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F. VANDENHENDE and P. LAMBERT

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Modeling Longitudinal Data with Non-Random Drop-Outs Using Copulas

François Vandenhende[1,2,*] **and Philippe Lambert**[2]

[1] Statistics and Information Sciences, Eli Lilly & Company, B-1348 Mont-Saint-Guibert, Belgium.

[2] Institute of Statistics, Université Catholique de Louvain, B-1348 Louvain-la-Neuve, Belgium.

$*$ To whom correspondance should be adressed.

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SUMMARY. This paper develops a class of parametric models for longitudinal data with non-random drop-outs. Marginal regression models are fitted to the repeated measurements and the drop-out profiles to account for covariate and time effects. The dependence between successive responses and between drop-out and response is also modeled using particular dependence functions, called copulas. Copulas are used to create a joint distribution with given marginal distributions. In our case, two copulas are used to obtain a parametric form for the joint density of the repeated responses and of the drop-out indicators. Parameters of the two marginal and copula models are jointly estimated using maximum likelihood. The method evenly applies to continuous or non-continuous ordinal responses and illustrations are provided for the two cases. A log-normal response (heart rate) is analysed in a toxicology study and a discrete ordinal variable (pain severity) is considered in a migraine trial. Three copula families are used: the *product* copula, the copula of Frank (1979) and a copula generated from the standard multivariate *normal* distribution. The use of copulas allows a consistent and flexible modeling of the dependence structure for continuous and non-continuous repeated measurements. Moreover, it permits a valid likelihood-based inference on marginal models for both the response and the drop-out process when the pattern of drop-out is not missing completely at random. In the two examples, serial dependence was detected in the data and the drop-out hazard was moderately depending on previous responses. Parameter estimates from the marginal models were found insensitive to the choice of the dependence model between drop-out and response.

email: francois@lilly.com

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1. Introduction

In many longitudinal studies, subjects drop out of the trial before completion. This produces unbalanced sets of data with unequal numbers of observations per subject. In addition to the longitudinal response, the drop-out rate can also be interesting to analyse. This was the case in a recent migraine trial in which drop-out occured after the intake of a rescue medication (RM). Both the pain severity profile and the rate of RM intake can be analysed to provide evidence of a potential treatment effect. Standard statistical software are available to analyse unbalanced repeated and survival data separately. But when the drop-out process is not independent of the response - for instance when patients tend to take a RM as their pain remains severe - a separate analysis of the two variables can bias the results.

Rubin (1976) introduced and Little and Rubin (1987) developed a taxonomy to distinguish several types of missing data according to their association to the response. The non-response process is termed *missing completely at random* (MCAR) when it is independent of responses. It is *missing at random* (MAR) when conditionally independent of the unobserved response(s) given the observed data. When neither MCAR nor MAR hold, it is termed *missing not at random* (MNAR). The analysis of repeated measures with non random drop-outs has been discussed by various authors. Likelihood methods were used by Diggle and Kenward (1994) for continuous responses and by Molenberghs, Kenward and Lesaffre (1997) for discrete ordinal responses. In the two cases, the joint density $f_{\mathbf{Y},D}$ of the response vector $\mathbf{Y}$ and drop-out time D is factored as $f_{\mathbf{Y}} f_{D|\mathbf{Y}}$. These classes of models are known as *selection models.* The conditional distribution of $(D|\mathbf{Y})$ is typically modeled as an event-time regression including $\mathbf{Y}$ as covariate. A distinction between MCAR, MAR and MNAR processes is made based upon the responses which have to be included in the modeling of $f_{D|\mathbf{Y}}$.

Another factoring is $f_{\mathbf{Y}|D} f_D$. This is known as *pattern mixture* models. This approach stratifies the data over the different patterns (e.g. times) of drop-out and then applies a different model to each pattern. An application is given by Little (1993). A taxonomy equivalent to that of Rubin (1976) was developed by Molenberghs, Michiels, Kenward and Diggle (1998) in the framework of pattern mixture models.

Both selection and pattern mixture models have merit in either the longitudinal or the survival settings but the interpretation of parameters is different in the two models. A marginal and a conditional model are explicitely available in the two cases. The conditional model applies to the drop-out process in a selection model and to the response in a pattern mixture specification. The transformation from one probability model to the other is generally not straightforward (Little, 1994) and the choice between one factorization or the other is generally determined by the variable of primary interest and the plan for its analysis.

When the two conditional models $f_{\mathbf{Y}|D}$ and $f_{D|\mathbf{Y}}$ are of direct interest, Molenberghs, Michiels and Kenward (1998) have developed a pseudo-likelihood method for their joint analysis. In this paper, we focus on the specification of marginal models $f_{\mathbf{Y}}$ and f_D for the response and drop-out indicator, respectively. We develop a likelihood method that permits a valid joint inference on these models when drop-outs are not MCAR. To do so, we create a joint distribution for $\mathbf{Y}$ and D in which the dependence between the marginal distributions is modeled using *copulas*.

A copula $C(\cdot)$ is a multivariate distribution on $[0,1]^J$, where J is the variable dimension. Sklar (1959) showed that for any set of random variables $Z_1, ..., Z_J$ with marginal distributions $F_j(z_j)$, the construction

$$F(z_1, ..., z_J) = C[F_1(z_1), ..., F_J(z_J)] \tag{1}$$

generates a J-variate joint distribution for the Z_j. Conversely, any joint distribution $F(z_1, ..., z_J)$ can be expressed as a (copula) function of its marginal distributions. Hence, we propose to use copulas to generate a joint density $f_{\mathbf{Y},D}$ with marginal densities $f_{\mathbf{Y}}$ and f_D. Given $f_{\mathbf{Y},D}$, a likelihood-based analysis is possible to jointly estimate the parameters of the marginal distributions and of the copula which specify the dependence structure.

As a joint distribution is obtained whatever the marginal distributions $F_j(z_j)$ involved in (1), copula models can thus evenly be applied to continuous or to non-continuous responses, or to random variables of mixed types. Oakes (1994) and Shih and Louis (1995) use copulas to model multivariate survival data. Meester and MacKay (1994) gave an application to the modeling of clustered categorical data. Trégouet, Ducimetière, Bocquet, Visvikis, Soubrier and Tiret (1999) presented a copula model for the analysis of familial binary data. In this paper, we consider longitudinal data of either continuous or discrete (ordinal) type and we also use copulas to model the dependence between repeated responses. The techniques proposed by Lambert and Vandenhende (2000) and by Vandenhende and Lambert (2000) are used to model the dependence in continuous and ordinal longitudinal data respectively.

The layout of the paper is as follows. Notations are introduced in Section 2. The joint likelihood for repeated responses and drop-outs is given in Section 3. Copula models for repeated measures are defined in Section 4 and models for the dependence between response and drop-out are proposed in Section 5. In Section 6, we present the copula functions that will be used in the examples and review their dependence properties. Two examples are given in Section 7. A continuous response (heart rate) is modeled in an acute toxicology study and a discrete ordinal response (pain severity score) is considered in a clinical trial on migraine. A discussion of key results is then made in Section 8.

2. Some Notations

We consider longitudinal studies with the same number of measurements T scheduled for all subjects. For simplicity, notations are introduced without subscript for the subject's indicator. Let the random vector $\mathbf{Y}$ be the complete set of T measurements on a subject and let $\mathbf{O}$ be the associated *response indicator*. For a particular realization $(\mathbf{y}, \mathbf{o})$, an element of $\mathbf{o}$ takes the value 1 when the corresponding element of $\mathbf{y}$ is observed and a value 0, when missing. This paper does not consider intermittent but only monotone patterns of missing data (i.e., drop-outs). In this situation, the information contained in the vector $\mathbf{O}$ can be replaced by a random variable D indicating the first time t_d at which no response is available for the subject. We shall set $d = T + 1$ for completers. A series of covariates is recorded together with the data. Parametric models indexed by a vector of parameters β will be considered to relate covariates to the responses and to drop-out hazards. The vector β^T is partitioned as $(\beta_Y^T, \beta_D^T, \theta^T)$ where β_Y and β_D are for the marginal models of the response and drop-out respectively. The dependence model between $\mathbf{Y}$ and D is given by a copula $K(\cdot;\theta)$ with parameter θ. The vector β_Y^T is further partitioned into (α^T, ρ^T) where α is the set of parameters for the marginal models at each time. The dependence model between repeated responses is given by a copula $Q(\cdot;\rho)$ indexed by ρ.

3. Likelihood for a Selection Model

Let us consider the realisations $(\mathbf{y}, \mathbf{o})$ for any subject dropping at the dth measurement time. In a selection model, the contribution to the likelihood $f(y_1, ..., y_{d-1}, d; \beta)$ for this subject can be written as (Diggle and Kenward, 1994)

$$f(y_1, ..., y_{d-1}; \beta_Y) \prod_{j=1}^{d-1} \Pr(O_j = 1 | O_{j-1} = 1, y_1, ..., y_j, \beta)$$
$$\int \Pr(O_d = 0 | O_{d-1} = 1, y_1, ..., y_d; \beta) g(y_d | y_1, ..., y_{d-1}; \beta_Y) dy_d. \quad (2)$$

The first factor in (2) is the joint density of all observed responses $y_1, ..., y_{d-1}$

for the subject; the next factor is the joint probability of being observed up to time t_{d-1} conditional on the historical responses; and the last factor expressed as an integral is the expected (conditional) drop-out hazard at time t_d under the full conditional density $g(y_d|y_1, ..., y_{d-1})$ for the non-observed response Y_d.

For subjects who complete the study, $d = T + 1$ and (2) reduces to

$$f(y_1, ..., y_T; \beta_Y) \prod_{j=1}^{T} \Pr(O_j = 1|O_{j-1} = 1, y_1, ..., y_j; \beta).$$

Under MCAR mechanisms, the drop-out hazard is totally independent of $\mathbf{y}$ and (2) can be rewritten as

$$f(y_1, ..., y_{d-1}; \beta_Y) \prod_{j=1}^{d} \Pr(O_j = o_j|O_{j-1} = 1; \beta_D). \quad (3)$$

The density of the observed responses and the probability model for the drop-out hazard clearly separate in (3). Parameter vectors β_Y and β_D are distinct and a separate estimation of the two models (e.g. using maximum likelihood) produces unbiased estimates.

When the drop-out process is MAR, Equation (2) becomes

$$f(y_1, ..., y_{d-1}; \beta_Y) \prod_{j=1}^{d} \Pr(O_j = o_j|O_{j-1} = 1, y_1, ..., y_{j-1}; \beta_Y, \beta_D, \theta). \quad (4)$$

Little and Rubin (1987) have suggested that, under MAR mechanisms, the drop-out process could be *ignorable* for a likelihood-based analysis of the response model. The ignorability condition requires that the set of parameters for the models $f_{\mathbf{Y}}$ and $f_{D|\mathbf{Y}}$ be distinct (the assumption of separability). In our case, we do not specify a parametric model for $f_{D|\mathbf{Y}}$ directly. Instead, it is a consequence of the chosen marginal models f_D and $f_{\mathbf{Y}}$ and of the copula used to relate them. The complete vector of parameters $(\beta_Y^T, \beta_D^T, \theta^T)$ is involved in the modeling of $f_{D|\mathbf{Y}}$. The assumption of separability between β_Y and (β_D^T, θ^T) is not always verified in our approach so that ignorability does not necessary hold for all dependence models. Consequently, maximum likelihood estimators of β_Y can differ in (3) and (4) even with an identical response models.

4. Dependence between Repeated Responses

We start by specifying a marginal model $F(y_j; \alpha)$ for the distribution of the response variable Y_j at each observation time t_j $(j = 1, ...d)$. For any subject dropping at t_d, the joint distribution of the $d-1$ successive observations is then modeled as in (1) using a copula $Q(\cdot;\rho)$ indexed by a vector of parameters ρ. This yields

$$F(y_1, ..., y_{d-1}; \beta_Y) = Q[F(y_1; \alpha), ..., F(y_{d-1}; \alpha); \rho]. \tag{5}$$

When the response is absolutely continuous, the joint density is obtained by taking the derivative of (5) with respect to $Y_1, ..., Y_{d-1}$. Assuming that $q(\cdot;\rho)$ is the density associated to $Q(\cdot;\rho)$, $Y_1, ..., Y_{d-1}$ have joint density

$$q[F(y_1; \alpha), ..., F(y_{d-1}; \alpha); \rho] \prod_{j=1}^{d-1} f(y_j, \alpha), \tag{6}$$

where $f(y_j; \alpha)$ is the marginal density of Y_j derived from $F(y_j; \alpha)$.

Assume that the response is discrete ordinal. Without loss of generality, we assume that the response is distributed across K consecutive categories $k = 1, ..., K$ at all times. The joint probability mass function $\Pr(Y_1 = y_1, ..., Y_{d-1} = y_{d-1}; \beta_Y)$ is (Joe, 1997, p. 237)

$$\sum_{l_1=y_1-1}^{y_1} \cdots \sum_{l_{d-1}=y_{d-1}-1}^{y_{d-1}} (-1)^{\sum_{j=1}^{d-1}(y_j-l_j)} Q[F(l_1; \alpha), ..., F(l_{d-1}, \alpha); \rho]. \tag{7}$$

For simplicity, (7) will also be termed density and referred as $f(y_1, ..., y_{d-1}; \beta_Y)$ in the remaining.

The conditional density $g(y_d|y_1, ..., y_{d-1}; \beta_Y)$ of the unobserved response Y_d at drop-out does not need to be from the same family as the conditional density obtained from the joint density $f(y_1, ..., y_{d-1}; \beta_Y)$ for the observed responses. The choice of a density $g(\cdot; \beta_Y)$ is merely arbitrary as the adjustment of that model to the non-observed data cannot be verified. As raised by many discussants of Diggle and Kenward (1994), MNAR models rest upon untestable hypotheses and should therefore be interpreted with caution. When MNAR models are considered, sensitivity analyses are recommended to evaluate the robustness of conclusions to changes in the distributional assumptions. Such analyses are however not in the scope of this paper.

In our approach, we assume that the marginal distribution $F(y_d; \alpha)$ is of the same family as distributions at previous times. The conditional distribution $g(\cdot; \beta_Y)$ is then computed in the usual way, as the ratio of a joint density $h(y_1, ..., y_d)$ of the d responses over $f(y_1, ..., y_{d-1})$. The joint density $h(\cdot)$ is constructed in a similar way as $f(\cdot)$, from equations (6) and (7) in the continuous and the ordinal cases respectively.

5. Dependence between Drop-out and Response

We specify a marginal Bernoulli model indexed by a parameter vector β_D for the drop-out status O_j, given that $(O_{j-1} = 1)$ at any time t_j, $j = 2, ..., d$. The joint distribution of $(O_j | O_{j-1} = 1)$ and of the responses $Y_1, ..., Y_j$ up to t_j is modeled using a copula $K(\cdot; \theta)$ with parameter θ. The joint distribution $F(y_1, ..., y_j, o_j | O_{j-1} = 1; \beta)$ is defined as

$$K[F(y_1, ..., y_j; \beta_Y), \Pr(O_j \leq o_j | O_{j-1} = 1; \beta_D); \theta]. \tag{8}$$

The conditional distribution of O_j given the historical responses $y_1, ..., y_j$ is then computed from the derivation of Equation (8) with respect to $F(y_1, ..., y_j; \beta_Y)$:

- with continuous responses, $\Pr(O_j \leq o_j | O_{j-1} = 1, Y_1 = y_1, ..., Y_j = y_j; \beta)$ is (Joe, 1997, p. 245)

$$\left. \frac{\partial K[x, \Pr(O_j \leq o_j | O_{j-1} = 1; \beta_D); \theta]}{\partial x} \right|_{x = F(y_1, ..., y_j; \beta_Y)}. \tag{9}$$

- with discrete ordinal responses (on $k = 1, ..., K$), it is

$$\frac{\sum_{l_1 = y_1 - 1}^{y_1} \cdots \sum_{l_j = y_j - 1}^{y_j} (-1)^{\sum_{m=1}^{j} (y_m - l_m)} K[F(l_1, ..., l_j; \beta_Y), \Pr(O_j \leq o_j | O_{j-1} = 1; \beta_D); \theta]}{f(y_1, ..., y_j; \beta_Y)}, \tag{10}$$

where $f(y_1, ..., y_j; \beta_Y)$ is given in (7).

6. Some Copula Distributions and Dependence Properties

In this section, we review the copula distributions that will be used in the illustrations. Other parametric families of copulas can be found in Joe (1997, ch. 5). As defined in (1), copulas are direct functions of the marginal distributions $F_j(z_j)$. They characterise the type and the strength of dependence between margins. When all the Z_j are mutually independent, the joint distribution is the product of the marginal distributions. A particular copula, called the *product*, is used to characterise independence. It is

$$\Pi(u_1, ..., u_J) = u_1 ... u_J. \tag{11}$$

Another copula is created from the multivariate standard normal distribution $\Phi_J(\cdot; R)$, with correlation matrix R. It is given as

$$C_\Phi(u_1, ..., u_J; R) = \Phi_J[\Phi_1^{-1}(u_1), ..., \Phi_1^{-1}(u_J); R], \tag{12}$$

where $\Phi_1(\cdot)$ is the univariate standard normal distribution.

The dependence between random variables U_j is modeled in (12) using the correlation matrix R. Under independence, R is the identity and $C_\Phi(\cdot; R)$

reduces to $\Pi(\cdot)$. When all marginal distributions $F_j(z_j)$ are normal, (12) generates a multivariate normal distribution for the Z_j. The matrix R is then the correlation matrix for the Z_j. However, when the Z_j are not all normal, R still quantifies dependence but it is not a formal correlation matrix anymore. Standard dependence structures such as exchangeable or autoregressive can be specified using R (Lambert and Vandenhende, 2000). In the heart rate example, the copula $C_\Phi(\cdot; R)$ with R indexed by the parametric vector ρ will be used to model the dependence between the responses.

Another copula considered in the examples is the family of Frank (1979) with one parameter γ. It is equal to

$$-\frac{1}{\gamma}[1 + \frac{\prod_{j=1}^{J}(e^{-\gamma u_j} - 1)}{(e^{-\gamma} - 1)^{J-1}}]. \tag{13}$$

Nelsen (1999) discussed various dependence properties of copulas. Random variables $U_1, ..., U_J$ are termed *positively* dependent when large (or small) values are more likely to occur simultaneously than if they were independent. Then, we have

$$C(u_1, ..., u_J) \geq \Pi(u_1, ..., u_J),\ \forall u_j \in [0, 1].$$

Negative dependence occurs when $C(u_1, ..., u_J) \leq \Pi(u_1, ..., u_J)$, $\forall u_j \in [0, 1]$. In the bivariate case (J=2), both positive and negative associations can be modeled using γ in the copula of Frank. Positive dependence occurs when $\gamma > 0$ and negative dependence occurs when $\gamma < 0$. The case $\gamma = 0$ does not produce a copula distribution but it is a limiting case for independence ($C = \Pi$). When $J > 2$, Equation (13) defines a copula distribution if and only if $\gamma > 0$ (Kimberling, 1974). Therefore, only positive exchangeable dependences can be modeled in this generalisation. A bivariate Frank's family parametrized by the vector θ will be used to model the dependence between drop-out and responses in the two examples. The same family with parameters ρ will be used for the dependence between repeated measures in the migraine example.

The indicator of drop-out O_j has been ordered in such a way that a low value (0) indicates drop-out and a large value (1) indicates observation. Positive dependence in Equation (8) implies that dropout (i.e., a small value for O_j) is more likely to happen with *small* responses. Negative dependence implies the opposite, i.e. that subjects tend to drop with large responses. This parameterization requires some care in the interpretation of the dependence parameters θ in the illustrations.

Copula parameters ρ and θ quantify the dependence between marginal distributions. When all random variables are continuous, these parameters are directly related to rank-based dependence measures such as Kendall's tau or Spearman's rho. This relationship is presented and discussed in Nelsen (1999, ch. 5). With non-continuous random variables, copula parameters do not characterize rank-based dependence measures anymore. The relationship between Kendall's tau-b coefficient, adjusted for ties and the copula-based distributions has been studied by Vandenhende and Lambert (2000) for discrete ordinal variables. Considering ordered copulas, they observe a monotonic relationship between the copula parameter and tau-b for a range of marginal distributions. This monotonicity supports the interpretation of copula parameters as dependence measures, though an exact quantification of tau-b would also require information from the marginal models.

7. Illustrations

A continuous response (heart rate) is modeled in the first example and a discrete ordinal variable (pain severity score) is analysed in the second example.

7.1 *Heart rate in Toxicology Study*

An acute toxicology study was performed in male rats. Five dose levels of an investigational drug (0, 3, 10, 30 and 100 mg/kg) were randomly administered to groups of 6 animals each. Heart rate (HR) was recorded in beats per minute at baseline and at the following times post-dosing: 30, 60, 120 and 240 minutes. Results are summarised in Table 1. Mean baseline HR were comparable between groups. Treatment tends to decrease mean HR but the effect is not dose-related. A few animals died during the study, predominantly at the high dose. The two animals dying within 30 minutes had baseline HR slightly above the average. Thereafter, HR recorded in animals prior to death were below or close to the group's geometric mean at time of measurement. This suggests that a time-varying dependence between drop-out and HR is possible. The following models were fitted to the data. All computation, including the maximisation of the likelihood and the estimation of standard errors from the observed information matrix were performed using the *Mathematica*^{TM} package.

A marginal log-normal distribution was taken for HR and a log-linear regression on $\log(t_j)$ was fitted to each group separately. Due to the similarity of mean baseline values between groups, a single intercept was estimated across groups. The model was parametrized as $E[\log(Y_j)] = \alpha + \alpha_{group} \log(t_j)$, where α is the intercept and α_{group} are dose-specific slopes. The dependence between repeated responses was modeled using the copula defined in (12) for $Q(\cdot; \rho)$, with ρ indexing the correlation matrix R. A first-order autoregressive dependence structure was chosen so that the $(j, l)^{th}$ element of R was equal to $\rho^{|j-l|}$ $(0 \leq \rho \leq 1)$. The drop-out hazard was assumed constant over time and

Table 1

Summary statistics on heart rate (beats/min) in male rats after intake of an investigational drug at dose levels of 0, 3, 10, 30 and 100 mg/kg. Six animals were randomised to each group but some animals died during the study. Heart rates taken before animals' death are in parentheses.

Dose	(mg/kg)	Time (min) after dosing				
		0	30	60	120	240
0	N	6	6	6	6	6
	G. Mean	461	495	481	524	513
	CV(%)	11	12	8	7	4
3	N	6	6	6	6 (330)	5
	G. Mean	458	374	355	335	331
	CV(%)	11	9	4	4	7
10	N	6	6	6 (370)	5	5
	G. Mean	454	369	361	352	338
	CV(%)	6	7	6	4	1
30	N	6	6 (330)	5	5	5
	G. Mean	479	373	382	382	356
	CV(%)	8	10	5	2	4
100	N	6 (490,500)	4 (390,380)	2	2	2
	G. Mean	457	397	440	395	380
	CV(%)	8	7	6	2	0

modeled using a logistic regression. The logit of $p_j = \Pr(O_j = 0|O_{j-1} = 1)$ was linearly regressed on the administered dose as

$$\text{logit}(p_j) = \beta_{Dint} + \beta_{Ddose}\text{dose}.$$

Two models for the dependence between drop-out probability and response were developed. A MCAR process was modeled using the product copula in (11). A MAR process was modeled assuming that drop-out probability was conditionally independent of the historical data, given the last prior observation. A bivariate Frank's copula as in (13) was used for $K(\cdot;\theta_j)$ to relate $\Pr(O_j \leq o_j|O_{j-1} = 1)$ and $F(y_{j-1})$. The copula parameter θ_j was allowed to vary across times as $\theta_j = \theta^0 + \theta^1 \log(t_{j-1})$. The baseline time ($t_1$) was taken as 1 minute instead of zero for identifiability of the above model. This yields a dependence equal to θ^0 between response and drop-out when occuring prior to 30 min (j=2) and, then a monotonic change in the dependence over time.

The maximum likelihood estimate (MLE) $\widehat{\theta^0}$ of the MAR model (-2 log lik=-310.1; 12 parameters) is equal to -6.37 (s.e.=5.13). A reduced MAR model with θ^0 fixed to zero was also fitted. This model implies independence between drop-out and responses for deaths prior to 30 min. Parameter estimates from the MCAR and the reduced MAR models are presented in Table 2. The reduced MAR model (-2 loglik=-306.6; 11 parameters) is selected as it performs slightly better than the initial MAR and than the MCAR (-2log lik=-302.2; 10 parameters) models. Estimates and standard errors of parameters common to the three models are comparable (result not shown for the initial MAR model). Compared to placebo, the drug decreases HR but a reversed trend is observed with dose. The decrease is more important at low than at high doses. The drop-out hazard (death rate) increases significantly with dose. Predicted probabilities of death are 2.3, 2.5, 3.0, 5.3 and 29.8 % in the 0, 3, 10, 30 and 100 mg/kg groups respectively. A significant positive estimate of θ^1 is found in the reduced MAR model. As discussed previously, this indicates a negative dependence between HR and death after 30 minutes post-dosing. From that point, animals with a low HR are more likely to die than those with a high rate and the trend inflates with time.

As illustrated in this example, our modeling strategy allows for marginal analyses of the repeated response and drop-out rates, while controlling for their dependence. The selected MAR model does not permit separability between parameter sets $\{\alpha, \alpha_{dose}, \sigma^2, \rho\}$ and $\{\beta_{Dint}, \beta_{Ddose}, \theta^1\}$. Therefore, different MLEs and standard errors for $\{\alpha, \alpha_{dose}, \sigma^2, \rho\}$ are obtained in the MCAR and MAR columns of Table 2. The difference is reasonably small and does not alter conclusions. Parameter sets are also moderately correlated

Table 2

Maximum likelihood estimates (s.e.) for the joint repeated-measures and survival analyses of the heart rate data.

Parameter	MCAR Model (-2 loglik=-302.2)	MAR Model (-2 loglik=-306.7)
Marginal model on heart rate		
α	6.14 (0.013)	6.14 (0.013)
α_0	0.0194 (0.0047)	0.0197 (0.0047)
α_3	-0.0629 (0.0048)	-0.0616 (0.0047)
α_{10}	-0.0588 (0.0049)	-0.0575 (0.0049)
α_{30}	-0.0522 (0.0052)	-0.0524 (0.0052)
α_{100}	-0.0341 (0.0066)	-0.0353 (0.0062)
σ^2	0.0049 (0.0007)	0.0049 (0.0007)
Dependence between successive heart rates		
ρ	0.442 (0.091)	0.450 (0.091)
Marginal model of drop-out hazard		
β_{Dint}	-3.75 (0.68)	-3.76 (0.68)
β_{Ddose}	0.0283 (0.010)	0.0290 (0.009)
Dependence between drop-out and heart rate		
θ^1	-	1.01 (0.56)

(result not shown) in this example. A maximum correlation of 0.30 is found between α_{100} and β_{Ddose}.

A drop-out probability model which is conditional on the response is also readily available from Equation (9). Such models are useful for the interpretation of the drop-out process, in relation to the response variable. Some conditional drop-out profiles (from the reduced MAR model) are presented for the 100 mg/kg group in Figure 1. At 30 min, the drop-out probability (29.8%) is identical whatever the response. This is the marginal estimate. Thereafter, the drop-out probability increases with decreasing HR. Our model assumes a monotonic change of the dependence parameter θ_j over time. However, when considering a particular HR level (e.g., 375 beats/min), we do not observe a monotonic change in conditional probabilities anymore; the drop-out probability peaks at 1h and decreases thereafter. The marginal distribution of HR is also changing over time (decreased mean, constant CV). A HR as low as 375 beats/min is rather atypical in the 100mg/kg group at 1h post-dose but this value is closer to the predicted mean at subsequent times. This explains the reversed trend in conditional drop-out probability after 1h at that level.

7.2 *Clinical Trial on Migraine*

The second example is a clinical trial on acute migraine. Thirty nine patients with a moderate to severe migraine were randomised into 3 treatment groups (0, 5 or 20 mg of LY334370 i.v.). Pain severity (PS) was measured on a four-grade scale (no, mild, moderate, severe) at 8 occasions after dosing: 0.5, 1, 1.5, 2, 3, 4, 6 and 24h. Subjects were allowed to take a rescue medication from 2 hours post-dose but, thereafter, PS was not collected anymore. The cumulative incidence of PS and drop-outs is displayed in the upper panel of Figure 2. There is a progression towards lower severity with time and the PS decrease is more important in the two treated groups than under placebo. The rate of drop-outs is also larger when not treated. A copula-based analysis of these PS data ignoring drop-outs has been given by Vandenhende and Lambert (2000). We shall use their final model for the response and add modeling components for the drop-out hazard and the dependence between drop-out and PS.

Pain severity is an ordinal response with four possible values ($K = 4$). No pain is coded as $k = 1$, mild pain as 2, moderate as 3 and severe as 4. A cumulative regression model with complementary log-log link was selected. The model included 3 threshold parameters α_k for the levels $k = 1, 2, 3$, two parameters α_{5-0} and α_{20-0} for the contrasts between the treated groups (5 and 20 mg respectively) and placebo and a log-time effect α_{time}. The dependence between successive responses was modeled based on a bivariate Frank's copula, with parameter ρ and the joint distribution of responses was constructed

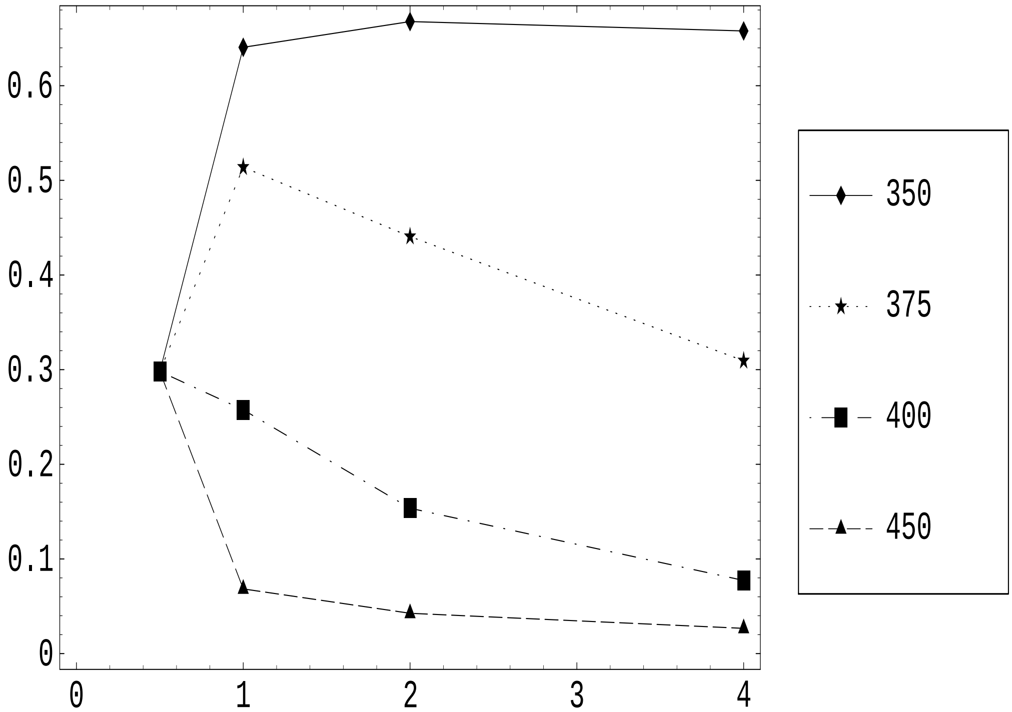

Figure 1. Predicted conditional drop-out hazard profiles (v.s. time in hours) in the 100 mg/kg group from the MAR model of Table (2). The marginal hazard (29.8 %) is plotted at 0.5h, when drop-out is assumed independent of heart rate. Lines are drawn over time for constant heart rates of 350, 375, 400 and 450 beats/min.

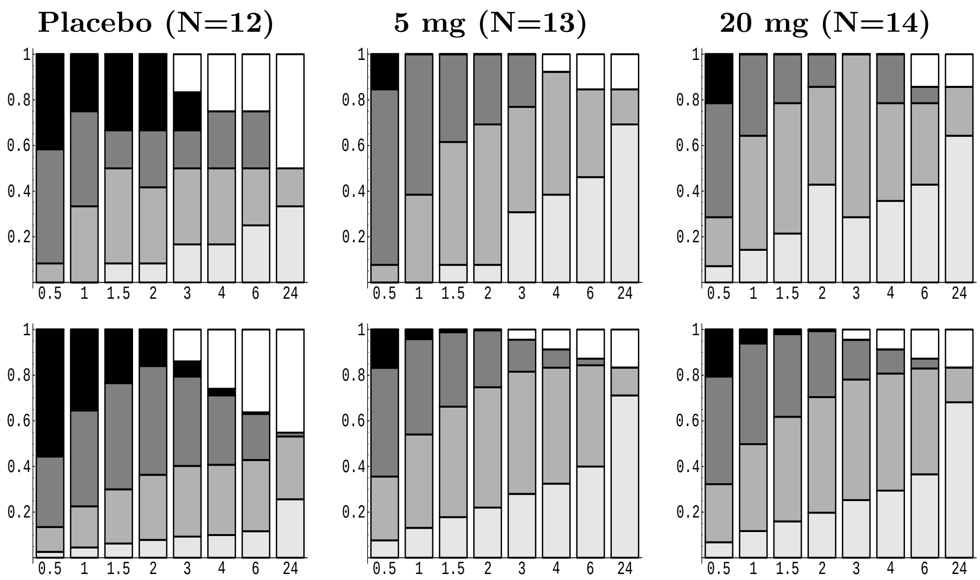

Figure 2. Empirical (upper panel) and predicted (lower panel) cumulative distributions of pain severity: no (10% gray), mild (30% gray), moderate (50% gray), severe (black) and drop-out (white) over time in the three treatment groups. Predictions are obtained from estimates of the MAR model in Table 3.

Table 3

Maximum likelihood estimates (s.e.) for the joint repeated-measures and survival analyses of the migraine data.

Parameter	MCAR model (-2 loglik=443.6)	MAR model (-2 loglik=427.1)	MNAR model (-2 loglik=429.9)
Marginal model on pain severity score			
α_1	-3.13 (0.40)	-3.08 (0.40)	-3.09 (0.40)
α_2	-1.44 (0.29)	-1.37 (0.29)	-1.46 (0.29)
α_3	-0.0066 (0.23)	0.036 (0.23)	-0.07 (0.24)
α_{time}	0.81 (0.10)	0.82 (0.10)	0.75 (0.09)
α_{5-0}	1.19 (0.31)	1.11 (0.31)	1.22 (0.31)
α_{20-0}	1.10 (0.32)	0.99 (0.32)	1.05 (0.33)
Dependence between successive scores			
ρ	13.9 (2.14)	13.8 (2.12)	14.5 (2.22)
Marginal model for the probability of rescue medication (RM) intake			
β_0	-1.74 (0.44)	-1.82 (0.48)	-1.79 (0.52)
$\beta_{5,20}$	-3.19 (0.51)	-3.07 (0.52)	-3.16 (0.53)
Dependence between RM intake and pain			
θ	-	-6.88 (2.76)	-11.9 (8.96)

assuming a first order Markov process. An autoregressive dependence structure for the response is considered with dependence decreasing with lag time. Drop-out hazard was modeled using a time-independent logistic regression including a different parameter for placebo (β_0) and for active therapy ($\beta_{5,20}$). Dependence models for MCAR, MAR and MNAR drop-out processes were considered. The MAR and MNAR models were created from the bivariate Frank's copula with parameter θ under a conditional independence hypothesis. The MAR model relates $\Pr(O_j \leq o_j | O_{j-1} = 1)$ to $F(y_{j-1})$ as in the previous example. The MNAR model relates it to $F(y_j)$, the distribution of the possibly unobserved response at t_j. All marginal distributions of the response $F(\cdot)$ are multinomial and the distribution at drop-out is extrapolated from the distributions of previously observed data using the same Markov model based on Frank's copula as above. Parameters were jointly estimated using maximum likelihood. Results are in Table 3.

MLEs and standard errors of parameters common to the three models are comparable. Compared to placebo, LY334370 reduces PS and the effect is comparable between doses. A strong positive dependence is found between successive responses (Kendall's tau-b ≈ 0.75). The drop-out rate is larger under placebo (14%) than under active therapy (4%). These estimates are from the MAR model (-2 loglik=427.1; 10 parameters), which performs better than the MCAR (-2 loglik=443.6; 9 parameters) and the MNAR (-2 loglik=429.9; 10 parameters) models. A positive dependence between drop-out and response is detected (Kendall's tau-b $\approx 50\%$), implying than patients are more likely to take a rescue medication when their PS is large. The predicted cumulative distributions of PS and drop-out are in the lower panel of Figure 2. Predicted and empirical (see the upper panel) distributions are comparable. This provides evidence for the good adjustment of the MAR model to the data.

8. Discussion

Our interest was in the specification of marginal models for repeated responses and drop-out events in longitudinal studies with non-random attrition. The dependence between successive responses and between drop-out and response was modeled using copulas and a full likelihood-based method was proposed.

A series of parametric copula families is available; see Joe (1997, ch. 5). The selection of a candidate is either made by convenience (e.g. when choosing the multivariate normal copula) or based on the comparison of the adjustment of different models using likelihood ratios (see e.g. Vandenhende and Lambert, 2000). Genest and Rivest (1993) have developed a goodness of fit test and a graphical method to select copula models by examining the empirical dependence found in the data. Their method applies to a subfamily of bivariate copulas named *Archimedian*. Extensions to other families and to the multivariate case would be worth considering.

The issue of sensitivity is often raised when dealing with non-random drop-outs. As illustrated by Kenward (1998), several selection models with a comparable adjustment can yield very different conclusions. This is related to the untestable distributional assumption for the unobserved responses at time of drop-out. In the HR example, we decided not to further investigate MNAR models for this reason. Here, drop-out is synonymous of death and model predictions (obtained from data collected in a living state) were in no case satisfactory to meet the physiological inactivation of the heart at death. The situation in the PS example was somewhat different in the sense that PS was still evaluable (and predictable from previous responses) around the intake of a rescue medication. As noted by Kenward (1998), *"the MNAR analysis tells us about inadequacies of the original model rather than the adequacy of the MNAR model"*. In our example, the MAR model was not nested within the MNAR model but the adjustment of the latter was not better than that of the former model.

Our copula models relate the drop-out process to the (marginal) *distribution* of response before (MAR) or at (MNAR) time of drop-out. This contrasts with standard specifications of selection models, in which the drop-out hazard is modeled in relation to the *actual level* of the response (using e.g. logistic regressions). When the distribution of response is evolving over time, the two specifications provide distinct natural interpretations for the conditional drop-out process. Let us illustrate that point in the migraine trial example. During a classical migraine crisis, pain severity tends to decrease over time and usually terminates within 48 hours. It is also natural to assume that the probability of drop-out (RM intake) increases with pain intensity. However, the risk of drop-out for a patient with a mild pain severity will probably be larger at 24 hour than at 2 hour post-dosing. This is because mild pain is not considered as unacceptable (abnormal value) at 2 hours, whereas it is rather atypical and more worrying when still present 24-hour after the crisis onset. The time by response interaction will need to be taken into account and properly modeled in classical conditional survival models. In our approach, no such modeling is needed. The conditional drop-out probability model is automatically adjusted for the distribution of responses at the time of drop-out. This behavior is further illustrated in Figure 1 for the heart rate example.

Résumé

Cet article présente une classe de modèles paramétriques pour données longitudinales avec arrêts prématurés non aléatoires. Des modèles marginaux de régression sont ajustés aux réponses successives et au risque d'arrêt, prenant en compte l'effet des covariables et du temps. La dépendence entre réponses successives et entre l'arrêt et la réponse est aussi modélisée en utilisant des fonctions de dépendence appelées copules. Les copules sont utilisées pour créer un distribution jointe en combinant les distributions marginales. Dans notre cas, ceci donne une forme paramétrique à la distribution conjointe des réponses et des arrêts prématurés. Les paramètres des deux modèles marginaux et des deux modèles de dépendence sont conjointement estimés par maximum de vraissemblance. La méthode s'applique aussi bien à des données continues ou non continues. Une illustration est fournie pour chacun des cas. Une réponse log-normale (la pulsation cardiaque) est analysée dans une étude de toxicologie et une variable discrète ordinale (la sévérité de la douleur) est étudiée dans une étude sur la migraine. Trois familles de copules sont utilisées: le produit d'indépendance, la copule de Frank

et une copule générée sur base de la distribution multivariée normale standardisée. L'utilisation des copules permet une modélisation flexible et consistante de la structure de dépendence pour des mesures répétées continues ou pas. De plus, elle permet de tirer des conclusions valides d'une analyse conjointe par maximum de vraissemblance des deux modèles marginaux sur la réponse et l'arrêt lorsque les arrêts prématurés ne sont pas totalement independants des réponses. Dans les deux exemples, une importante dépendence de type autoregressif fût trouvée dans les données. La probabilités d'arrêt est modérément dependante de la réponse précédente. Les valeurs estimées des paramètres des modèles marginaux ne sont pas sensibles au choix d'un modèle de dépendence entre l'arrêt et la réponse.

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