cancer data using multi-state models

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aim

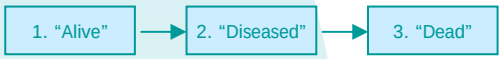
Present Multi-state models as an alternative for the analysis of survival data where the survival is the ultimate outcome but where intermediate (transient) states (events) are observed.

Multi-state models (MSM)

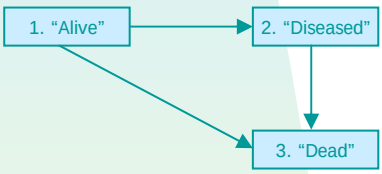
A MSM is a model for a stochastic process in continuous time allowing individuals to move between a finite number of states. An individual moves from one state to another through time. The next state to which the individual moves, and the time of change, are specified through transition intensities that provide the instantaneous hazard for movement out of one state into another.

Some MSM

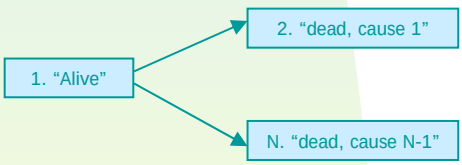
The mortality model



The progressive three-state model



The Illness-death model



The Competing risks model

classical approaches

Cox Markov (semi-Markov) Model: the transition intensities, are modeled using Cox-like models of the form $\alpha_{hj}\left(t|F_{t-}\right)=\alpha_{hj0}\left(t\right)\exp\left(\beta^{T}Z_{hj}\right)$

Homogeneous Markov model: the transition probabilities can be simply expressed in terms of the transition intensities, through the Kolmogorov relation P(t) = exp(tQ).

Piecewise Homogeneous Markov Model: consists of partitioning the whole study period in two or more intervals and then fitting a piecewise constant intensities model, leading to transition intensity functions as step functions.

Assumptions

Testing the Markov assumption **:** For the three-state model, we must show that the time spent in state 1 (past) is not important on the transition from state 2 into state 3. We may consider Z = 'time spent in state 1' and test if the covariate effect is significant for transition leaving state 2.

Testing the Homogeneity assumption**:** A piecewise model can be used to assess this assumption.

Colon Cancer Data

For the Colon cancer data (Moertel et al. 2000) we may consider the recurrence as an associated state of risk, and use the illness-death model with states "alive and disease-free", "alive with recurrence" and "dead".

Interests:

(a) Investigate the effect of the recurrence on survival;
(b) explore the potential fixed covariate effects, namely: age, sex (1=male), rx (1=observation,2=Lev(amisole), Lev(amisole)+5-FU), nodes and obstruct (1=yes).

Colon Cancer Data: assumptions

We verify that the covariate "time spent in state 1" is significant for the transition leaving state 2. We therefore consider the Cox semi-Markov model.

Table: Estimated effects in Cox models for the recurrence intensity, $\alpha_{12}\left(t\right)$, and for the mortality, $\alpha_{23}\left(t-T_{12}\right)$, after recurrence in the Colon cancer data.

Transitions	Covariate	$\hat{\beta}$	SE	HR	p-value
$1\rightarrow 2$	Sex	-0.137	0.094	0.872	0.150
	Age	-0.003	0.004	0.997	0.460
	Rx 2	-0.037	0.109	0.964	0.740
	Rx 3	-0.525	0.121	0.592	0.000
	pspline(nodes), linear	0.096	0.011	1.100	0.000
	pspline(nodes), nonlin				0.000
	Obstruct	0.243	0.116	1.275	0.036
$2\rightarrow 3$	Sex	0.227	0.103	1.250	0.028
	Age	0.012	0.004	1.012	0.003
	Rx 2	0.100	0.117	1.105	0.390
	Rx 3	0.357	0.132	1.429	0.007
	pspline(nodes), linear	0.060	0.012	1.062	0.000
	pspline(nodes), nonlin				0.021
	Obstruct	0.276	0.125	1.318	0.028

SE = Standard Error, HR = Hazard Ratio; T_{12} transition time from state 1 to state 2.

Conclusions

➔ While Time-dependent Cox regression model suggested a negligible effect of the covariate "Obstruct", multi-state models indicated a statistically significant effect in both transitions.
➔ When using MSMs, the covariates "sex" and "age" only shows a statistically significant effect in the mortality transition.
➔ While multi-state models provide non-biased estimates of the importance and ability of covariates to predict the course of the illness, these issues cannot be fully explored using Cox models alone.

References

Andersen, P.K., Borgan, O., Gill, R.D. and Keiding, N. (1993). *Statistical Models Based on Counting Processes*. Springer, New York.