n z_n^m e^{-z_n M}/g^*(M, m), \qquad n = 1, 2, \tag{10}$$

and

$$g^*(M, m) = \sum_{n=1}^{2} p_n z_n^m e^{-z_n M}.$$

These two formulas immediately generalize to N-point distributions.

Finally, consider two other discrete distributions, the binomial and the negative binomial. The Laplace transform of the binomial distribution with parameters p and n is

$$g^*(M, 0) = (pe^{-M} + 1 - p)^n.$$

It follows that

$$g^*(M, m) = \sum_{i=1}^{m} k_{im} \cdot (n!/(n-i)!) \cdot p^i \cdot e^{-iM} \cdot (pe^{-M} + 1 - p)^{n-i},$$

where the coefficient k can be recursively calculated by

$$k_{im} = k_{i-1,m-1} + ik_{i,m-1},$$

with the convention that $k_{0,m} = 0$ and $k_{m+1,m} = 0$, all m, and starting condition $k_{11} = 1$. The Laplace transform of the negative binomial distribution with parameters π and x can be written

$$g^*(M, 0) = (pe^{-M} + 1 - p)^n,$$

where $n = -x$ and $p = -\pi/(1-\pi)$. Because this transform is the same as the transform used above for the binomial distribution, the same formula holds for g^*.

Note that for some of these distributions, including the Poisson, compound Poisson, binomial, and negative binomial, there is a finite probability that an individual's frailty is zero, implying the individual is immortal. This might be true in survival analysis of hazards that do not affect everyone: e.g., some individuals may be immune to certain diseases, never give birth, never get married, never emigrate, never learn Chinese, or never start to smoke.

Application: Hutterite Fertility

Larsen and Vaupel (1989) used the general method described above to analyze the pattern of effective fecundity (i.e., monthly probability of live birth conception) over age for 419 Hutterite couples who had 3206 live births. In one of their models, the hazard of a live-birth conception at age t and parity (i.e., number of live births) i for woman j is

$$\lambda_{ij}(t) = z_j \phi_i Y_j(t) \lambda^0(t),$$

where z_j denotes fecundity (i.e., frailty), ϕ describes the effect of parity, Y is an indicator that is zero if the couple is sterile at age t and one otherwise, and λ^0 describes the baseline hazard over age. Note that frailty groups consist of repeated events rather than related individuals.

The function ϕ_i was estimated by a piecewise linear function with bends, in one run of the model, at parities 2, 3, 4, 8, and 15. Similarly, $\lambda^0(t)$ was estimated by a piecewise linear function with bends, in one run of the model, at ages 20, 25, 30, 35, 40, and 45. Two different distributions were used for the prior distribution of frailty $g^0(z)$: a gamma distribution and a 2-point distribution.

Using this model, Larsen and Vaupel (1989) found that the prevalence of sterility increased sharply with age after age 40, that the hazard of a live-birth conception declined substantially as parity increased, and that, controlling for the effect of parity, the hazard of live-birth conception among fecund (i.e., non-sterile) couples was approximately level over age. This level was about 0.15 per month for a standard couple with frailty one. The variance in frailty was roughly 0.5; models with heterogeneity in frailty fit the data significantly better than corresponding homogeneous models.

Application: Longevity of Twins

In studies of genetic and early environmental components of the longevity of twins, the frailty z_j of a MZ twin pair might be defined as the relative risk the two twins share (Hougaard, 1986b). Data are available on the day, month, and year of birth and death of Danish twins born from 1870 through 1930 (Hauge *et al.*, 1968; Holm, 1983) and a proposal to analyze these data has been prepared by Vaupel *et al.* (1988). To explore

the estimability of frailty models applied to Danish twin data, 5 mortality data sets were generated that might resemble the actual data set for Danish male MZ twins. It was assumed that for twin pairs unbroken at age 35 mortality rates were given by the Gompertz trajectory $\lambda(t) = a \exp(-\rho y + bt)$, where t is age, y is the birth cohort (varying from zero in 1870 to 60 in 1930), a determines the level of mortality, ρ is the rate of progress in reducing this level, and b determines how quickly mortality rates increase with age. In the simulation, a was 0.0002, b was 0.10, and ρ was 0.01. Frailty was assumed to be gamma distributed with a mean of 1 and a variance of 0.25; in the simulation, the inverse of the variance, k, was used and set equal to 4. The data set generated consisted of 15 twin pairs in the 1870 cohort, gradually increasing to 45 twin pairs in the 1930 cohort. The last year of observation was 1991; all survivors were censored at this time.

Parameter values were then estimated from the simulated data using the likelihood function in (5). The results are given in Table I. Reassuringly, the parameter estimates are close to actual values, with no evidence of important bias, and the estimated SD's are consistent with the SD's of the estimates. This suggests that if the longevity of twins can be captured by a frailty model, then it may be possible to estimate the parameters of this model using a data set such as the Danish twin register.

TABLE I

Comparison of Actual and Estimated Parameters of Five Simulated Data Sets Generated by the Frailty Model Described in the Text

	Parameters				
	a	b	ρ	k	σ^2
Actual Values	0.0002	0.1	0.01	4.0	0.25
Estimated values and (SDs):					
Data Set 1	0.00019	0.101	0.0107	3.87	0.26
	(0.00002)	(0.002)	(0.0015)	(0.49)	
2	0.00019	0.098	0.0081	4.70	0.21
	(0.00002)	(0.002)	(0.0015)	(0.69)	
3	0.00023	0.102	0.0130	4.10	0.24
	(0.00003)	(0.002)	(0.0015)	(0.57)	
4	0.00022	0.102	0.0125	3.50	0.29
	(0.00003)	(0.002)	(0.0016)	(0.43)	
5	0.00019	0.099	0.0090	4.00	0.25
	(0.00002)	(0.002)	(0.0015)	(0.53)	

Application: Stopping Clinical Trials Early

In a clinical trial of a new therapy, the trial may be stopped early if the probability of death (or other adverse consequence) sufficiently exceeds that for the standard therapy (Berry, 1985, 1987, 1989; Canner, 1977, 1984). Suppose that the hazard function for the standard therapy is known to be

$$\lambda(t, x) = e^{0.001t + 0.5x - 5},$$

where t represents days since initiation of therapy and x is a covariate (e.g., an index of age or severity) related to the level of mortality. Furthermore suppose that the hazard function for the new therapy is assumed to be

$$\lambda'(t, x) = z \cdot \lambda(t, x),$$

where z is an uncertain quantity with prior probability distribution $g^0(z)$. Finally, suppose that 6 patients have received the new therapy, with the interim results shown in Table II. As the table indicates, three patients are still undergoing treatment (or have withdrawn) and three patients died.

Is this new therapy a menace? The probability distribution of z can be calculated, if the prior distribution $g^0(z)$ is given. Methods are available for assessing g^0 (Chaloner and Duncan, 1983; Spiegelhalter and Freedman, 1986). For illustrative purposes, consider two possibilities:

(1) g^0 is a two-point distribution such that $g^0(0.5) = 0.9$ and $g^0(1.5) = 0.1$.

(2) g^0 represents a flat, continuous prior such that $g^0(z_1) = g^0(z_2)$, all $z_1, z_2 > 0$.

The data in Table II indicate that M is 4.94 and m is 3. Using (10) and the two-point prior it is readily calculated that $g(0.5; M, m) = 0.998$ and

TABLE II

Interim Data for Six Patients Receiving a New Treatment

Patient	Days in Study	Died?	Value of Covariate
1	60	yes	1.2
2	100	no	0.3
3	10	yes	0.1
4	50	yes	3.2
5	80	no	1.7
6	30	no	0.5

$g(1.5; M, m) = 0.002$. For the flat prior, as discussed earlier, $g(z; M, m)$ follows an Erlang distribution: calculations indicate that the mean is 0.81 and

$$\Pr(z > 1) = e^{-M} \cdot \sum_{i=0}^{m} M^i/i! = 0.27.$$

Thus, the interim data suggest that the risk of the new therapy is less than that of the standard therapy, despite the three deaths.

Discussion

Frailty modeling of survival data has three broad, overlapping purposes:

(1) Sometimes the distribution of frailty is of secondary interest; indeed, frailty may be a nuisance parameter. Frailty is nonetheless important because if it is neglected, estimates of the parameters of interest may be biased (Holt and Prentice, 1974; Gail *et al.*, 1984; Heckman and Singer, 1984; Morgan, 1986; Struthers and Kalbfleisch, 1986; Heckman and Walker, 1987; Lagakos, 1988; Bretagnolle and Huber-Carol, 1988).

(2) In other analysis it is the initial distribution of frailty and the shape of the hazard function over time that are of interest; covariates may not even be included in the analysis. The applications to the fertility of Hutterites and to the longevity of twins given above are cases in point; other examples are in Manton, Stallard, and Vaupel (1981, 1986).

(3) Finally, some research focuses on estimating the distribution of the frailty z_j for a frailty group conditional on the available survival data. An example is the application to clinical trials given above. More generally, this use of frailty modeling pertains to any situation where individuals can be divided into discrete groups (e.g., treatment or risk groups with proportional hazards) and estimates are needed of the relative risk of each group (with regard to failure, cure, conception, unemployment, etc.). These very broad areas of application can be viewed as a Bayesian alternative to classical methods of statistical analysis of survival data.

The results presented above are of direct use in applications of this third type and in applications of the first and second types when individuals or events can be grouped. Frailty modeling of kindred survival data has at least two advantages over the more usual applications to unrelated individuals experiencing a single duration. First, the definition of frailty is clear: a group's frailty is the relative risk shared by all members of the group. With data on unrelated individuals and events, it is sometimes difficult to precisely specify which of the multitude of unobserved risk

factors are included in frailty and which are left to generate the distribution of death times given a particular frailty value. Second, in statistical inference it may be possible to produce more accurate estimates with smaller data sets if there are multiple indirect sightings on the hidden frailty covariate that has to be accounted for.

The main result of this article is the derivation of expressions for the likelihood of kindred survival data and for the distribution of frailty conditional on these data. The proofs are almost obvious and the expressions are simple in form: the entire history of survival data on grouped individuals or repeated events, with covariates and a mixture of death times and censoring times, can be summarized by three statistics, the total log hazard at observed death times h, the total cumulative hazard M, and the number of deaths m. This simplicity and the range of applications suggest that more attention should be given to frailty modeling of kindred survival data. In particular, since kindred frailty modeling can be viewed as a hybrid of the divergent approaches used by geneticists and demographers to analyze life histories and since, as illustrated more fully in Vaupel (1989) and Larsen and Vaupel (1989), kindred frailty models can be based on biological theories and observations, the method may serve as a productive focus for interdisciplinary research in the population sciences.

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