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THE EFFECT OF REMOVING CANCER AS A CAUSE OF DEATH WHEN IT IS CORRELATED WITH OTHER CAUSES

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ABSTRACT

Currently, multiple decrement theory is based on the assumption that competing causes of decrement are stochastically independent even though this assumption is usually not true in reality. This paper presents some fundamental results towards a dependent decrement theory. First, we show how to model dependence with copula functions and next we present a theorem that characterizes the mathematical relationship between the crude and net probabilities when the decrements are dependent. Finally, we apply our results by examining the effect of removing cancer from the United States population when cancer is correlated with the other causes of death.

1. INTRODUCTION

The book *Actuarial Mathematics* [2] develops multiple decrement theory under the assumption that the competing causes of decrement are stochastically independent. Notwithstanding the rarity of completely independent decrements, it is often convenient to assume independence. We believe that the errors in analysis that occur from this convenient assumption are unacceptable. To rectify this situation, this paper presents some fundamental results towards a dependent decrement theory.

We show how to characterize the dependence structure of any continuous multivariate probability distribution with a *copula* function. This will allow us to generalize the current independent decrement theory to a *dependent decrement theory*. Finally, we will investigate the effect of removing cancer, as a cause of death, from the United States population, assuming that cancer is dependent on the other causes. We discover that if the correlation between decrements is negative then removing a cause of death will extend the median lifetime more than if the correlation is positive.

2. DEFINITIONS AND BASIC RESULTS

Following the example of Elandt-Johnson and Johnson [5], let $0 \leq T_j < \infty$ for $j = 1, \ldots, m$ be the *latent* random time of withdrawal, due to cause j, for a life aged $a \geq 0$. Note that these random variables may be stochastically dependent and they are not observable in a competing risk or multiple decrement model. We will assume that these random variables are not defective, that is $Pr(T_j < \infty) = 1$. Let $t_j \geq 0$ for $j = 1, \ldots, m$. Consider the multivariate survival function

$$S(t_1, \ldots, t_m) = Pr(T_1 > t_1, \ldots, T_m > t_m). \tag{2.1}$$

See Tucker [14] for a nice discussion about multivariate probability distributions. Throughout the paper, we will assume that $S(t_1, \ldots, t_m)$ is absolutely continuous. That is, there exists a function $f(t_1, \ldots, t_m)$ such that

$$S(t_1, \ldots, t_m) = \int_{t_1}^{\infty} \cdots \int_{t_m}^{\infty} f(s_1, \ldots, s_m)\, ds_m \ldots ds_1. \tag{2.2}$$

In reality, some decrements occur only at year-ends and so the absolute continuity assumption is not valid in all cases but we believe that this is a good approximating assumption.

Let $t \geq 0$ and consider the *net* survival function

$$S'^{(j)}(t) = Pr(T_j > t). \tag{2.3}$$

Next, consider the random variable $\min(T_1, \ldots, T_m)$ and the index random variable

$$J = \sum_{j=1}^{m} j\, \mathrm{I}(\min(T_1, \ldots, T_m) = T_j). \tag{2.4}$$

Using (2.4) we can define the *crude* survival function as

$$S^{(j)}(t) = Pr(\min(T_1, \ldots, T_m) > t,\ J = j). \tag{2.5}$$

To ensure that all the mass of J is on the integers $1,\ldots,m$ we will assume that $Pr(T_j = T_i) = 0$ whenever $j \neq i$.

The following lemma is a well-known result in the theory of competing risks. This result gives a representation of the crude survival function, that will be useful later. An alternate proof of this lemma may be found in Tsiatis [13].

Lemma 1: If $S(t_1, \ldots, t_m)$ is differentiable with respect to $t_j > 0$ for all $j = 1, \ldots, m$; then

$$S^{(j)}(t) = \int_t^\infty - S_j(r, \ldots, r) \; dr, \tag{2.6a}$$

where

$$S_j(r, \ldots, r) = \frac{\partial}{\partial t_j} S(t_1, \ldots, t_m)\big|_{t_k = r, \forall k} . \tag{2.6b}$$

Proof: $S^{(j)}(t) = Pr(\min(T_1, \ldots, T_m) > t, \; J = j) = Pr([T_k > t \text{ and } T_j \leq T_k \;\; \forall k]) =$ $Pr(T_j > t \text{ and } [T_k > T_j \; \forall k \neq j]) = \int_t^\infty \left\{ \int_{t_j}^\infty \cdots \int_{t_j}^\infty f(t_1, \ldots, t_m) \prod_{k \neq j} dt_k \right\} dt_j =$ $\int_t^\infty \left\{ -\frac{\partial}{\partial t_j} S(t_1, \ldots, t_m)\big|_{t_k = t_j, \forall k} \right\} dt_j$, which is exactly equal to (2.6a-b). □

3. COPULAS AND MEASURES OF ASSOCIATION

In this section, we will show how to characterize the dependence structure of any continuous multivariate probability distribution. This will allow us to generalize the current independent decrement theory to a *dependent decrement theory* or equivalently, a dependent theory of competing risks.

Let $\mathbf{u} = (u_1, \ldots, u_m)' \in [0, 1]^m$ and let $C(\mathbf{u})$ denote the so-called *copula* function that is associated with every multivariate distribution. Following the example of Schweizer and Sklar [12], *we define a copula*, $C(\mathbf{u})$, *as a multivariate cumulative distribution* function that has uniform marginals with support on the hyper-cube $[0, 1]^m$. This means that for all $j = 1, \ldots, m$ we have $C(u_1, \ldots, u_{j-1}, 0, u_{j+1}, \ldots, u_m) = 0$ and $C(1, \ldots, 1, u_j, 1, \ldots, 1) = u_j$. An example of a copula is $C(\mathbf{u}) = \prod_{j=1}^m u_j$ and another is $C(\mathbf{u}) = \min(u_1, \ldots, u_m)$. Some examples of 2-dimensional copulas may be found in Barnett [1] or Mardia [9]. The copula function is very useful in understanding the dependence structure of multivariate probability distributions because of the following lemma. This lemma states that if we know the form of the copula, $C(\mathbf{u})$, and we know the net survival functions, $S'^{(j)}(t) \; \forall j$, then $S(t_1, \ldots, t_m)$ is identifiable.

Lemma 2: There exists a unique copula $C(\mathbf{u})$ such that

$$S(t_1, \ldots, t_m) := C\Big(S'^{(1)}(t_1), \ldots, S'^{(m)}(t_m)\Big). \tag{3.1}$$

Proof: Let $C(\mathbf{u}) = Pr\Big\{ \bigcap_{j=1}^{m} [S'^{(j)}(T_j) \le u_j] \Big\}$. It is well known that if $S'^{(j)}(t)$ is a continuous survival function then the transformed random variable $S'^{(j)}(T_j)$ has a uniform distribution on $[0, 1]$. Therefore, $C(\mathbf{u})$ is a copula because it is a cumulative distribution function with uniform marginals. Next, $C\Big(S'^{(1)}(t_1), \ldots, S'^{(m)}(t_m)\Big) =$

$$Pr\Big\{ \bigcap_{j=1}^{m} [S'^{(j)}(T_j) \le S'^{(j)}(t_j)] \Big\} = Pr\Big\{ \bigcap_{j=1}^{m} [T_j > t_j] \Big\} = S(t_1, \ldots, t_m),$$

because the event $[S'^{(j)}(T_j) \le S'^{(j)}(t_j)]$ is equal to $[T_j > t_j]$, except on a set of probability 0. Let us suppose that $C(\mathbf{u})$ is not unique; then there exists $C^*(\mathbf{u}) \ne C(\mathbf{u})$ such that $S(t_1, \ldots, t_m) = C\Big(S'^{(1)}(t_1), \ldots, S'^{(m)}(t_m)\Big) = C^*\Big(S'^{(1)}(t_1), \ldots, S'^{(m)}(t_m)\Big)$. Let $\mathbf{u}^* = (u_1^*, \ldots, u_m^*)' \in [0, 1]^m$ be a value such that $C^*(\mathbf{u}^*) \ne C(\mathbf{u}^*)$. Using the continuity of $S'^{(j)}(t_j)$, we know there exists $t_j^* \in [0, \infty]$ such that $S'^{(j)}(t_j^*) = u_j^*$. Therefore $C\Big(S'^{(1)}(t_1^*), \ldots, S'^{(m)}(t_m^*)\Big) \ne C^*\Big(S'^{(1)}(t_1^*), \ldots, S'^{(m)}(t_m^*)\Big)$. This is a contradiction to our supposition that $C(\mathbf{u})$ is not unique, therefore $C(\mathbf{u})$ is unique. □

Let us give a few facts about copulas. If $T_1, \ldots, T_m$ are stochastically independent; then the unique copula associated with $S(t_1, \ldots, t_m)$ is equal to $\prod_{j=1}^{m} u_j$. Moreover, if $T_1 = \cdots = T_m$; then the unique copula associated with $S(t_1, \ldots, t_m)$ is equal to $\min(u_1, \ldots, u_m)$. This last copula is actually an upper bound because $C(\mathbf{u}) \le \min(u_1, \ldots, u_m)$, for any copula $C(\mathbf{u})$ and for all $\mathbf{u} \in [0,1]^m$. For more information about copulas, consult Genest and MacKay [6] or Kimeldorf and Sampson [7].

We are now in a position to give a representation of the crude survival function, in terms of copulas. Using the results in *Lemma* 1 and *Lemma* 2, along with the chain rule, we get the following result.

Theorem 3: If $C(u_1, \ldots, u_m)$ is differentiable with respect to $u_j \in (0, 1)$ and $S'^{(j)}(t_j)$ is differentiable with respect to $t_j > 0$ for all $j = 1, \ldots, m$; then

$$\frac{d}{dt}S^{(j)}(t) = C_j\left(S'^{(1)}(t), \ldots, S'^{(m)}(t)\right) \times \frac{d}{dt}S'^{(j)}(t) \ , \tag{3.2a}$$

where
$$C_j(u_1, \ldots, u_m) = \frac{\partial}{\partial u_j} C(u_1, \ldots, u_m) \, . \tag{3.2b}$$

Measures of Association

Nonparametric measures of association are very useful for understanding the nature of the dependence in a copula. They are also useful for parametrizing families of copulas, as we will see later. An example of a measure is Spearman's ρ. Given a bivariate copula function $C(u_1, u_2)$, we can calculate this correlation coefficient as follows,

$$\rho = 12 \int_{[0,1]^2} u_1 u_2 \, dC(u_1, u_2) - 3, \tag{3.3}$$

Note that $|\rho| \le 1$, and $\rho = -1$ if and only if $C(u_1, u_2) = \max(0, u_1+u_2-1)$ and $\rho = +1$ if and only if $C(u_1, u_2) = \min(u_1, u_2)$. The copulas $\max(0, u_1+u_2-1)$ and $\min(u_1, u_2)$ are called the Frechet bounds because $\max(0, u_1+u_2-1) \le C(u_1, u_2) \le \min(u_1, u_2)$ for all $C(u_1, u_2)$. For more information, see Genest and MacKay [6] or Carriere and Chan [4].

The Normal Copula

Finally, let us give an example of a bivariate copula. Specifically, let us give the probability density function of the copula associated with the bivariate normal distribution. For $t, z \in \Re$, define

$$\Phi(t) = \int_{-\infty}^{t} \phi(z) \quad dz, \tag{3.4}$$

where

$$\phi(z) = (2\pi)^{-1/2} \exp\left\{-z^2/2\right\}. \tag{3.5}$$

Next, for $u \in (0, 1)$ define $\Phi^{-1}(u)$ as the inverse function of $\Phi(t)$, that is $\Phi\left(\Phi^{-1}(u)\right) = u$. Next, let $\mathbf{R}$ denote an 2×2 non-singular correlation matrix with the off-diagonal element denoted as r_{12}. This is actually a variance-covariance matrix where all the diagonal elements are equal to 1. Note that $\mathbf{R}$ is a symmetric and positive definite matrix. Let $(z_1, z_2)' \in \Re^2$; then the probability density function of a standardized bivariate normal distribution is

$$h(z_1, z_2) = (2\pi)^{-1} |\mathbf{R}|^{-1/2} \exp\left\{-\frac{(z_1, z_2)\mathbf{R}^{-1}(z_1, z_2)'}{2}\right\}. \tag{3.6}$$

See Mardia, Kent and Bibby [10] for more details about the multivariate normal distribution. Let $(u_1, u_2)' \in (0, 1)^2$; then the density of the normal copula is

$$\frac{\partial^2 C(u_1, u_2)}{\partial u_1 \partial u_2} = \frac{h(\Phi^{-1}(u_1), \ \Phi^{-1}(u_2))}{\phi(\Phi^{-1}(u_1)) \times \phi(\Phi^{-1}(u_2))}. \tag{3.7}$$

We can express r_{12} as a function of Spearman's correlation coefficient. Using the results in Kruskal [8], we find that $r_{12} = 2\sin(\pi\rho/6)$, where ρ is Spearman's correlation for the bivariate normal copula with parameter r_{12}.

4. THE EFFECT OF REMOVING CANCER

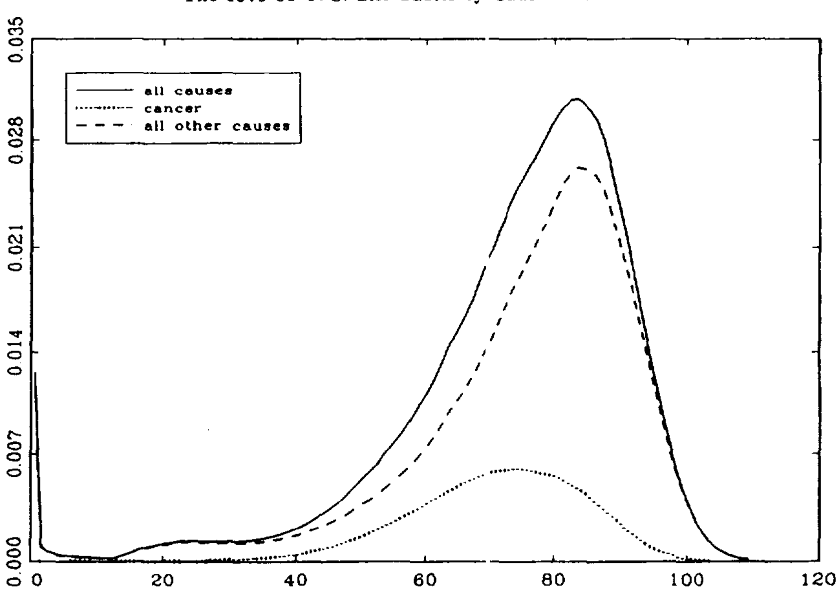
In this section, we will investigate the effect of removing cancer, as a cause of death, from the United States (U. S.) population. Specifically, we will calculate the net survival probabilities from the crude probabilities, assuming that this disease is dependent on the other causes. We will model the dependence with a normal copula.

The data comes from the National Center for Health Statistics [11]. This publication gives the number of deaths from cancer and from the other causes, in five year age groups. Using this data, we can calculate the crude survival functions $S^{(c)}(t)$ and $S^{(-c)}(t)$ for $t = 0, 5, \ldots, 95, 100$. The superscript (c) will denote that cancer is the cause of death while $(-c)$ will denote the other causes of death. Using the data, we find that the probability of dying from cancer is equal to ${}_{\infty}q_0^{(c)} = .1956$. Using an interpolating formula, we approximated the crude survival functions at $t = 0, 1, \ldots, 110$ and we estimated the densities $f_0^{(c)}(t)$ and $f_0^{(-c)}(t)$. Figure 1 is a plot of $f_0^{(r)}(t) = f_0^{(c)}(t) + f_0^{(-c)}(t)$ and of $f_0^{(c)}(t)$, $f_0^{(-c)}(t)$. All the graphs and calculations were done with the statistical computing language GAUSS.

FIGURE 1

A Plot of the Densities $f_0^{(r)}$, $f_0^{(c)}$ and $f_0^{(-c)}$ Based on

The 1979-81 U. S. Life Tables by Cause of Death



The net survival functions $S'^{(c)}(t)$ and $S'^{(-c)}(t)$ can be found by solving a system of differential equations. Consider the equations (3.2a-b) that relate the net and crude probabilities with the copula function. If we assume that the copula is normal, then we get the system

$$f_0^{(c)}(t) = C_1\left(S'^{(c)}(t),\ S'^{(-c)}(t) \mid \rho\right) \times f_0'^{(c)}(t), \tag{4.1a}$$

$$f_0^{(-c)}(t) = C_2\left(S'^{(c)}(t),\ S'^{(-c)}(t) \mid \rho\right) \times f_0'^{(-c)}(t), \tag{4.1b}$$

where

$$C_1(u,\ v \mid \rho) = \Phi\left(\left\{\Phi^{-1}(v) - r(\rho)\Phi^{-1}(u)\right\} \Big/ \sqrt{1 - r(\rho)^2}\right), \tag{4.1c}$$

and $C_2(u,\ v \mid \rho) = C_1(v,\ u \mid \rho)$ and $r(\rho) = 2\sin(\pi\rho/6)$. Note that we parametrized the copula with Spearman's ρ because we believe that this parametrization is informative, albeit complicated.

Let us describe how we solved this system numerically. Most of the techniques that we used are given in Burden and Faires [3]. First, we transformed the differential system into a system of difference equations. We did this by letting

$$\begin{aligned}
&f_0^{(c)}(k+.5) \approx S^{(c)}(k) - S^{(c)}(k+1),\\
&f_0^{(-c)}(k+.5) \approx S^{(-c)}(k) - S^{(-c)}(k+1),\\
&f_0'^{(c)}(k+.5) \approx S'^{(c)}(k) - S'^{(c)}(k+1),\\
&f_0'^{(-c)}(k+.5) \approx S'^{(-c)}(k) - S'^{(-c)}(k+1),\\
&S'^{(c)}(k+.5) \approx .5 \times \left\{S'^{(c)}(k+1) + S'^{(c)}(k)\right\},\\
&S'^{(-c)}(k+.5) \approx .5 \times \left\{S'^{(-c)}(k+1) + S'^{(-c)}(k)\right\},
\end{aligned}$$

for $k = 0,\ 1,\ \ldots,\ 110$. Using the initial condition $S'^{(c)}(0) = S'^{(-c)}(0) = 1$, we find that we can solve the problem recursively. Moreover, the problem reduces to finding the zeros of a sequence of nonlinear system of equations which were solved with Newton's method.

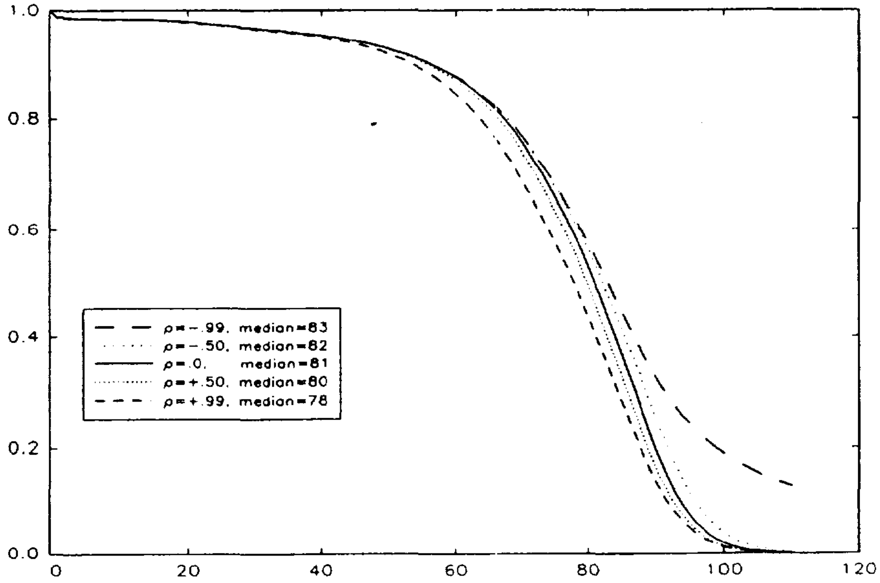
To verify our numerical solution, we checked that

$$C\left(S'^{(c)}(t),\ S'^{(-c)}(t) \mid \rho\right) = S^{(c)}(t) + S^{(-c)}(t). \tag{4.2}$$

We solved the system under the assumption that Spearman's correlation is equal to $\rho = -.99,\ -.50,\ 0,\ ,+.50\ +.99$. Note that the copula is not differentiable when ρ is equal to -1 or $+1$. If $\rho = 0$ then the net probabilities are independent and we have the standard analysis. But if the correlation is $+.99$ then this strong positive dependence means that removing cancer has little effect on survival. But if the correlation is $-.99$ then this strong negative dependence means that removing cancer will increase the chances of survival.

FIGURE 2

A Plot of $S'^{(-c)}(t)$ when Cancer is Correlated with the Other Causes



These effects can be seen in Figure 2 where $S'^{(-c)}(t)$ was plotted at $t = 0, 1, \ldots, 110$ and $\rho = -.99, -.50, 0, +.50, +.99$. These graphs indicate that $S'^{(-c)}(t)$ increases when ρ decreases. If $\rho = -.99$, then $S'^{(-c)}(t)$ is essentially an upper bound on the improvement that can be expected when cancer is removed. Moreover, if $\rho = +.99$, then $S'^{(-c)}(t)$ is essentially a lower bound on the improvement in mortality that can be expected when cancer is removed.

The graph also reveals that if we remove cancer then the median age at death of a newborn will increase as ρ decreases. Currently, the median age at death of a newborn is 77. Under the standard analysis ($\rho = 0$), removing cancer will increase the median age at death to 81. If $\rho = +.99$ then removing cancer will only increase the median age to 78 but if $\rho = -.99$ then the median age will increase to 83.

5. SUMMARY

We showed that the effect of removing a cause of death depends on the copula used in the analysis. We found that if the correlation between decrements is negative then removing a cause of death will extend the median lifetime more than if the correlation is positive. We also gave a theorem that characterizes the mathematical relationship between the crude and net probabilities when the decrements are dependent.

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