Published in final edited form as:
Per Med. 2011 November ; 8(6): 681–688. doi:10.2217/pme.11.72.

Caring about trees in the forest: incorporating frailty in risk analysis for personalized medicine

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Abstract

The analysis of frailty originated in studies of aging and demography in which the objective was to demonstrate that the hazard rates (mortality risks) of individuals in a population could significantly differ from the population hazard rate as a whole. The differences between these two hazard rates can arise from frailty – differences among individuals that are not observed in a study. We posit that frailty modeling is a useful approach for risk analysis in personalized medicine because it provides a way to address the important and perplexing question of how to translate findings from population studies to the diagnosis and treatment of disease in specific individuals. Our suggestion is based on three unique advantages of frailty modeling: frailty modeling offers an effective approach to analyze the risks at both the individual and population levels and can be used to infer relationships between the two; frailty modeling can be used to analyze the dependence between survival events – one of the most difficult issues in any field that involves common risks; and frailty modeling can be used to describe unobserved or unobservable risks. Finally, we suggest that frailty modeling should be particularly useful in the study and treatment of diseases that are caused or influenced by the human microbiome. By doing so, truly 'personalized' medicine can advance based on a better understanding of the risks to both 'trees' (individuals) and 'forests' (populations).

Keywords

frailty; frailty modeling; human microbiome; individual hazard function; personalized medicine; population hazard function; survival analysis

The term frailty is used in biomedicine more frequently than it is defined [1,2]. In many mainstream science and medical publications (e.g., [101,102]), the term frailty typically refers to "a person's health status and the risk of adverse events related to various health

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Financial & competing interests disclosure

This research was supported by grants UH2AI083264 and U19AI084044 from the NIH (USA). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

conditions" [101], and it is usually associated with older adults. For example, the frailty of older adults is sometimes compared with fitness of young adults [3]. Nevertheless, even with mainstream usage, there is not a consensus on use of the term or ways to determine the frailty status of an individual [2].

Frailty describes differences among individuals, and is a mathematical concept that can be quantitatively and unambiguously defined. In human healthcare, the term frailty originated in studies of aging and demography, and was introduced as 'longevity factor' by Beard [4] who was inspired by Makeham's law [5]. Vaupel *et al.* formally introduced frailty to account for individual differences in mortality hazard rates [6]. Both frailty and its prototype, longevity factor, are mathematical concepts invented to capture the differences among individuals in terms of their susceptibility or vulnerability to risks; furthermore, the factors that result in differential risk are not observed or not observable for various practical reasons. Frailty is associated with common risks, acting as a factor that modifies the hazard function that is a measure of risk in the context of biomedicine.

In engineering reliability, common risk is one of the three mechanisms that are abstracted to describe the failure dependence among components within a system. While in biomedicine, common risk describes the scenario in which the risk of an individual is dependent on common unobserved risks, such as genes common among siblings or members of a subpopulation. Because differences exist among individuals, different individuals can be affected differently by common risks. Hence, the rate of disease occurrence and the efficacy of various treatments may not be pertinent to some individuals in a population because the conclusions are often drawn from studies based on a population as a whole. So the puzzling question is how to translate the results from population-based studies so they are meaningful to the treatment of individuals within populations. We suggest that frailty analysis offers a powerful approach to answering this question. Our suggestion is based on three unique advantages of frailty modeling. First, frailty is a concept that can be defined mathematically for both individuals and populations, and furthermore, the relationship between individual and population frailties may be quantified [2,6,7]. Second, frailty offers a powerful tool to model dependence between failure events, one of the most difficult issues in any fields that involve common risks [8–10]. Third, frailty can be used to describe unobserved and unobservable risks [11]. These three issues are of obvious importance to personalized medicine.

Aalen *et al.* summarized three common sources of the individual variation (heterogeneity) or frailty in biomedical research: inherent or genetic differences; induced frailty owing to the stress of life, and; early or late diagnosis [11]. The first of these is a fixed entity, while the second can change. The third type of frailty exemplifies 'information eliminating uncertainty' – uncertainty that is removed after a reliable diagnosis [12]. Here, we suggest that in addition to the sources of frailty described by Aalen *et al.* [11] the bacterial communities that comprise the human microbiome contribute a fourth source of frailty.

Concepts & principles

As briefly introduced in the previous section, frailty refers to heterogeneity among individuals in a population, and the concept can be applied in various science and engineering contexts. For example, in computer science, 'individuals' can refer to individual nodes, and 'population' can refer to a network of nodes [13]. Today, frailty analysis has become one of two major areas of multivariate survival analysis, the other being Markov chain-based multistate modeling. In engineering reliability analysis frailty has been discussed theoretically, but applications seem to be limited to shared frailty modeling of parallel systems and more recently network reliability and survivability analysis (e.g.,

[12,13]). Individuals and populations, whether in biology or computer network design, can be described using a range of different mathematical models. Among the simplest is a set model in the form of P = (n_1,n_2, …,n_s), or a vector of P = [n_1,n_2, …,n_s], where P represents a population composed from *s* individuals, and an individual *i* has abundance n_i. These models are simple and conceptually useful, but they are too general to be useful in studying meaningful individual or network properties or behaviors such as reliability, survivability or performance. There are numerous other mathematical and computational models that can be applied to study the properties of populations, such as population dynamics models, individual-based models, cellular automata and evolutionary computing [14–16]. Compared with these more familiar modeling approaches, frailty modeling is unique in terms of its ability to deal with individual heterogeneity, particularly in studying the relationship between individual failure hazard and population hazard. Existing frailty modeling is hardly separable from survival analysis. On the one hand, survival analysis offers a mathematical framework to examine the effects of frailty on time-to-event random variables, which are also known as lifetime, survival time or failure time. Conversely, frailty modeling represents an attempt to take a deeper look at survival mechanisms than can be carried out using traditional survival analysis [103]. For a general introduction to survival analysis readers are referred to monographs such as that by Kalbfleisch and Prentice [17].

Two concepts in survival analysis need to be explained before undertaking a discussion of frailty modeling (Equations 1 & 2): survivor function and hazard function. The survivor function S(t) is defined as the probability that survival time, a random variable denoted as T, is at least as large as a value t,

$$S(t)=P(T \geq t), 0<t<\infty \qquad \text{Equation 1}$$

while the hazard function specifies the instantaneous rate of failure at T = t, conditional on survival to time t, and it is defined as:

$$h(t)=\lim_{\Delta t \to 0^+} \frac{P(t \leq T<t+\Delta t|T \geq t)}{\Delta t}=\frac{f(t)}{S(t)} \qquad \text{Equation 2}$$

Obviously, the survivor function and hazard function have the exact same form as the reliability function R(t) and the hazard function in engineering reliability analysis [18].

Survival analysis has developed more powerful approaches to study time-to-event random variables, of which failure time in reliability analysis is a special case. One such example is the proportional hazards models (PHM) originally proposed by Cox to capture the effects of covariates on the survivor (reliability) function [19] (Equations 3–5). In the PHM, $h_0(t)$ is the base hazard function that is conditional on the vector of covariates (Z):

$$h(t|Z)=h_0(t)exp(Z\beta) \qquad \text{Equation 3}$$

and the conditional survival function for T given Z is:

$$S(t|z)=[S_0(t)]^{exp(z\beta)} \qquad \text{Equation 4}$$

where:

$$S_0(t)=exp\left[-\int_0^t \lambda_0(u)du\right] \qquad \text{Equation 5}$$

numerous extensions to Cox's PHM [20,21] have been developed.

Frailty modeling can be classified using one of several schemes. One simple classification scheme is based on whether or not covariates are observed. When covariates are not observed or of no interest, only survival or failure time data are available. The following model (Equations 6 & 7) may be adopted to describe frailty when covariates are not involved:

$$h(Y,t)=Yh_0(t)+\tilde{h}(t) \quad \text{Equation 6}$$

where $\tilde{h}(t)$ is the 'background' hazard, and Y is a non-negative random variable representing frailty. When covariates are observed, a vector of covariates Z is observed and the frailty model takes the following form:

$$h(Y,Z,t)=Yh_0(t)exp(Z\beta) \quad \text{Equation 7}$$

where β is a vector of parameters that reflect the effects of covariates (Z). In both Equations 6 & 7, frailty is considered to have a multiplicative effect on the hazard function used in survival analysis, which is a measurement of instantaneous risk of failure at time t. Therefore, Equations 6 & 7 treat frailty as a random variable that has a multiplicative effect on the instantaneous failure rate. The assumption of multiplicative frailty is merely a mathematical convenience and other kinds of effects, such as additive effects, are also possible. Even so, it has been found that simple multiplicative frailty models are very useful in many applications.

It is important to note that hazard and frailty models (Equations 3–7) are individual based [10]. In Equation 7, frailty Y is a random mixture variable that varies across the population from individual to individual. It is assumed that a scale factor common to all individuals in the population may be absorbed into the baseline hazard function $h_0(t)$, such that frailty distributions are standardized to E(Y)=1. The variance of Y,V(Y), indicates the heterogeneity in baseline risk across the population. When V(Y) is small, the values of frailty (Y) are closely concentrated around one. When V(Y) is large, the values of Y are more dispersed, which reflects greater heterogeneity in individual hazard [10]. Therefore, frailty analysis acknowledges two types of factors (covariates) that influence individual hazards: those accounted for by the observed covariates that may be represented by parameter vector β, as in PHM, and those due to unobserved or unobservable individual heterogeneity (Y). The above two models exemplify univariate frailty modeling wherein frailty (Y) is used to account for unobserved or unobservable covariates.

Multivariate frailty models have also been developed. Early efforts at multivariate frailty modeling exploited the concept of shared frailty or common risks. These are ideal for studying possible interdependence of lifespans (such as twins or family membership) or dependent failures of parallel systems in engineering reliability analysis (e.g., [9]). For multivariate systems with three or more failure variables, the ideal models should accommodate varying degrees of dependence. The theory for generalization of shared frailty modeling to general multivariate systems is an active field of research and only *ad hoc* extensions are currently available [9].

Because frailty is a random variable, it has a probability distribution. Indeed, the precise nature of the relationship between individual and population hazards depends on the precise distribution of frailty among individuals. The choice of frailty distributions can therefore have a profound influence on frailty modeling because it describes the degree of heterogeneity in the population under study. Several distributions including, exponential, γ, log-normal, negative binomial, Weibull, power variance function (PVF) have been studied.

The γ distribution seems to be the most common choice owing to the mathematical simplicity of its use.

Relationship between individual & population hazard functions

Within frailty theory there are strict distinctions between individual hazard functions versus population hazard functions, and between individual survivor functions versus population survivor functions. For example, when the background frailty in Equation 6 is ignored, the population hazard function can be shown to be (Equations 8 & 9) [11]:

$$\mu(t)=h(t)\frac{-\ell'A(t)]}{\ell[A(t)]} \quad \text{Equation 8}$$

where:

$$A(t)=\int_0^t h(s)ds\ \ell[.] \quad \text{Equation 9}$$

is the Laplace transform of Y. In Equation 8, the frailty distribution is not specified, and therefore Equation 8 is a general model for estimating population hazard rate when frailty is assumed to act multiplicatively. A similar relationship also exists between individual survivor and population survivor functions.

The derivation of Equation 8 is rather complex, so here we cite two relatively simple examples to further explain the distinction between individual and population hazard functions. In these examples, the distribution of frailty is specified and the frailty assumed to be multiplicative. By doing so the models specify a concrete relationship between population and individual hazard functions.

The first example is one initially proposed by Beard [4] along with the term longevity factor, which is essentially the prototype of frailty that Vaupel *et al.* later introduced [6]. The following brief introduction is based on the discussion in Duchateau and Janssen [2]. As it will become clear, the first example shows how to compute the population hazard function from the individual hazard function. The second example shows the opposite. In his model Beard [4] adopted Makeham's law [5], which is (Equation 10):

$$h(t)=\alpha+\beta exp(\lambda t) \quad \text{Equation 10}$$

where $h(t)$ is the hazard function, α is the constant basic hazard, and β, λ are parameters that can be chosen so that the hazard function $h(t)$ will continue to increase with time (or age). Strictly speaking, Makeham's law referred to individual hazard, but this distinction is hardly meaningful until Beard's longevity factor u (the prototype of frailty) is added to the model.

$$h_i(t)=\alpha+u_i\beta exp(\lambda t) \quad \text{Equation 11}$$

where u_i is a random variable with probability density function f_u. Beard was particularly interested in the changes of hazard function with time [4], which can be better examined by transforming Equation 11 into Equation 12, which is the following differential equation:

$$\frac{dh_i(t)}{dt}=u_i\beta\lambda exp(\lambda t) \quad \text{Equation 12}$$

The population survivor function can then be obtained as (Equation 13):

$$S_p(t)=\int_0^\infty exp(-\alpha t)exp\left(-u\beta\int_0^t exp(\lambda v)dv\right)f_u(u)du \quad \text{Equation 13}$$

where Beard used a two-parameter γ probability density function (pdf) for f_u [4]. Duchateau and Janssen further restricted this frailty distribution to a one-parameter γ distribution with mean one and variance θ [2]. This is a convention used in frailty analysis when the γ frailty distribution is assumed. Equation 14 shows the one-parameter γ with mean 1, which is represented by the following pdf:

$$f_u(u)=\frac{u^{1/\theta-1}exp(-u/\theta)}{\theta^{1/\theta}\Gamma(1/\theta)} \quad \text{Equation 14}$$

where τ is the γ function. With this γ pdf, population survivor function Equation 13 becomes Equation 15:

$$S_p(t)=exp(-\alpha t)\left[1+\frac{\beta\theta}{\lambda}(exp(\lambda t)-1)\right]^{-1/\theta} \quad \text{Equation 15}$$

The population hazard function can be derived as Equations 16–18:

$$h_p(t)=-\frac{dlogS_p(t)}{dt}=\alpha+\frac{B\,exp(\lambda t)}{1+C\,exp(\lambda t)} \quad \text{Equation 16}$$

with

$$B=\frac{\beta\lambda\theta^{-1}}{\lambda\theta^{-1}-\beta} \quad \text{Equation 17}$$

and

$$C=\frac{\beta}{\lambda\theta^{-1}-\beta} \quad \text{Equation 18}$$

The above population hazard function is actually in the form of a logistic curve, which starts with basic hazard α and increases over time towards the horizontal asymptotic line specified with the value α+λ/θ.

The second example we briefly introduce is from Vaupel *et al.*, who first defined the term frailty quantitatively [6]. The major objective of their work was to demonstrate that in demography, population hazard rates may be a poor indicator for the hazard rates of individuals from that population. Vaupel's model is essentially the same as Equation 6, here we briefly introduce Vaupel's original work [6] based on the discussion presented in Duchateau and Janssen [2]. Vaupel *et al.* assumed that the ratio of hazard rates of two individuals at anytime should equal the ratio of their time-constant frailties (u_i, u_j) (Equation 19) [6].

$$\frac{h_i(t)}{h_j(t)}=\frac{u_i}{u_j} \quad \text{Equation 19}$$

or equivalently if one individual with frailty equal to 1 is chosen as the baseline or reference individual (Equation 20), then:

$$h_i(t)=u_i h_0(t) \quad \text{Equation 20}$$

In other words, an individual with frailty equal to 2 is twice as likely to die as the baseline individual; while an individual with 0.5 frailty is half as likely to die as the baseline individual. Typically, mortality rates for individuals increase faster with age than the observed mortality of the whole population and the risks of more frail individuals are typically higher than that of the whole population. Vaupel *et al.* [6] assumed that u follows the γ distribution with mean 1 and variance θ. They then derived the hazard function of the baseline individual to be (Equation 21):

$$h_0(t)=h_p(t)S_p^{-\theta}(t) \quad \text{Equation 21}$$

and the hazard function for an arbitrary individual $h_i(t)$ to be (Equation 22):

$$h_i(t)=u_i h_p(t)S_p^{-\theta}(t) \quad \text{Equation 22}$$

where $h_p(t)$ and $S_p(t)$ are the population hazard function and survivor function, respectively. Equation 20 can then be written as (Equation 20):

$$h_i(t)=\frac{u_i h_p(t)}{E(U|T>t)} \quad \text{Equation 23}$$

in which the denominator is the conditional mean of the frailty at time t. From Equation 20 it can be seen that because the conditional mean of frailty decreases over time, the hazard rates of more frail individuals should on average be higher and they would die sooner.

Application to studies of the human microbiome & disease

The human microbiome consists of microbial communities that exist in and on human bodies that contribute to host nutrition and protect against infectious disease. This occurs through finely balanced commensal, and often symbiotic relationships that reflect the coevolution of human hosts and their microbiota. The species that make up these communities have been demonstrated to vary between individuals [22–24], probably as a result of differences that exist among hosts in terms of medical history, diet, host genotype, ecological interactions within hosts and a plethora of other factors just now being discovered, as well as purely stochastic factors. It is becoming increasingly apparent that these differences may have important consequences for human health given the associations discovered in recent years between the human microbiome and obesity, cardiovascular disease, autism, diabetes, colon cancer, gastrointestinal disease, asthma, some autoimmune diseases and other conditions [25–37].

It is equally clear that various events such as antibiotic use, diet, personal habits and practices can disturb communities of the human microbiome resulting in loss of community performance and dysbiosis. Thus, the risks to diseases influenced by the human microbiome are likely to differ markedly among individuals and change over time. This greatly complicates risk assessment and makes it nearly impossible to infer the risk of an individual to disease based on population-based studies of risk.

The potential importance of differences between individuals can be illustrated by what has been learned about the vaginal microbiome. Cross-sectional studies have documented

striking differences in the composition of vaginal bacterial communities [23,24]. At least five bacterial community types (referred to as 'states') are common in healthy reproductive age women, and the frequencies of these states vary among women of different ethnic groups. More recent longitudinal studies have demonstrated these communities to be dynamic within an individual and dramatic changes in the species composition can occur over short time scales [38] and [Gajer *et al.*, Unpublished Data]. At present, the patterns of change seem highly individualized. An understanding of factors that influence that stability of these communities and drive changes in composition is important to understanding a woman's risk to bacterial vaginosis (BV) a disease common in reproductive-age women that results in millions of healthcare visits annually and increases risks to the acquisition of sexually transmitted infections and adverse pregnancy outcomes. Although the etiology of BV remains an enigma [39] there is growing evidence that the symptoms associated with the disease are accompanied by, and perhaps caused by, alterations in the composition and structure of vaginal microbial communities. During episodes of BV, species of bacteria that produce lactic acid are commonly reduced in number and the community is 'overgrown' by strictly anaerobic organisms. The notion that BV is linked to ecological disturbances in vaginal communities is consistent with epidemiological data showing that various habits and practices that alter the vaginal environment such as menstrual blood, new sexual partners, frequent intercourse and vaginal douching are all risk factors for BV, which have in common that they alter the vaginal environment. The disease is prevalent, with rates ranging from 20–40% depending on the population of women sampled [40]. However, too little is known about the relationship between vaginal community states and changes in community composition that lead to the symptomatology associated with BV. This leads us to posit that a failure to account for heterogeneity among individuals confounds the clinical diagnosis, prevention and treatment of BV. Without accounting for differences among women there are few mathematical approaches that can be employed to obtain a balanced view of vaginal community properties at both individual and population levels.

When frailty modeling is used for BV risk analysis, the risk of each individual can be described using an individual-specific hazard function such as in the following form (Equation 24):

$$h_{ij}(t, z)=h_0(t)exp(z\beta+f_i) \qquad \text{Equation 24}$$

where h_{ij} is the risk of individual i with race group j (or some grouping based on another factor such as age), $h_0(t)$ is the baseline risk for a person with $z = 0$, z is a vector of covariates or any observed factors that may influence BV risks, and f_i is the frailty of individual i caused by unobserved or unobservable factors. The development of frailty models for BV require data on BV occurrence times (t), and concurrent measures of covariates (z) such as bacterial community composition, metatranscriptome data and selected metadata. The requisite studies to gather these data are now in progress. In such a model frailty f can be described with an assumed distribution model such as γ, Weibull, or PVF distributions. The choice of frailty distribution is a key step because it determines the ability of the model to capture the influence of unobserved or unobservable factors. The choice would be a compromise between mathematical tractability and biomedical realism of the selected distribution model. For example, the γ distribution could be used because of its tractability, but PVF may be more realistic when the frailty distribution is highly skewed. In simplified cases, frailty may be treated as constant within a subpopulation or group but variable across groups, while in more complex analyses frailty could be treated as a stochastic process. It should be noted that frailty may change over time, but this can be dealt with via 'distribution updating' in frailty analysis. For more complex frailty models, readers may refer to Hougaard [9], Ma and Krings [12] and Ma [13].

Future perspective

The preceding discussion of frailty associated with vaginal microbial community diversity and dynamics reveals an important difference between microbial-community-based diseases such as BV and most single-pathogen-based infectious diseases. In single-pathogen-based infectious diseases, the three frailties that Aalen *et al.* summarized may be sufficient for modeling the diseases [11]. Those elements of frailty are essentially, 'born' differences (genomics), heterogeneities in life experiences (e.g., stress from life), and information heterogeneity (e.g., early vs late diagnosis). From a broad perspective, they correspond to inherent individual differences, environment and information. Here, we argue that in addition to these a fourth element of frailty – namely variation in the human microbiome – must also be taken into account. Fortunately, it is now possible to investigate the composition and variability of microbial communities associated with the human body given the dramatic advances made by DNA sequencing and computational technologies, and the simultaneous emergence of tools for data analysis and studies of molecular microbial ecology. These make the study of microbial community diversity possible [41], and can be used to illuminate and characterize heterogeneity in the microbiomes of humans, which will lead to a better understanding of disease risks for specific individuals.

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Executive summary

- Frailty is a mathematical concept introduced to capture differences among individuals in terms of their susceptibility or vulnerability to risks and account for individual differences in mortality hazard rates.
- The most attractive feature of frailty analysis for personalized medicine is that it can be applied to assess the risks at both individual and population levels, and evaluate the relationship between them.
- There are three common sources of frailty relevant to biomedical research: inherent or genetic differences, induced frailty owing to the stress of life and early or late diagnosis. Here, we suggest that differences in the bacterial communities that comprise the human microbiome contribute a fourth source of frailty.