Analysis of multistate data with realistic rate models and multiple time scales: A dogmatic approach

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The dogma [1]

- do not condition on the future — indisputable
- do not count people after they are dead — disputable (artifact)
- stick to this world — expandable

P. K. Andersen and N. Keiding:
Interpretability and importance of functionals in competing risks and multistate models
Stat Med, 31:1074–1088, 2012

stick to this world

- the "net" survival or "cause specific survival" for cause c:

$$S_c(t) = \exp\left(-\int_0^t \lambda_c(s)\ \mathrm{d}s\right)$$

- not a proper probability
- the probability of survival if
  - all other causes of death than c were absent
  - c-specific mortality rate were still the same
- merely a transformation of the cause-specific rate
  — but with **no** real world interpretation
- Do not label quantities "survival" or "probability" if they are not

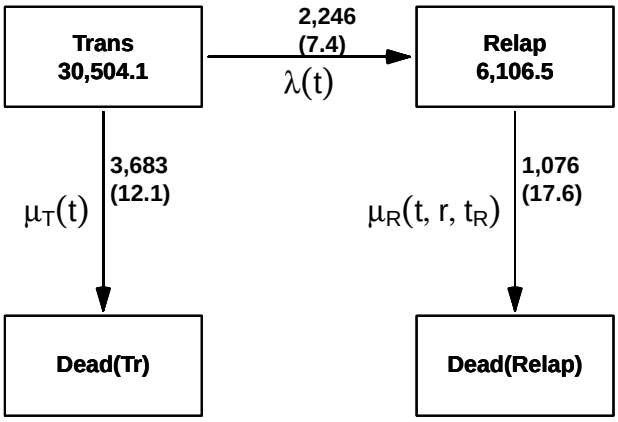
sticking to this world — time scales

- rates are **continuous** (*i.e.* smooth) functions of time
- rates may depend on **more** than one time scale
- . . . which and how are **empirical** questions
- there is no such thing as primary or secondary time scale — time scales (and other quantitative covariates) should be modeled using the same machinery
- effects of multiple time scales should be reported **jointly** — silly to report the effect of increasing disease duration for a fixed age
- facilitated by parametric modeling of rates

Practicalities of parametric analysis of rates

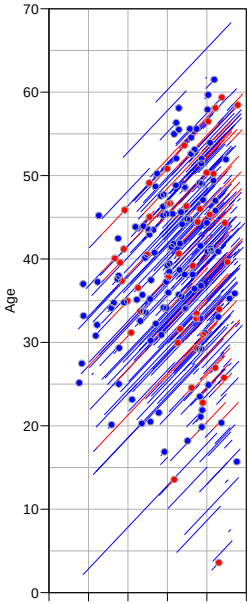
- Split follow-up time in small intervals (length y_i)
- each interval has a value for each time scale (covariates)
- . . . and an event indicator and length (response)
- Fit Poisson models using time scales as covariates with smooth effects, *e.g.* splines
- . . . and $(\text{event} = A)$ as response and $\log(y_i)$ as offset
- This gives a model for the transition rates to state A.

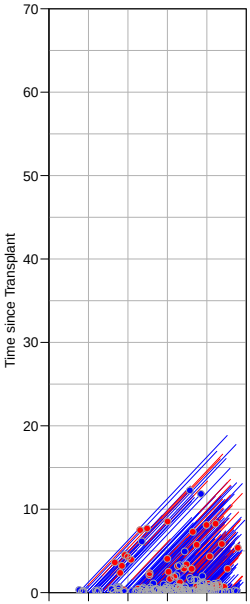
EBMT transplant data[2]

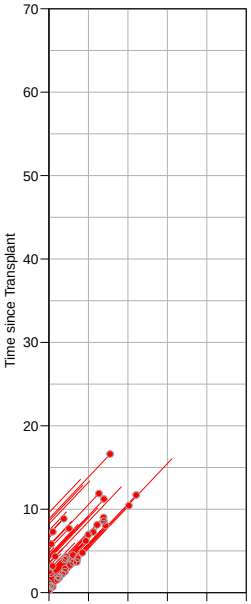


other covariates: Age and date at Tx, sex, donor type, CML type

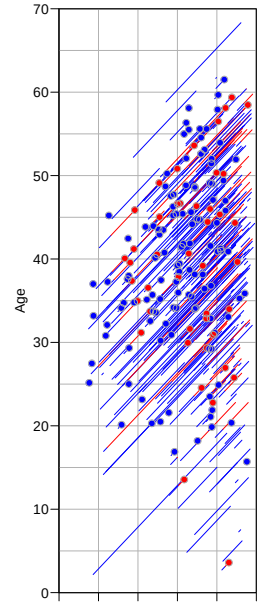
Iacobelli & Carstensen: Multistate Models with Multiple Timescales, Stat Med 2013

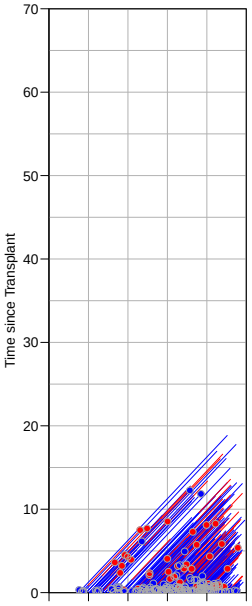

Age
Date
0
10
20
30
40
50
60
70
1980
1990
2000

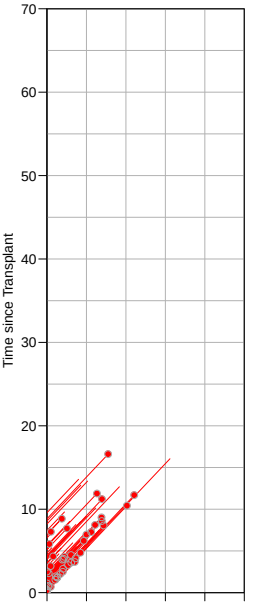

Time since Transplant
Date
0
10
20
30
40
50
60
70
1980
1990
2000

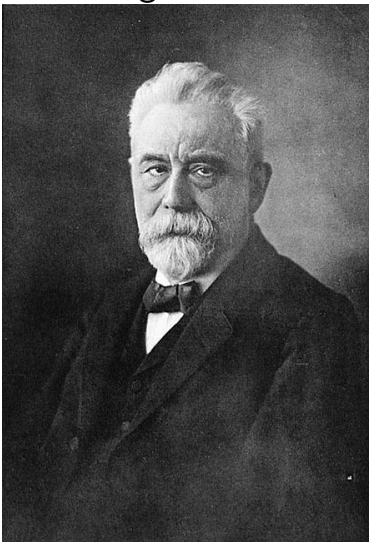

Time since Transplant
Time since Relapse
0
10
20
30
40
50
60
70
0
5
10
15
20
25

Lexis diagrams

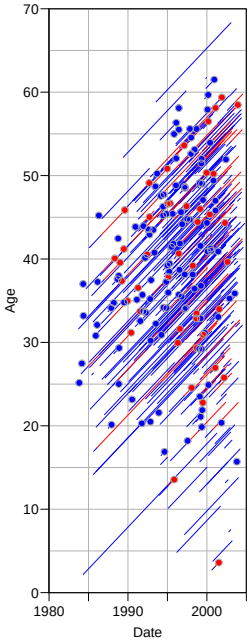


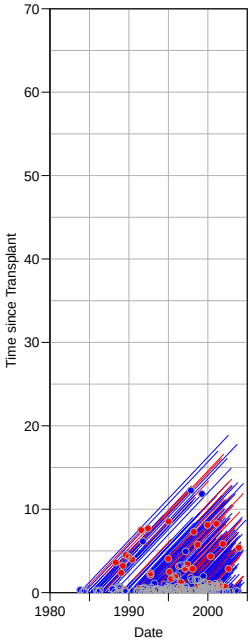


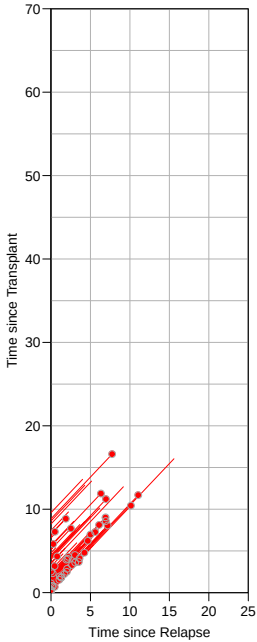


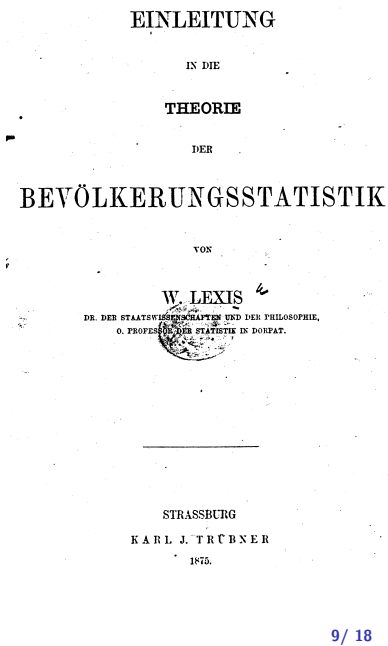


Wilhelm Lexis (1837–1914)









EINLEITUNG

IN DIE

THEORIE

DER

BEVÖLKERUNGSSTATISTIK

VON

W. LEXIS

DR. DER STAATSWISSENSCHAFTEN UND DER PHILOSOPHIE,
O. PROFESSOR DER STATISTIK IN DORPAT.

STRASSBURG

KARL J. TRÜBNER

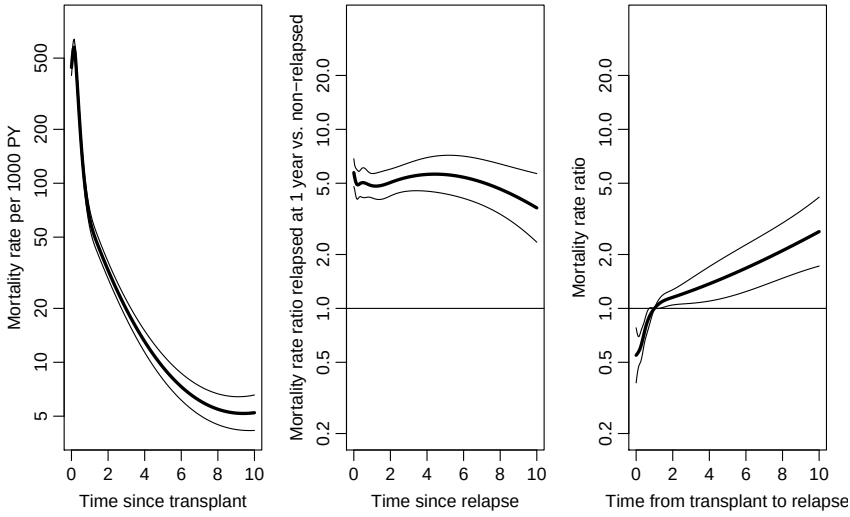
1875.

Markov property: Empirical question

Model for mortality rates:

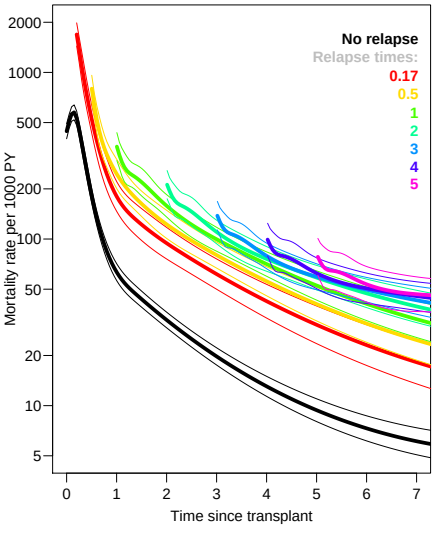
- t time since transplant
- r time since relapse (if relapsed)
- t_r time from transplant to relapse
- $\ldots +$ other covariates
- Fit the model for both mortality transitions:
  - split follow-up time
  - fit Poisson model with covariates
  - and spline terms for each time scale and $t_r = t - r$.
- `Lexis` machinery [3, 4] from the **Epi** package for **R** used for representation and manipulation of follow-up data.

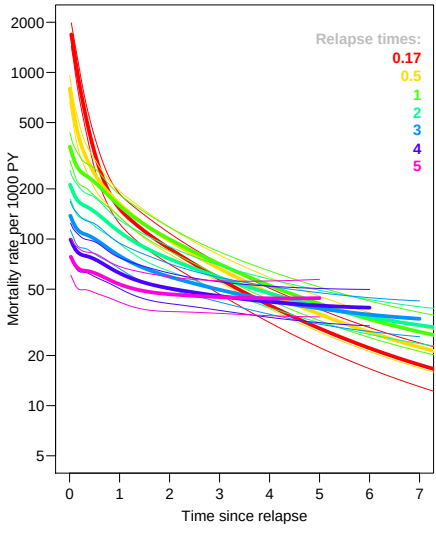
$$\log(\mu) = h(t) + k(r) + g(t - r) + X\beta$$



t: time since transplant r: time since relapse

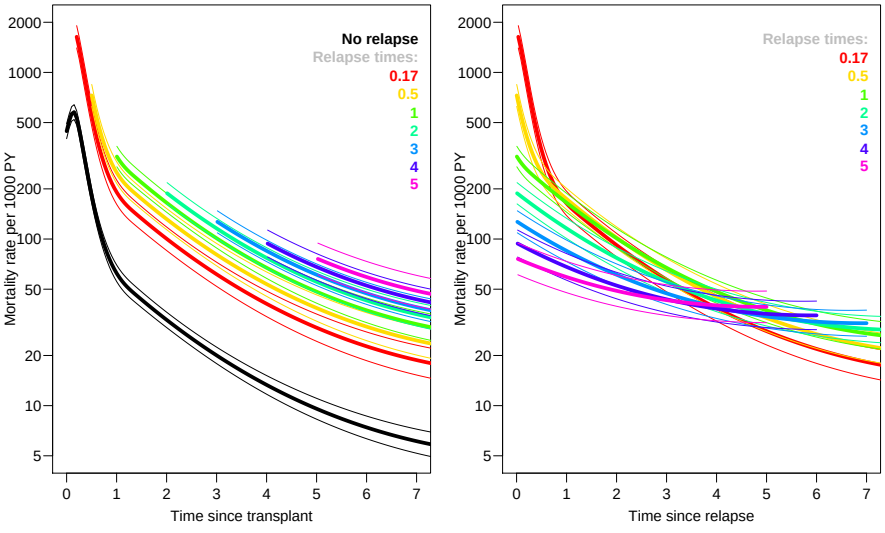
$$\log(\mu) = h(t) + k(r) + g(t - r) + X\beta$$





t: time since transplant r: time since relapse

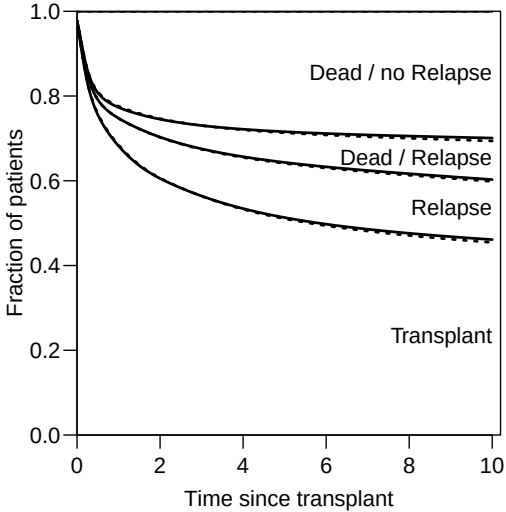
$$\log(\mu) = h(t) \qquad +g(t-r) + X\beta$$

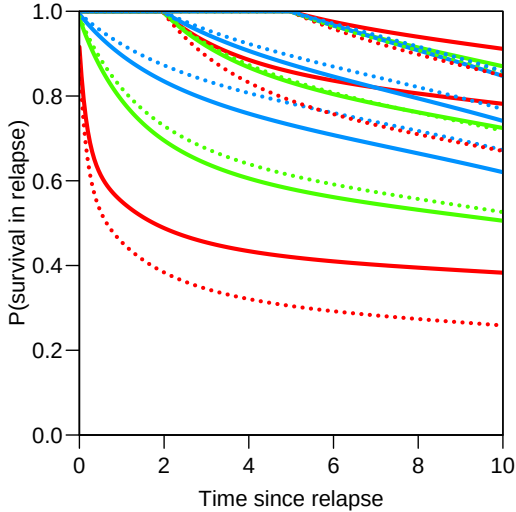


t: time since transplant $\quad r$: time since relapse

From rates to probabilities in multistate models

- There is a one-to-one correspondence between:
  - rates between states + initial state distribution
  - state distribution by time
- Model for rates
  $\Rightarrow$ probability of being in a given state at any given time
- Single time-scale for all transitions:
  - Aalen-Johansen
  - Parametrically derived transition probability matrices
- Multiple time-scales:
  - **Analytically:** a nightmare
  - **Simulation** is the answer





Full lines: based on the model with effects of time since transplant and time to relapse
Broken lines: based on the Markov model with only time since transplant.

Practical advice for multistate analysis

- Get **dates** for all events
- Draw boxes and arrows
- Draw Lexis diagrams of follow-up for pairs of time scales
- Divide absorbing states by transition type (origin)
- Transitions **out** of a state are **un**likely to be related
- Transitions **into** the same state are likely to be related
- Rates are smooth functions of time scale**s**
- Easier to obtain expected sojourn times and other derived measures if rates modeled parametrically.
- `Lexis` from `Epi` in **R**
  `multistate` in Stata (M Crowther) [5]

Dogma for multistate analysis

- do not condition on the future
- do not label quantities 'probability' or 'survival' if they are not
- do label interactions "**interactions**" if they are
- stick to this world:
  - rates are smooth functions of time scales
  - rates are likely to depend on more than one time scale
    — empirical examination requred
  - report time scale effects jointly

Thanks for your attention

References I

P. K. Andersen and N. Keiding.
Interpretability and importance of functionals in competing risks and multistate models.
Stat Med, 31:1074–1088, 2012.

S. Iacobelli and B. Carstensen.
Multiple time scales in multi-state models.
Stat Med, 32(30):5315–5327, Dec 2013.

Martyn Plummer and Bendix Carstensen.
Lexis: An R class for epidemiological studies with long-term follow-up.
Journal of Statistical Software, 38(5):1–12, 1 2011.

Bendix Carstensen and Martyn Plummer.
Using Lexis objects for multi-state models in R.
Journal of Statistical Software, 38(6):1–18, 1 2011.

M. J. Crowther and P. C. Lambert.
Parametric multistate survival models: Flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences.
Stat Med, 36(29):4719–4742, Dec 2017.

`http://bendixcarstensen.com`