Biometrical Journal **47** (2005) 6, 1–9 DOI: 10.1002/bimj.200410170

A Semi-Markov Model Based on Generalized Weibull Distribution with an Illustration for HIV Disease

Yohann Foucher[*,1], **Eve Mathieu**[1], **Philippe Saint-Pierre**[1], **Jean-François Durand**[2], and **Jean-Pierre Daurès**[1]

[1] Institut Universitaire de Recherche Clinique, Laboratoire de Biostatistique – 641, avenue du Doyen Gaston Giraud – 34093 Montpellier, France

[2] Département des maladies infectieuses, CHU de Nice – Route Saint Antoine de Ginèstiere – 06202 Nice, France

Received 19 November 2004, revised 29 March 2005, accepted 25 July 2005

Summary

Multi-state stochastic models are useful tools for studying complex dynamics such as chronic diseases. Semi-Markov models explicitly define distributions of waiting times, giving an extension of continuous time and homogeneous Markov models based implicitly on exponential distributions. This paper develops a parametric model adapted to complex medical processes. (i) We introduced a hazard function of waiting times with a *U* or inverse *U* shape. (ii) These distributions were specifically selected for each transition. (iii) The vector of covariates was also selected for each transition. We applied this method to the evolution of HIV infected patients. We used a sample of 1244 patients followed up at the hospital in Nice, France.

Key words: Multi-state model; Semi-Markov process; Generalized Weibull distribution; Hazard function; HIV; longitudinal analysis.

1 Introduction

Markov models are widely used in medicine, particularly in the study of chronic diseases, extending classical survival models (Cox, 1972) to the analysis of multi-state processes. Indeed, the progression of a disease cannot be summarized by two inevitablestates. In cancerology (e.g. Kay, 1986), the dynamic can be defined through various states as life without disease, appearance of symptoms, metastasis and eventually death. This type of method has also been applied recently with success for HIV (Human Immunodeficiency Virus) by Alioum et al. (1998), Mauskopf (2000) or Jackson et al. (2003). Likewise for asthma, we can cite Boudemaghe and Daures (2000), Combescure et al. (2003) or Saint-Pierre et al. (2003).

However, in many of these applications, Markov chains are assumed to be homogeneous when the evolution of the process is independent from the time spent in the state (memoryless). In our clinical problem, this constraint is far too restrictive. Semi-Markov processes can be considered as an extension of ordinary Markov processes with discrete states and continuous time, because waiting time distributions are explicit.

This paper develops a semi-Markov model adapted to medical problematics. Its main originality consists in the introduction of a generalized Weibull distribution as defined by Mudholkar et al. (1996) or by Bagdonavicius and Nikulin (2002), offering a more global parametric method than those

[*] Corresponding author: e-mail: Yohann.Foucher@iurc.montp.inserm.fr, Phone: +33467415921, Fax: +33467542731

frequently used as Perez-Ocon and Ruiz-Castro (1999) or Satten and Sternberg (1999). Indeed, it gives a U or inverse U shape of the hazard function. We also defined a transition-specific strategy for modeling, in which distributions of waiting times and vectors of covariates can change between transitions. This model is parsimonious.

Section 2 develops the method by defining the semi-Markov process, the possible parametric distributions, and incorporates covariates and a maximum likelihood estimation. Section 3 applies the method to the follow-up study of people infected with HIV. Section 4 concludes the paper.

2 Modeling Semi-Markov Processes

2.1 The transition-specific semi-Markov model

Let $E = \{1, 2, \ldots, r\}$ a finite state space. Consider the random processes $(T, X) = \{(T_n, X_n) : n \geq 0\}$, in which $0 = T_0 < T_1 < \ldots < T_n$ are the consecutive times of entrance to the states $X_0, X_1, \ldots, X_n \in E$, with $X_{p+1} \neq X_p$, $\forall p \geq 0$ and X_p not persistent. n represents the number of transitions. The sequences $X = \{X_n,\, n \geq 0\}$ form an embedded homogeneous Markov chain. The probabilities of jumping from i to j, associated with this chain, can be written as:

$$P_{ij} = P(X_{n+1} = j \,|\, X_n = i)\,. \tag{1}$$

If state i is not persistent, then $P_{ij} \geq 0$ for $i \neq j$ and $P_{ij} = 0$ for $i = j$. Otherwise, if state i is persistent, then $P_{ij} = 0$ for $i \neq j$ and $P_{ij} = 1$ for $i = j$. In the following developments, we will suppose that state i is transient. As we can see, the Markov chain does not deal with the duration of states. The waiting times are defined explicitly. These processes (T, X) are called semi-Markovian, if the distribution of waiting times $(T_{n+1} - T_n)$ satisfies:

$$P(T_{n+1} - T_n \leq x,\, X_{n+1} = j \,|\, X_0,\, T_0,\, X_1, \ldots, X_n,\, T_n) = P(T_{n+1} - T_n \leq x,\, X_{n+1} = j \,|\, X_n)\,.$$

The density probability function, of the waiting time in state i before passing to state j, is given by:

$$f_{ij}(x, \theta_{ij}) = \lim_{h \to 0^+} \frac{P(x < T_{n+1} - T_n < x + h \,|\, X_{n+1} = j,\, X_n = i)}{h} \tag{2}$$

in which θ_{ij} is the parameter vector of the density probability function $f_{ij}(\,)$. The distribution and the value of parameters can vary between transitions. This method is more parsimonious, than the one in which only parameters can fluctuate (e.g. Perez-Ocon and Ruiz-Castro, 1999). To simplify notations, we will write $f_{ij}(x)$ in the place of $f_{ij}(x,\, \theta_{ij})$. As usual in survival analysis, we deduce from $f_{ij}(x)$ the distribution function, the corresponding survival function and hazard function, respectively $F_{ij}(x)$, $S_{ij}(x)$ and $\lambda_{ij}(x)$:

$$\lambda_{ij}(x) = \lim_{h \to 0^+} \frac{P(x < T_{n+1} - T_n < x + h \,|\, T_{n+1} - T_n \geq x,\, X_{n+1} = j,\, X_n = i)}{h}\,. \tag{3}$$

The marginal density probability function is deduced from the Eqs. (1) and (3):

$$f_{i.}(x) = \sum_{j \neq i} P_{ij} f_{ij}(x)\,. \tag{4}$$

By definition, the hazard function of the semi-Markovian process corresponds to the probability of jumping towards state j, given that the process occupies state i for a duration x:

$$\begin{aligned} \alpha_{ij}(x) &= \lim_{h \to 0} \frac{P[x \leq T_{n+1} - T_n < x + h,\, X_{n+1} = j \,|\, T_{n+1} - T_n \geq x,\, X_n = i]}{h} \\ &= \frac{P_{ij} f_{ij}(x)}{S_{i.}(x)} \quad \text{with} \quad \begin{cases} i \neq j \\ i, j \in E \\ \alpha_{ii}(x) = -\sum\limits_{j \neq i} \alpha_{ij}(x) \end{cases} \end{aligned} \tag{5}$$

2.2 Distribution of waiting times

We based our strategy for modeling on three different distributions. By increasing complexity:

- *Exponential distribution* $E(\sigma_{ij})$ – The hazard function is constant, without memory. In this particular case, we found a homogeneous Markov model. The hazard function of the waiting time is given by $\lambda_{ij}(x) = \dfrac{1}{\sigma_{ij}}\ \forall x \geq 0,\ \forall \sigma_{ij} > 0.$
- *Weibull distribution* $W(\sigma_{ij}, \nu_{ij})$ – The hazard function is defined as $\lambda_{ij}(x) = \nu_{ij} \left(\dfrac{1}{\sigma_{ij}}\right)^{\nu_{ij}} x^{\nu_{ij}-1}\ \forall x \geq 0,$ $\forall \nu_{ij} > 0$ et $\forall \sigma_{ij} > 0$. For ν_{ij} equal to 1, we find the formulation of the exponential distribution.
- *Generalized Weibull distribution* WG $(\sigma_{ij}, \nu_{ij}, \theta_{ij})$ – We chose a hazard function, able to fit a U or inverse U shape: $\lambda_{ij}(x) = \dfrac{1}{\theta_{ij}} \left(1 + \left(\dfrac{x}{\sigma_{ij}}\right)^{\nu_{ij}}\right)^{\frac{1}{\theta_{ij}}-1} \dfrac{\nu_{ij}}{\sigma_{ij}} \left(\dfrac{x}{\sigma_{ij}}\right)^{\nu_{ij}-1}\ \forall x \geq 0,\ \forall \nu_{ij} > 0,\ \forall \sigma_{ij} > 0$ and $\theta_{ij} > 0$. If we fix θ_{ij} at 1, we found exactly the same Weibull formulation. Therefore, this method generalizes the Semi-Markov model based on Weibull distribution.

These distributions have the advantage of being nested. Thus, the Likelihood Ratio Statistic (LRS) can be used to evaluate the relevance of a larger number of parameters.

2.3 Incorporation of covariates

To take covariates into account in the model, we used the assumption of risk proportionality. The additional assumption was that covariates act on the waiting time distributions. Indirectly, from (5), their effects are reflected on the hazard functions of the semi-Markov process. Let $z_{ij} = (z_{ij}^1, z_{ij}^2, \ldots, z_{ij}^{n_{ij}})$, the vector of n_{ij} covariates, specific to the transition $i \to j$. This transition-specific method allows certain factors to influence certain transitions, but not all of them. Therefore, the number of parameters to estimate (e.g. sex on the transition $1 \to 2$) decreases, and the total number of different factors (e.g. sex, age, etc.) increases. The hazard function with covariates is defined by:

$$\lambda_{ij}(x, z_{ij}) = \lambda_{0,ij}(x)\ \eta(z_{ij})$$

in which $\eta(z_{ij})$ is any function of covariates and $\lambda_{0,ij}(x)$ is the baseline hazard function of the transition $i \to j$. Parallel to the treatment of Markov processes by Andersen et al. (1991), the model is semiproportional, in that the proportionality of hazards is assumed within each $i \to j$ transition but does not hold between. To obtain a strictly positive hazard function, we chose:

$$\eta(z) = \exp\left(\beta_{ij}^T z_{ij}\right) \tag{6}$$

in which $\beta_{ij} = (\beta_{ij}^1, \beta_{ij}^2, \ldots, \beta_{ij}^{n_{ij}})$ is the vector of n_{ij} regression parameters associated with z_{ij}. An interpretation as relative risk (RR) can be made from the hazard function of waiting times. Conditioning on the future state is thus necessary from (3). The impact of covariates on the semi-Markovian hazard function is more complex and only interpretable graphically.

2.4 Parameter estimations and likelihood methods

Suppose a sample is constituted by n subjects, denoted by h $(h = 1, 2, \ldots, n)$. The h-th subject moves $m_h - 1$ times into different states at times $T_{h,1} < T_{h,2} < \ldots < T_{h,m_h-1}$. At these times, he occupies the state $X_1^h, X_2^h, \ldots, X_{m_h-1}^h$, with $X_p^h \neq X_{p+1}^h\ \forall p \geq 0$. At the last time of the follow-up, T_{h,m_h}, the h-th individual can move again, or be censored. The Likelihood can therefore be written as the product of all of these contributions:

$$L = \prod_h \prod_{r=1}^{m_h} \left\{P_{X_{r-1}^h, X_r^h} f_{X_{r-1}^h, X_r^h}(T_{h,r} - T_{h,r-1},\ z_{X_{r-1}^h, X_r^h})\right\}^{\delta_{h,r}} \left\{S_{X_{r-1}^h .}(T_{h,r} - T_{h,r-1},\ z_{X_{r-1}^h, X_r^h})\right\}^{1-\delta_{h,r}}$$

in which $\delta_{h,r}$ is equal to 1 if the transition r is observed for the individual h, and 0 if censored.

Our purpose was to find the best model, based only on interesting parameters. With this objective, we used the LRS as follows:

$$\text{LRS} = -2(\ln(L_0) - \ln(L_1)) \rightsquigarrow \chi^2_{p\ ddl}$$

in which L_1 represents the Likelihood of the model based on $k+p$ parameters and L_0 the Likelihood of the model based on k parameters.

2.5 Modeling strategy

Stratified modeling – One model for each modality of covariates was calculated. We could then identify, by looking at the distance between hazard functions, whether a covariate seemed to affect a transition and whether the assumption of risk proportionality was respected.

Univariate modeling – After this first stage, we calculated one model for each previously selected covariate. We still supposed generalized Weibull distributions. Models were said to be univariate, because only one factor was taken into account,even if it could influence a few transitions. At this stage, we could test the significance of regression parameters ($p \geq 0.05$). This model selection is rather strict but necessary. Indeed, because the effect of the factors is specific to each transition and the number of covariables is thus large, this restriction is essential. This constraint is all the more significant as the number of covariables in such a semi-Markovian model must remain acceptable.

Multivariate modeling – All the previously selected covariates were included in the model. The vector of covariates were transition-specific. By a descending procedure, each coefficient with a p-value >0.05 was removed from the model.

Final modeling – This last step consisted of evaluating whether all transitions corresponded to generalized Weibull distributions. So we tested, still using LRS, whether parameters θ_{ij} were equal to 1 and then, whether parameters ν_{ij} were equal to 1. This was the final transition-specific model. Mathematical computing was carried out using *R* software version 1.9.1. We used the quasi-Newtonian algorithm to maximize Likelihood and calculate the Hessian matrix.

3 Application to HIV Data

3.1 Data and model descriptions

In this section, we applied semi-Markov modeling to data from a prospective study of HIV disease. The present application is interesting because the HIV disease progression is complex, without a con-

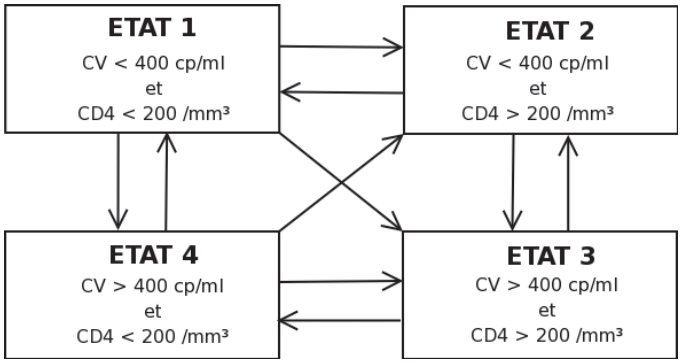

Figure 1 Four-state semi-Markov model.

Table 1 Frequency of the transitions observed.

Transition	Effective	Percentage	Median[1]
$1 \rightarrow$ *censoring*	31	0.6%	0.44
$1 \rightarrow 2$	282	5.9%	0.34
$1 \rightarrow 3$	58	1.2%	0.39
$1 \rightarrow 4$	174	3.6%	0.34
$2 \rightarrow 1$	152	3.2%	0.29
$2 \rightarrow$ *censoring*	605	12.6%	0.48
$2 \rightarrow 3$	994	20.7%	0.51
$3 \rightarrow 2$	1340	27.9%	0.48
$3 \rightarrow$ *censoring*	231	4.8%	0.73
$3 \rightarrow 4$	212	4.4%	0.41
$4 \rightarrow 1$	283	5.9%	0.42
$4 \rightarrow 2$	109	2.3%	0.36
$4 \rightarrow 3$	268	5.6%	0.30
$4 \rightarrow$ *censoring*	65	1.4%	1.56

[1] Median of waiting times (in years).

stant hazard function (Joly and Commenges, 1999). The database is constituted of HIV infected patients, followed up in the Hospital of Nice, France (NADIS database). We limited the sample to observations collected since 1996 and to individuals over 18 years old. The break point was fixed at April 30-th 2004. The chronological time of follow-up was calculated from the first biological analysis. Our sample was therefore constituted of 1244 persons, representing a total of 4804 observations. Men represent about 60% of individuals and 32% of transitions concerns patients over 40 years old. The means of contamination is equally distributed according to homosexuality, heterosexuality, drug addiction and accident.

Two markers are important in qualifying gravity level of disease: viral load (VL) and concentration of CD4 lymphocytes (CD4). CV represents the activity of virus, while CD4 identifies the immunological capability. Clinicians define four states of the disease and ten transitions from these two markers. We thus considered the process characterized by Figure 1. Table 1 describes the frequencies of transitions. States 2 and 3 seem to be the more transitive states, regarding the number of observed transitions. On average, a patient is seen every 2.5 months, the median is 2.3 months. Figure 2 shows this distribution of visits. However, a patient changes state every 10.6 months, the median is 5.9 months. Thus, certain visits correspond to a transition, but not all. Indeed, some medical appointments are only controls, which are planned in advance. During these controls, there are few chances to observe a transition. On the other hand, for unplanned consultations, when the state of the patient is deteriorates for example, it is logical to think that a transition is probably observed. By this method of follow-up, the clinicians suppose they can identify the transitions quite easily.

The purpose is to analyze the progression of HIV disease using this four-state semi-Markov model, according to the eight following factors: gender (women = 1; men = 0), age (1 = over 40 years old; 0 = otherwise), hepatitis B coinfection (1 = yes; 0 = no), hepatitis C coinfection (1 = yes; 0 = no) and the means of contamination which could be heterosexual (1 = yes; 0 = no), homosexual (1 = yes; 0 = no), by drug addiction (1 = yes; 0 = no), or by some other accidental way (1 = yes; 0 = no).

3.2 Results

According to stratified and univariate strategies, 11 factors out of 80 possible (8 covariates $\times$ 10 transitions), were selected. Finally, the multivariate model uses the 9 regression parameters given in

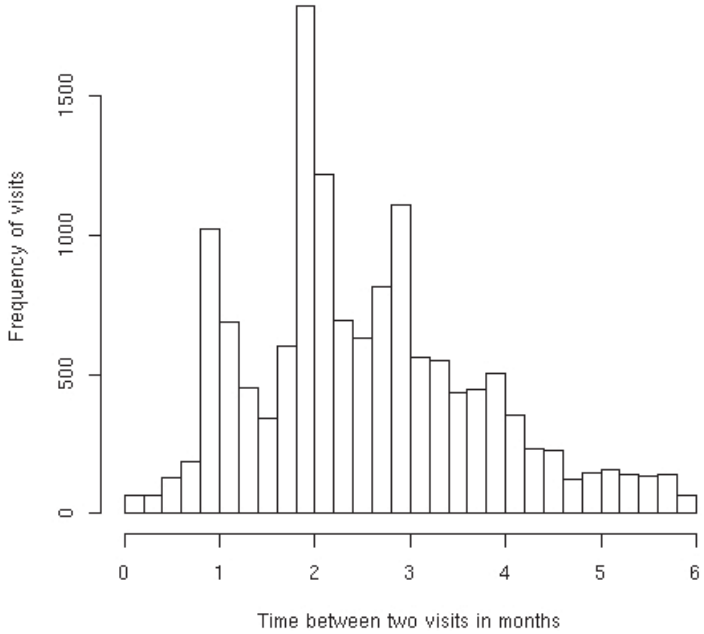

Figure 2 Distribution of time between two consecutive visits.

Table 2. We obtain a maximized Likelihood of -5704, corresponding to an AIC[1] at 11498. Women tend to move quickly from state 1 to state 3. More precisely, they are 1.7 times more likely to leave state 1 than men, given that they move to state 3. However, this information concerns only the distribution of waiting times and must be introduced in the hazard function of the semi-Markov process to establish the effect of a covariate. Likewise, being over 40, being coinfected with hepatitis C or contaminated by drug addiction, seem to accelerate the transition $2 \rightarrow 1$. Conversely, patients infected by homosexual relation, are 1.7 times likelier to leave state 2, given that state 1 follows. Lastly, an accidental means of contamination, heterosexuality, drug addiction or the fact of being a woman constitute respectively protective factors against transitions $2 \rightarrow 3$, $3 \rightarrow 2$, $4 \rightarrow 1$ and $3 \rightarrow 4$.

Without conditioning on the following state, Figure 3 presents examples of hazard functions of the semi-Markov process. Let us note that the transition-specific effect of a covariate is reflected on all transitions leaving from the same initial state, as explained by (5).

This application also involves the relevance of a inverse U shape concerning the hazard function. All the transitions correspond to this shape. Shortly after entering into a state, the risk of transition is high and increases. This observation corresponds to a clinical reality: a patient cannot move for an infinitesimal time, but his recent transition indicates high instability. However, if he stays for some time in this new state, his stability is reflected by a decrease in the hazard function.

If we follow the same strategy of modeling but using simple Weibull distribution, we obtain a maximized likelihood of -6127, corresponding to an AIC at 12307. This criterion is larger than the one obtained with a generalized Weibull distribution. Vectors of covariates also depend on this choice.

[1] The minimization of the Akaike Information Criterion makes it possible to select non-nested models. $AIC = -2 \times \text{Log}\,(L) + 2 \times \text{Number of parameters}$.

Table 2 Regression parameters β_{ij} of the final multivariate model.

Covariate	Transition	Parameter	Relative Risk[1]	Standard Deviation
Gender	$1 \rightarrow 3$	0.58	1.17	0.33
Age	$2 \rightarrow 1$	0.65	1.91	0.19
Hepatitis	$2 \rightarrow 1$	0.85	2.33	0.22
Homosexuality	$2 \rightarrow 1$	−0.55	0.58	0.28
Drug addiction	$2 \rightarrow 1$	0.44	1.56	0.22
Accidental infection	$2 \rightarrow 3$	−0.19	0.83	0.09
Heterosexuality	$3 \rightarrow 2$	−0.13	0.88	0.06
Gender	$3 \rightarrow 4$	−0.43	0.65	0.19
Drug addiction	$4 \rightarrow 1$	−0.28	0.76	0.13

[1] Relative Risk is deduced from (10): $RR = \exp(\beta)$.

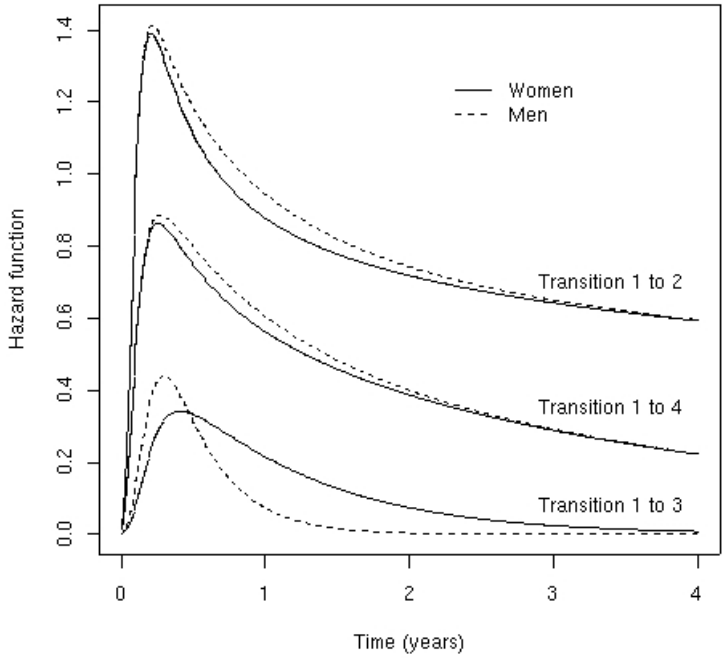

Figure 3 Hazard function of the semi-Markov process from the state 1 (CD4 < 400 cp $\cdot$ ml^{-1} and CV < 200 mm^{-2}).

4 Concluding Remarks

The results of our application show that homogeneous Markov models, with an exponential distribution of waiting times, are not adapted to the analysis of HIV dynamics, defined by CD4 and VL levels. The Weibull distribution also appears to be unsuitable compared with the generalized Weibull one, fitting an inverse *U* shape for the hazard function. Therefore, the use of this semi-Markov model seems to be more realistic for studying this type of biological or clinical process. This inverse *U* shape is perhaps due the arbitrary categorization of the states by two continuous variables. This implies for example that, after staying for some time in a certain state, we may expect a period with

Table 3 Transition probabilities of the Markov chain of the final multivariate model.

Transition	Probability	Standard Deviation
$1 \rightarrow 2$	0.55	0.02
$1 \rightarrow 3$	0.11	0.01
$2 \rightarrow 1$	0.20	0.02
$3 \rightarrow 2$	0.86	0.01
$4 \rightarrow 1$	0.44	0.02
$4 \rightarrow 2$	0.16	0.01

Table 4 Parameters of waiting time distribution of the final multivariate model.

Transition	ν_{ij}		σ_{ij}		θ_{ij}	
	Coeff.	SD	Coeff.	SD	Coeff.	SD
$1 \rightarrow 2$	2.85	0.43	0.13	0.01	5.46	1.09
$1 \rightarrow 3$	2.86	0.65	0.23	0.05	3.61	1.25
$1 \rightarrow 4$	2.67	0.39	0.15	0.02	4.59	0.89
$2 \rightarrow 1$	3.04	0.49	0.12	0.01	26.23	6.62
$2 \rightarrow 3$	2.61	0.20	0.18	0.01	7.20	0.82
$3 \rightarrow 2$	2.75	0.21	0.15	0.01	6.28	0.63
$3 \rightarrow 4$	2.19	0.36	0.13	0.02	5.58	1.25
$4 \rightarrow 1$	3.50	0.60	0.11	0.01	8.49	1.72
$4 \rightarrow 2$	3.38	0.85	0.15	0.02	6.32	2.11
$4 \rightarrow 3$	2.90	0.41	0.10	0.01	6.23	1.13

frequent switches between two states as a consequence of some randomfluctuation of the continuous variables, until the new state is finally reached for a longer time. This choice of distribution is also important because the covariates influencing transitions depend on it.

The results also measure the interest of a transition-specific model, enabling us to remove unimportant parameters and take into account many more different factors. The better adjustment, obtained with this method, is very useful for modeling the confusion or the interaction bias.

A few ways could extend the semi-Markov model presented in the paper. The main methodological issue consists of finding the right waiting time distribution. The models used in the first steps of our modeling strategy estimate all the parameters of the generalized Weibull distribution. This approach requires a large sample size of the study. In other applications, this point may be limiting. Therefore, a semi-parametric methodology, such as the one defined by Dabrowska et al. (1994) or Joly and Commenges (1999), could be an alternative approach, even if the hazard functions are not modeled. Another natural extension of the analysis would be to develop the non-homogeneity of the Markov chain contained in the semi-Markov process. This non-homogeneity would be based on chronological and waiting times (Papadopoulou and Vassiliou, 1999).

Lastly, the semi-Markovian property, according to which the evolution of the process is conditioned by the present state and the time spent in this state, is a strong assumption. The use of an embedded Markov chain, with an order higher than one, could constitute an extension.

Acknowledgements We thank the referee for his helpful comments that improved the article. The authors are grateful to the department of infectious disease of Nice Hospital for their kind permission to use the HIV disease data. We thank also Teresa Sawyers for her translation.

References

Alioum, A., Leroy, V., Commenges, D., Dabis, F., and Salamon, R. (1998). Effect of gender, age, transmission category, and antiretroviral therapy on the progression of human immunodeficiency virus infection using multistate Markov models. Groupe d'épidémiologie clinique du SIDA en Aquitaine. *Epidemiology* **9**, 605–612.

Andersen, P. K., Hansen, L. S., and Keiding, N. (1991). Assessing the influence of reversible disease indicators on survival. *Statistics in Medicine* **10**, 1061–1067.

Bagdonavicius, V. and Nikulin, M. (2002). *Accelerated Life Models*. Chapman and Hall/CRC, London.

Boudemaghe, T. and Daures, J. P. (2000). Modeling asthma evolution by a multi-state model. *Revue d'Epidémiologie et de Santé Publique* **48**, 249–255.

Combescure, C., Chanez, P., Saint-Pierre, P., Daures, J. P., Proudhon, H., and Godard, P. (2003). Assessement of variations in control of asthma over time. *European Respiratory Journal* **22**, 298–304.

Cox, D. R. (1972). Regression models and life-tables. *Journal of the Royal Statistical Society* **34**, 187–220.

Dabrowska, D. M., Sun, G., and Horowitz, M. M. (1994). Cox Regression in a Markov Renewal Model: an application to the analysis of bone transplant data. *Journal of the American Statistical Association* **89**, 867–877.

Jackson, C., Sharples, L., Thompson, S., Duffy, S., and Couto, E. (2003). Multistate Markov models for disease progression with classification error. *Journal of the Royal Statistical Society Series C* **52**, 193–193.

Joly, P. and Commenges, D. (1999). A penalized likelihood approach for a progressive three-state model with censored and truncated data: Application to AIDS. *Biometrics* **55**, 887–890.

Kay, R. (1986). A Markov model for analysing cancer markers and disease states and survival studies. *Biometrics* **42**, 855–865.

Mauskopf, J. (2000). Meeting the NICE Requirements: A Markov Model Approach. *Value Health* **3**, 287–287.

Mudoholkar, G., Srivastava, D., and Kollia, G. D. (1996). A Generalization of the Weibull distribution with application. *Journal of the American Statistical Association* **91**, 1575–1583.

Papadopoulou, A. and Vassiliou, P. (1999). *Semi-Markov Models and Applications*. Kluwer Academic Publishers, Dordrecht.

Perez-Ocon, R. and Ruiz-Castro, J. E. (1999). *Semi-Markov Models and Applications*. Kluwer Academic Publishers, Dordrecht.

Saint-Pierre, P., Combescure, C., Daures, J. P., and Godard, P. (2003). The analysis of asthma control under a Markov assumption with use of covariates. *Statistics in Medicine* **22**, 3755–3770.

Satten, G. and Sternberg, M. (1999). Fitting Semi-Markov Models to interval-Censored Data with Unknown Initiation Times. *Biometrics* **55**, 507–513.

