Forward, backward and time-adjusted recurrent event processes in the presence of a terminal event

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The Joint Pepper Centers Biostatistics Symposium

September 9, 2011

Outline

- **Description of data**
  recurrent events, time to terminal event (failure), marker measurements
- **Standard recurrent event data**: fundamental tools/models
  rate functions, conditional and marginal regression models
- **Current data**: three approaches
- **Descriptive examples** in mental health, cancer, AIDS
  Some data analysis, if time allows.

Recurrent events, markers, and terminal event

- **Recurrent event process:** $N(t)$
  - multiple tumors; repeated hospitalizations
- **Markers given occurrence of recurrent events**: $X(t)|_{dN(t)=1}$
  - health or prognostic measurement; biomarkers, medical cost
  - marker could be treated as covariate or outcome measurement
- **Terminal event**, T: time to terminal event
  - time to death, disease, failure
- **Data**: observe recurrent events, markers and covariates until terminal event or censoring, whichever occurs first.

Examples

Example 1. Denmark schizophrenia registry data

$N(t)$ is hospitalizations for schizophrenia

$X(t)|_{dN(t)=1}$ = prognostic measurements

T= time to death

Example 2. HIV-AIDS trials

$N(t)$: opportunistic diseases for HIV-infected patients

$X(t)|_{dN(t)=1}$ = prognostic measurement, severity score

T= time to AIDS

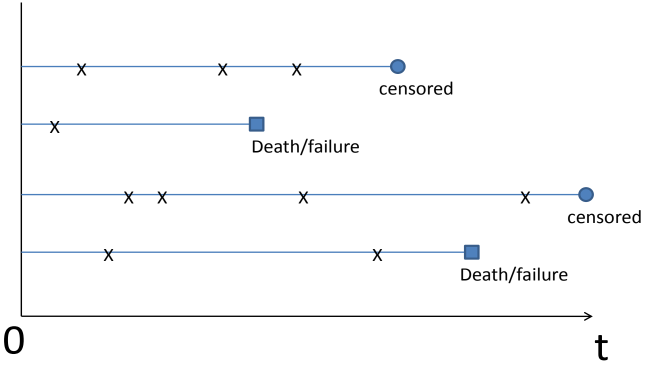
Example 3. Ovarian cancer SEER study

$N(t)$ is hospitalizations for ovarian cancer

$X(t)|_{dN(t)=1}$ = medical cost for hospitalization

T= time to death

Plot of observed data



Statistical challenges

- $N(t)$ is typically correlated with T; observation of recurrent events is subject to dependent censoring.
- When terminal event = death, survivor population changes over time - which population to focus on?
- Proper/interesting models? Accompanied statistical methods?
- Need methodology for analyzing integrated data:
  recurrent event data + survival data (+ marker data)

Fundamental functions for recurrent event process

- **Conditional rate function** is also called the **intensity function**, which is the rate function *conditional* on the event history,

$$\lambda(t|N_H(t)) = \lim_{\Delta t \to 0^+} \frac{\Pr(N(t+\Delta) - N(t) > 0 \mid N_H(t))}{\Delta},$$

$N_H(t) = \{N(u) : 0 \leq u \leq t\}$: recurrent event history before or at t

- **Marginal rate function** is the rate function *unconditional* on the event history $N_H(t)$:

$$\lambda(t) = \lim_{\Delta \to 0^+} \frac{\Pr(N(t+\Delta) - N(t) > 0)}{\Delta}.$$

Useful semiparametric models for recurrent events

- **Conditional rate model** $\lambda(t \mid N_H(t), Z_H(t)) = \lambda_0(t) exp\{X(t)\beta\}$
  $X(t) = \phi(N_H(t), Z_H(t))$: a transformation of $(N_H(t), Z_H(t))$

  Prentice, Williams and Peterson (1981); Andersen and Gill (1982)

  Marginal rate model $\lambda(t \mid Z_H(t)) = \lambda_0(t) exp\{Z(t)\beta\}$

  Lin et al. (2000)

- **Critiques.** These two useful models are defined over time (t) subject to the same population. Methods for these two models heavily rely on independent censoring assumption.
- **If terminal event is death, the models and methods become inappropriate!**

Our research

Data: observe recurrent events, possibly marker measurements until terminal event (death or failure) or censoring, whichever occurs first.

Proposed approaches: either nonparametric or semiparametric models

Approach 1. Joint model of recurrent events and time-to-failure

Approach 2. Failure-time-adjusted recurrent event models

Approach 3. Backward recurrent marker process model

1. Joint model of recurrent events and time-to-failure

Subject-specific joint modeling on $(N(t), T)$

$Z = z$: subject-specific latent variable

$X = x$: covariate vector

- **model**

  hazard function of T: $h(t) = zh_0(t)\exp(\beta' x)$

  rate function for $N(t)$: $\lambda(t) = z\lambda_0(t)\exp(\alpha' x)$

- **independent censoring assumption**

  $(N(\cdot), T, C)$ are independent conditioning on (x, z)

  C: censoring time for other reasons

- **methodological approach** conditional likelihood, estimating equations

  A nice feature is that distribution of Z is a nonparametric component.

1. Joint model of recurrent events and time-to-failure

Data application

- Denmark national-based registry data; long-term disease data recorded from 1st hospitalization to death

  - repeated psychiatric measurements
  - recorded hospitalization information over lifetime

- Recurrent events: schizophrenia-related hospitalizations
  - terminal event = death
  - administrative censoring

2. Failure-time-adjusted recurrent event process

Use T to adjust time-scale for recurrent event process $N(t)$

- **model**

  $\ln T = \beta' x + \ln T_0$

  $\mathrm{E}[dN(t\exp(\beta' x)) \mid T, X = x] = \exp(\alpha' x)\mathrm{E}[dN_0(t) \mid T_0],\ 0 \le t \le T_0$

  assuming: $(T, N(\cdot))$ is independent of C conditional on $X = x$

- **example.** If $x = 0, 1;\ \alpha = 0, \beta = 0.5$, then

  $\mathrm{E}[dN_{ctrl}(t) \mid T_{ctrl}] = \mathrm{E}[dN_0(t) \mid T_0]$

  $\mathrm{E}[dN_{tr}(1.65t) \mid T_{tr}] = \mathrm{E}[dN_0(t) \mid T_0]$

  example. If $x = 0, 1;\ \alpha = 0, \alpha = 0.2, \beta = 0.5$, then

  $\mathrm{E}[dN_{ctrl}(t) \mid T_{ctrl}] = \mathrm{E}[dN_0(t) \mid T_0]$

  $\mathrm{E}[dN_{tr}(1.65t) \mid T_{tr}] = 1.22 \cdot \mathrm{E}[dN_0(t) \mid T_0]$

2. Failure-time-adjusted recurrent event process

Data application

- Terry Beirn Community Programs for Clinical Trials on AIDS (CPCRA)

  - HIV-infected patients
  - didanisine (ddI) v.s. zalcitabine (ddC) treatments

- - recurrent events: repeated opportunistic diseases
  - terminal event: diagnosis of AIDS
  - censoring: loss to follow-up or administrative censoring

3. Backward recurrent marker process model

- **Backward model**
  - using death as time-origin and counting time backward
  - model $N(t)$ and $M(t) = \int_0^t X(t)dN(t)$
  - $X(t)$= cost per hospitalization, $M(t)$= total cost in t-unit time
- **Research interest**
  - pattern changes of $N(t)$, $M(t)$ within k months before death
  - estimation of E$[M(t)]$, rate of $M(t)$,... etc.
    (average total cost within t months before death, rate of cost at t months before death,... etc)
- **Methodological challenge**
  - methods developed to deal with 'censoring for backward data'
  - nonparametric, semiparametric

3. Backward recurrent marker process model

Data application.

- SEER-Medicare linked data for ovarian cancer
  - Ovarian SEER data provide information of ovarian cancer incidence and follow-up.
  - Medicare data provide information of medical costs for 97% US population 65 years or older
- - Recurrent events: multiple hospitalizations due to o.c.
  - Marker measurements: hospitalization cost
  - Terminal event: death
  - Censoring: administrative censoring
- Research interest: pattern of hospitalization cost before death, in relation to diagnosis category and treatment plans.

Discussion for aging research

- For aging research, it is not uncommon to deal with

  - recurrent events (repeated falls, injuries)

  - marker measurements (biomarkers, medical cost)

  - terminal event (death, MCI, AD, ...)

- For 'backward process', statistical methods in literature are ad hoc and some in error!

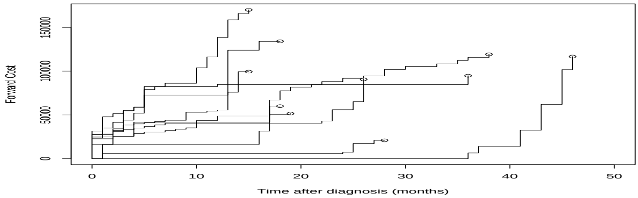
  - change-point for biomarkers, in relation to failure event

- Integration of different data sources

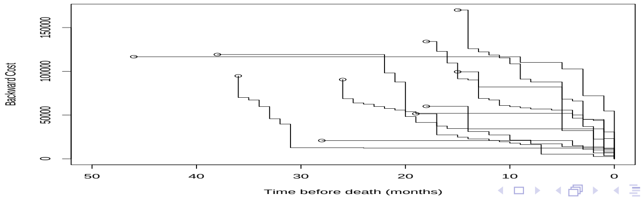
THANK YOU !

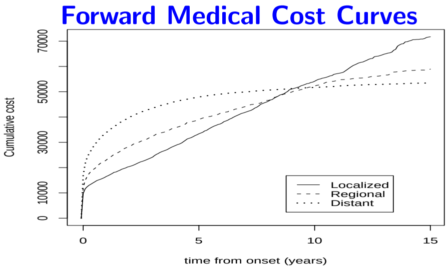
Approach 3: Data analysis

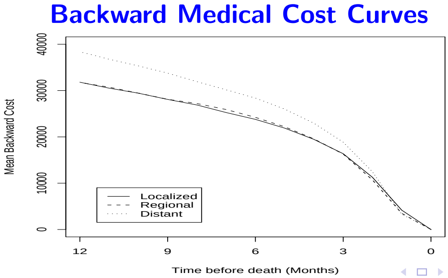
Forward Medical Cost Data

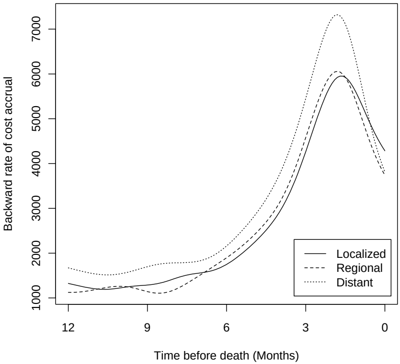


Backward Medical Cost Data




Forward Medical Cost Curves
Cumulative cost
0
10000
30000
50000
70000
0
5
10
15
time from onset (years)
Localized
Regional
Distant


Backward Medical Cost Curves
Mean Backward Cost
0
10000
20000
30000
40000
12
9
6
3
0
Time before death (Months)
Localized
Regional
Distant


Backward rate of cost accrual
1000
2000
3000
4000
5000
6000
7000
12
9
6
3
0
Time before death (Months)
Localized
Regional
Distant

- Estimated Pearson correlation coefficient between $M^B(1\ year)$ and T, conditioned on $T \geq 1$ year, is

localized	regional	distant
-0.65	-0.31	-0.46

- Estimated final-year medical cost is

localized	regional	distant
\$31802	\$31752	\$38377

(s.e.: \$1229, \$2205, \$896)

Approach 2: Analysis of CPCRA Trial

	$\widehat{\beta}_T$	Model A: $\widehat{\beta}_R^A$	Model B: $\widehat{\beta}_R^B$
Estimate	.179	.153	.195
95% Wald-type CI	(−.023, .381)	(−.199, .504)	(−.056, .447)
95% bootstrap CI	(−.015, .375)	(−.217, .508)	(−.061, .458)
P-value	.082	.394	.129

NOTE: Treatment is coded 0 for ddI and 1 for ddC.

Approach 1: too much for 30 min. presentation (see our papers for schizophrenia data analysis

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