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Higher Dimensional Clayton–Oakes Models for Multivariate Failure Time Data

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Summary

The Clayton–Oakes bivariate failure time model is extended to dimensions $m > 2$ in a manner that allows unspecified marginal survivor functions for all dimensions less than m . Special cases that allow unspecified marginal survivor functions of dimension q with $q < m$, while making some provisions for dependencies of dimension greater than q , are also described.

Some key words

Bivariate survivor function; Clayton–Oakes model; Copula; Cross ratio; Multivariate survivor function

1. Introduction

The Clayton–Oakes model (Clayton, 1978; Oakes 1982; 1986; 1989) for the joint survivor function F , defined by $F(t_1, t_2) = \text{pr}(T_1 > t_1, T_2 > t_2)$ for failure time variates $T_1 > 0$ and $T_2 > 0$, can be written

$$F(t_1, t_2) = \{F(t_1, 0)^{-\theta} + F(0, t_2)^{-\theta} - 1\}^{-1/\theta} \vee 0, \quad (1)$$

where $\vee$ denotes maximum. This expression approaches independence as $\theta \rightarrow 0$, and the upper Frechet bound $F(t_1, 0) \wedge F(0, t_2)$ as $\theta \rightarrow \infty$, where $\wedge$ denotes minimum. The bivariate density from (1) remains everywhere non-negative for $\theta \geq -1/2$, but positive probability begins to accumulate along the lower Frechet boundary $0 \vee \{F(t_1, 0) + F(0, t_2) - 1\}$ for $\theta < -1/2$, with all probability eventually accruing to this boundary as $\theta \rightarrow -1$. All points (t_1, t_2) away from this lower boundary are continuity points for (T_1, T_2) , for all $\theta \in [-1, \infty)$.

An important property of (1) is that the cross ratio function α_{11} , defined at continuity points (t_1, t_2) by

$$\alpha_{11}(t_1, t_2) = \Lambda(dt_1, dt_2) / \{\Lambda_{10}(dt_1, t_2)\Lambda_{01}(t_1, dt_2)\},$$

where

$$\Lambda_{11}(dt_1, dt_2) = \text{pr}\{T_1 \in [t_1, t_1 + dt_1], T_2 \in [t_2, t_2 + dt_2]; T_1 \geq t_1, T_2 \geq t_2\},$$

is the double failure hazard rate at (t_1, t_2) , and $\Lambda_{10}(dt_1, t_2)$ and $\Lambda_{01}(t_1, dt_2)$ are corresponding single failure hazard rates at (t_1, t_2) , for example $\Lambda_{10}(dt_1, t_2) = \text{pr}\{T_1 \in [t_1, t_1 + dt_1]; T_1 \geq t_1, T_2 \geq t_2\}$, is equal to $1 + \theta$ for all t_1 and t_2 . This property implies a useful interpretation, for example in the context of family studies in genetic epidemiology, since $1 + \theta$ can be viewed as the ratio of the T_1 hazard rate given $T_2 = t_2$ to the T_1 hazard rate given $T_2 \geq t_2$, with a corresponding expression of ratios of T_2 hazard rates.

In general the cross ratio function α_{11} measures local dependence between T_1 and T_2 on a relative scale. Together with the marginal distributions $F(t_1, 0)$ and $F(0, t_2)$, or equivalently the marginal hazard rates $\Lambda_{10}(dt_1, 0)$ and $\Lambda_{01}(0, dt_2)$, the cross ratio function determines F . The cross ratio provides a convenient estimation target in that $\alpha_{11}(t_1, t_2)$ can take any value in $[0, \infty)$, regardless of marginal hazard rates, at continuity points of F .

The model (1) has a copula form

$$F(t_1, t_2) = C_\theta\{F(t_1, 0), F(0, t_2)\},$$

where $C_\theta(u_1, u_2) = (u_1^{-\theta} + u_2^{-\theta} - 1)^{-1/\theta} \vee 0$ for $0 \leq u_i \leq 1$ ($i = 1, 2$). There is a vast literature on copula models (e.g. Joe, 1997; Nelsen, 2007). Several authors have proposed the copula model

$$F(t_1, \dots, t_m) = C_\theta\{F(t_1, 0, \dots, 0), F(0, t_2, 0, \dots, 0), \dots, F(0, \dots, 0, t_m)\}, \quad (2)$$

with $C_\theta(u_1, \dots, u_m) = \{u_1^{-\theta} + u_2^{-\theta} + \dots + u_m^{-\theta} - (m-1)\}^{-1/\theta} \vee 0$ as a generalization of (1) to m failure time variates $T_1, \dots, T_m$. This model, however, requires each pairwise cross ratio to be equal to that for every other pair of the failure time variates. This restriction may be untenable, for example in a family genetic epidemiology study with differing relationships among family members.

Here we consider a class of copula-type models in which the m -variate survivor function is specified as a function not only of its univariate marginal survivor functions, but also of its marginal survivor functions for all subsets of dimension less than m . Some special cases in which each pairwise cross ratio is allowed to take a distinct value, as well as regression and other generalizations, are briefly described.

2. Trivariate Generalization of Clayton–Oakes

First consider dimension $m = 3$. A trivariate generalization of (1), with unrestricted marginal and pairwise marginal survivor functions is

$$F(t_1, t_2, t_3) = \{F(t_1, t_2, 0)^{-\theta} + F(t_1, 0, t_3)^{-\theta} + F(0, t_2, t_3)^{-\theta} - F(t_1, 0, 0)^{-\theta} - F(0, t_2, 0)^{-\theta} - F(0, 0, t_3)^{-\theta} + 1\}^{-1/\theta} \vee 0. \quad (3)$$

The parameter $-1 - \theta < \infty$ governs dependencies among T_1 , T_2 and T_3 , beyond those emanating from the pairwise marginal survivor functions. More specifically, one can define a trivariate cross ratio function at all continuity points of F , in an obvious notation, by

$$\alpha_{111}(t_1, t_2, t_3) = \Lambda_{111}(dt_1, dt_2, dt_3) / \{\Lambda_{100}(dt_1, t_2, t_3)\Lambda_{010}(t_1, dt_2, t_3)\Lambda_{001}(t_1, t_2, dt_3)\},$$

so that α_{111} measures local departure from independence on a relative scale. Straightforward calculations under (3) give

$$\alpha_{111}(t_1, t_2, t_3) = (1 + \theta)[(1 - \theta) + \{\alpha_{110}(t_1, t_2, t_3) - 1\} + \{\alpha_{101}(t_1, t_2, t_3) - 1\} + \{\alpha_{011}(t_1, t_2, t_3) - 1\}],$$

where, for example

$$\alpha_{110}(t_1, t_2, t_3) = \Lambda_{110}(dt_1, dt_2, t_3) / \{\Lambda_{100}(dt_1, t_2, t_3)\Lambda_{010}(t_1, dt_2, t_3)\}.$$

One sees that dependencies emanating from the pairwise marginal distributions are augmented by $(1 - \theta)$ and rescaled by $(1 + \theta)$ to give the trivariate cross ratio. Note that $\alpha_{111}(t_1, t_2, t_3)$, and therefore also $\Lambda_{111}(dt_1, dt_2, dt_3)$, approaches zero at all continuity points as $\theta \rightarrow -1$.

Also in (3), consideration of $\log F(t_1, t_2, t_3)$ and application of L'Hôpital's rule shows that (3) approaches

$$F(t_1, t_2, 0)F(t_1, 0, t_3)F(0, t_2, t_3) / \{F(t_1, 0, 0)F(0, t_2, 0)F(0, 0, t_3)\}$$

as $\theta \rightarrow 0$, approaches the upper bound $F(t_1, t_2, 0) \wedge F(t_1, 0, t_3) \wedge F(0, t_2, t_3)$ as $\theta \rightarrow \infty$, and approaches the lower bound $0 \vee \{F(t_1, t_2, 0) + F(t_1, 0, t_3) + F(0, t_2, t_3) - F(t_1, 0, 0) - F(0, t_2, 0) - F(0, 0, t_3) + 1\}$ as $\theta \rightarrow -1$. All (t_1, t_2, t_3) values away from this lower bound are continuity points for (T_1, T_2, T_3) , for any $\theta \in [-1, \infty)$.

As a special case of (3) one can restrict the pairwise marginal survivor functions in (3) to be of the form (1) with respective parameters θ_{12} , θ_{13} and θ_{23} , thereby allowing distinct cross ratios for each pair of failure times, along with a provision for additional trivariate dependency via the parameter θ . The model (2) is the further special case in which $\theta_{12} = \theta_{13} = \theta_{23} = \theta$.

3. Higher Dimensional Survivor Function Models

Expression (3) can be generalized to an arbitrary dimension m in a conceptually simple, even if notationally awkward, manner. Specifically, a model for the m -dimensional survivor function F in terms of marginal survivor functions of dimensions less than m can be written

$$\begin{aligned}
 F(t_1, \dots, t_m) = & \{ F(t_1, \dots, t_{m-1}, 0)^{-\theta} + F(t_1, \dots, t_{m-2}, 0, t_m)^{-\theta} + \dots + F(0, t_2, \dots, t_m)^{-\theta} \\
 & - F(t_1, \dots, t_{m-2}, 0, 0)^{-\theta} - F(t_1, \dots, t_{m-3}, 0, t_{m-1}, 0)^{-\theta} - \dots - \\
 & F(0, t_2, \dots, t_{m-1}, 0)^{-\theta} - \dots - F(0, 0, t_3, \dots, t_m)^{-\theta} \\
 & + F(t_1, \dots, t_{m-3}, 0, 0, 0)^{-\theta} + \dots + F(0, 0, 0, t_4, \dots, t_m)^{-\theta} - \dots - \\
 & + (-1)^{m-2} F(t_1, 0, \dots, 0)^{-\theta} + (-1)^{m-2} F(0, t_2, 0, \dots, 0)^{-\theta} + \dots + \\
 & (-1)^{m-2} F(0, \dots, 0, t_m)^{-\theta} + (-1)^{m-1} \}^{-1/\theta} \vee 0
 \end{aligned}
 \tag{4}$$

where, for example, the second component of expression (4) consists of all $m(m-1)/2$ pairs with two arguments equal to zero, and the third component is comprised of all $m(m-1)(m-2)/6$ triplets with three arguments equal zero. The upper bound for (4), given by $F(t_1, \dots, t_{m-1}, 0) \wedge F(t_1, \dots, t_{m-2}, 0, t_m) \wedge \dots \wedge F(0, t_2, \dots, t_m)$, is approached as $\theta \rightarrow \infty$, while the lower bound is given by (4) evaluated at $\theta = -1$. As $\theta \rightarrow 0$ (4) approaches the product of all marginal survival probabilities having a positive sign divided by the product of all marginal survival probabilities having a negative sign, on the right side of (4).

The parameter θ in (4) again reflects m -variate dependency beyond that attributable to dependencies among subsets of $q < m$ of the variates. One can define an m -variate cross ratio $\alpha_{11\dots 1}$ by

$$\alpha_{11\dots 1}(t_1, t_2, \dots, t_m) = \Lambda_{11\dots 1}(dt_1, \dots, dt_m) / \{ \Lambda_{10\dots 0}(dt_1, t_2, \dots, t_m) \Lambda_{010\dots 0}(t_1, dt_2, \dots, t_m) \cdots \Lambda_{0\dots 01}(t_1, t_2, \dots, dt_m) \}.$$

Then $\alpha_{11\dots 1}(t_1, \dots, t_m)$ from (4) is complex but includes an overall $(1 + \theta)$ factor multiplied by a function of θ plus a function of departures from unity for lower dimensional cross ratio functions. As such, θ in (4) reflects any m -variate dependence beyond that emanating from its lower dimensional marginal survivor functions scaled by $(1 + \theta)$, so that the m -dimensional failure density approach zero at all continuity points as $\theta \rightarrow -1$.

An interesting reproductive property arises from (4) if each of the marginal survivor functions of dimension greater than q , for any $1 \leq q < m$ also adheres to a model of the form

(4) with a common value of θ . One can then express $F(t_1, \dots, t_m)$ as a function of θ and its marginal survivor functions of dimension q or less, which can remain unspecified. Specifically one can then write

$$\begin{aligned}
 F(t_1, \dots, t_m) = & [F(t_1, \dots, t_q, 0, \dots, 0)^{-\theta} + F(t_1, \dots, t_{q-1}, 0, t_{q+1}, \dots, 0)^{-\theta} + \dots + F(0, \dots, 0, t_{m-q+1}, \dots, t_m)^{-\theta} \\
 & + \binom{m-q}{1} (-1) \{F(t_1, \dots, t_{q-1}, 0, \dots, 0)^{-\theta} + F(t_1, \dots, t_{q-2}, 0, t_q, 0, \dots, 0)^{-\theta} + \dots + F(0, \dots, 0, t_{m-q+2}, \dots, t_m)^{-\theta}\} \\
 & + \binom{m-q+1}{2} (-1)^2 \{F(t_1, \dots, t_{q-2}, 0, \dots, 0)^{-\theta} + F(t_1, \dots, t_{q-3}, 0, t_{q-1}, 0, \dots, 0)^{-\theta} + \dots + F(0, \dots, 0, t_{m-q+3}, \dots, t_m)^{-\theta}\} \\
 & + \dots \\
 & + \binom{m-2}{q-1} (-1)^{q-1} \{F(t_1, 0, \dots, 0)^{-\theta} + \dots + F(0, \dots, t_m)^{-\theta}\} + \binom{m-1}{q} (-1)^q]^{-1/\theta} \vee 0.
 \end{aligned}
 \tag{5}$$

While the copula terminology seems to have been applied only to functions that bring together the univariate marginal survivor functions to form the m -dimensional survivor function, expression (5) can be viewed as a q -variate copula function that brings together all marginal survivor functions of dimension $q < m$ to yield the m -dimensional survivor function. Marginal survivor functions of dimension s , where $q \leq s < m$, also have the form (5), with m replaced by s .

The special case of $q = 1$ gives (2) while $q = 2$ reduces to

$$\begin{aligned}
 F(t_1, \dots, t_m) = & \{F(t_1, t_2, 0, \dots, 0)^{-\theta} + F(t_1, 0, t_2, 0, \dots, 0)^{-\theta} + \dots + F(0, \dots, 0, t_{m-1}, t_m)^{-\theta} \\
 & - (m-2)F(t_1, 0, \dots, 0)^{-\theta} - (m-2)F(0, t_2, 0, \dots, 0)^{-\theta} - \dots - (m-2) \\
 & F(0, \dots, 0, t_m)^{-\theta} + \frac{(m-1)(m-2)}{2}\}^{-1/\theta} \vee 0.
 \end{aligned}
 \tag{6}$$

This expression provides a class of survivor functions having unspecified univariate and pairwise marginal survivor functions. The pairwise survivor functions can, for example, be modeled by Clayton–Oakes models (1), each with its own θ -parameter to allow pairwise associations to depend, for example, on familial relationships, while also making a provision for higher order dependencies among the failure times through the parameter θ . Other classes of bivariate survivor function models could also be entertained in (6), including models that allow the cross-ratio to vary with regression variables, or with its time components.

4. Generalizations and Discussion

Regression generalizations of the models described above will be needed in many applications. Suppose that $(T_1, \dots, T_m)$ is accompanied by a regression variable $z = (z_1, \dots, z_p)$ available at $(T_1, \dots, T_m) = (0, \dots, 0)$. One can consider a regression model

$$\theta(z) = \alpha^{\exp(z\gamma)} - 1 \quad (7)$$

for $\theta = \theta(z)$ in (4), where α and $\gamma = (\gamma_1, \dots, \gamma_p)'$ are parameters to be estimated. Under (7) the direction of any m -variate dependence, beyond that arising from the lower dimensional marginals, is determined by α , with $\theta(z) \rightarrow -1$ as $\alpha \rightarrow 0$, $\theta(z) \rightarrow 0$ as $\alpha \rightarrow 1$, and $\theta(z) \rightarrow \infty$ as $\alpha \rightarrow \infty$, at all continuity points of $(T_1, \dots, T_m)$. This model allows regression variables to affect the strength, but not the direction of this m -variate dependence. Similarly a regression model $\theta(z)$ of the form (7) could be considered for θ in (5), and could also be considered for the regression modeling of lower dimensional survivor functions, including the pairwise survivor functions in (6), each with its specific α and γ parameters. Furthermore, the assumption of cross-ratios that are constant in time for these pairwise survivor functions can be relaxed to allow cross-ratios that differ among the elements of a rectangular grid formed by the follow-up times for the two failure times (Nan et al., 2006). The larger m -dimensional model (4) can be extended to allow the θ -parameters, and the associated (α, γ) parameters in regression generalizations, to vary among the m -dimensional cubes formed by partitions of the follow-up periods for each of the failure time variates.

The classes of models just described are fully parametric provided that parametric models are specified for the lower dimensional survivor functions included in the model specification. As such, under the usual independent censorship assumptions, standard likelihood-based testing and estimation procedures can be expected to apply.

The use of (4)–(7) with nonparametric or semiparametric model specifications is also of considerable interest. For example, Andersen et al. (1993) and Glidden & Self (1999) consider the application of (2) with Cox (1972) models for the univariate marginal survivor functions. One could similarly, for example, consider (6) with Cox model marginal survivor functions and with each pairwise marginal survivor functions adhering to (1) with cross ratio parameter of the form (7) for each failure time pair. This type of model may be flexible enough for many application, though it may be necessary to allow cross ratios to vary over a grid determined by the study follow-up period in some applications. One could even entertain semiparametric regression models of the form

$$\theta(t_i, t_j; z) = \alpha_{ij}(t_i, t_j)^{\exp\{x(t_1, \dots, t_m)\gamma_{ij}\}} - 1$$

with regression variable $x(t_1, \dots, t_m)$ defined from functions of the preceding history $Z(t_1, \dots, t_m) = z(0, \dots, 0) \vee \{z(u_1, \dots, u_m); u_1 < t_1, \dots, u_m < t_m\}$ of covariates that may be evolving over time. The application of semiparametric models of this type will require a

specialized development, perhaps aided by likelihood approximations within m -cubes defined by the uncensored failure times for the m failure time variates in conjunction with regression models deriving from (7), thereby generalizing available partial likelihood procedures for estimation in the univariate Cox model (e.g. Breslow, 1974). This type of development may help to address the longstanding question of whether data on companion failure times can materially strengthen marginal hazard rate estimation for a censored failure time variate.

The Clayton–Oakes model (1) with $\theta = 0$ can also be derived by transformation of a frailty model under which T_1 and T_2 are independent given the value of a shared frailty variate, that follows a rescaled gamma distribution with mean one and variance θ , that acts multiplicatively on the hazard rates for the two variates. There is a substantial literature on more general frailty model constructions for deriving multivariate survivor function models (e.g., Andersen et al., 1993; Duchateau & Janssen, 2008; Wienke, 2011). Frailty models also have potential for comprehensive analysis of multivariate failure time data, with the choice between frailty and copula approaches dependent on model flexibility, ease of application, and parameter interpretation. On the last issue one can note that regression parameters in frailty models mostly have an interpretation that derives from associations conditional on the hypothesized frailty variates, whereas in copula-type models, including for the generalized copula notion described here, regression parameters pertain to marginal distribution associations with parameters having a population interpretation. See Bandeen-Roche & Liang (1996) for an approach to building multivariate survival models that combine aspects of the frailty and copula approaches in a recursive fashion.

Additional developmental work on estimation procedures for these valuable classes of multivariate failure time models, and comparison of the efficiency, robustness and interpretation of the associated parameter estimates, is strongly encouraged.

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