Models for Repeated Events Data

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My interest

- Multivariate failure time data
- Very diverse field
- Complications: dependence, complex censoring and semi-parametrics
- Analogies with other clustered data

Outlines

- Multivariate Failure Time Data
- Repeated events data
- Contrasting modeling strategies
  - How much conditioning
  - Full versus gap times

Multivariate Failure Time Data (MVFT)

- Clustered: cluster sampled failures of same `type'
- Multiple Event: subjects with multiple events of different types
- Repeated Event: subjects with repeated events of same type

Clustered FT Data

- Ex: age of schizophrenia onset in twins
- Data is
  - hierarchical
  - number of failures is bounded
  - dependence is across subunits
  - dependence is not hard to model

Multiple Events Data

- Ex: HIV+ subjects at risk of various infections and death
- Features:
  - multiple events
  - events occur in various orders
  - dependent across time
  - multistate representation useful

Repeated Event Data

- Ex: Exacerbations in cystic fibrosis
- Features:
  - recurrent events of same type
  - dependent across times
  - longitudinal data of counts
  - risk heterogeneous across time and subjects with varied follow-up

Repeated Event Notation

- $N_i(t)$: # of events by time t in subj i
- $Z_i(t)$: covariates at time t in subj i
- $Y_i(t)$: risk indicator at time t in subj i
- $\mathcal{H}_i(t)$: history of events & covariates up to time t in subject i

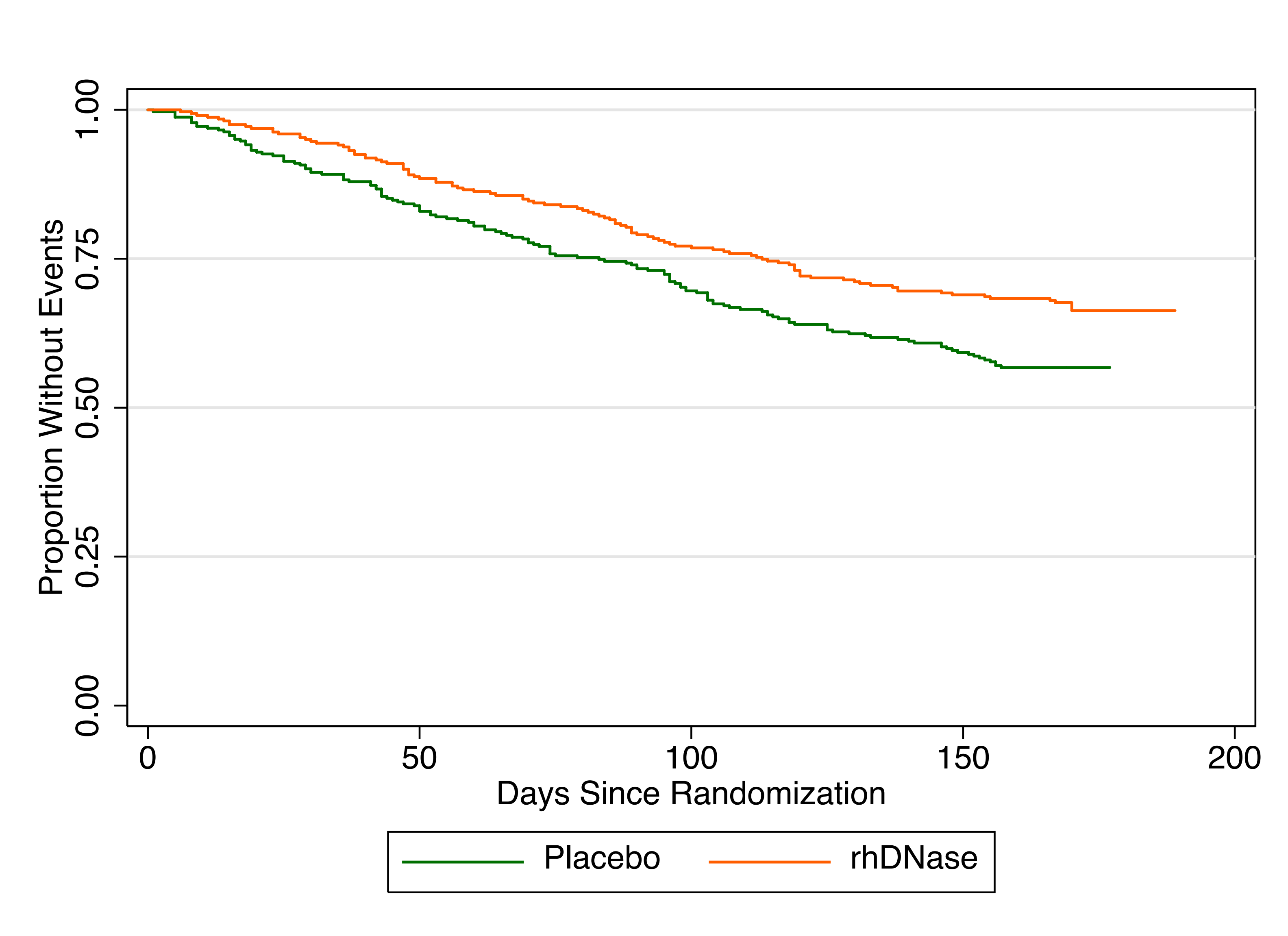
rhDNAase study

- Clinical trial of enzyme rhDNAase
- 645 subjects (324 placebo, 321 rhDNAase)
- Followed for 169 days
- Event: pulmonary exacerbation (infection)
- 38% of subjects have more than 1 event

Some Simple Strategies

- Compare
  - Time to first event
  - Average numbers of events
  - Average rate of events

First Exacerbation



Cox Model for First Exacerbation

```
No. of subjects =          645                     Number of obs   =        645
No. of failures =          243
Time at risk    =        85011
                                                   LR chi2(1)      =       7.98
Log likelihood  =   -1511.9297                     Prob > chi2     =     0.0047

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .6948066   .0901047    -2.81   0.005     .5388618    .8958812
------------------------------------------------------------------------------
```

What’s missing?

- Umm, like, 1/3 of the data
  - 243 first events but 361 total events
- Hard to address long term questions
  - follow-up period is shorter
- Does treatment effect fade?

Number of Exacerbations by Rx

# Excer.	Placebo	DNase
0	185	217
1	97	65
2	24	30
3	13	6
4	4	3
5	1	0
Tot.	324	321

Count Based Analysis

- Mean # of exacerbations:
  - 0.63 on placebo: 205/324
  - 0.48 on rhDNase: 155/321
  - Rel. Means = 0.48/0.63 = 0.68
  - 32% reduction

What's missing

- Follow-up
  - Subjects followed for varying times
  - No allowance for treatment times
- How to allow for FEV1
- Is treatment effect transient?

Rate Analysis

- Overall rate:
- 1.51/yr on placebo:
  - 206 events/135.8 pers years
- 1.13/yr on rhDNase
  - 155 events/137.6 pers years
- Rel. Rate = 0.74

What’s missing

- Risk may vary with time
  - average rates awkward with uneq. fu
- Covariates:
- Subject-to-subject variation
- Treatment effect in time

Wei, Lin, Weissfeld

- Define a series of times... $(T_1, \ldots, T_5)$
- T_k = time from randomization to kth event
- Model hazard for kth failure

  $$\lambda_k(t) = \lambda_{0k}(t) \exp(\beta_k^T Z)$$

- possibly with $\beta_1 = \ldots = \beta_k$

What's missing?

- If first event delayed, all others are too
- Interpretation of coefficient is awkward
- Treats longitudinal data cross-sectionally
- Model is pretty implausible

WLW Analysis

```
No. of subjects      =         4362                 Number of obs   =      4362
No. of failures      =          361
Time at risk         =       480997
                                                    Wald chi2(1)    =      5.43
Log pseudo-likelihood =   -2257.7291                Prob > chi2     =    0.0198

                              (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .7107947   .1041686    -2.33   0.020     .5333332    .9473048
------------------------------------------------------------------------------
                                                           Stratified by enum
```

WLW Analysis

Event	HR	95% CI
1st	0.69	(0.54,0.89)
2nd	0.90	(0.58,1.40)
3rd	0.47	(0.21,1.04)
4th	0.60	(0.14,2.53)

$$\text{test for homogeneity}, p < 0.0001$$

Modeling Approaches

- Full intensity:
  - parametric:
  - non-parametric
- Marginal model:
  - model an average count
  - model an average rate

The Full Intensity

- Full intensity: $\lambda(t|\mathcal{H}(t))$
- $$\lambda(t|\mathcal{H}(t)) = \lim_{\Delta \downarrow 0} \frac{\mathrm{pr}\{\text{event in}(t+\Delta, t]|\mathcal{H}(t)\}}{\Delta}$$
- Models the rate of events given history
- Such a specification leads to a likelihood
- What's a reasonable model for dependence?

Andersen and Gill

- Full intensity approach

$$\lambda(t|\mathcal{H}(t)) = \lambda_0(t)\exp(\beta^T Z(t))$$

- Prior events don't affect future risk
- Non-homogenous Poisson process
- Can be extended to allow some history
  - e.g. make # prior events a covariate

Andersen Gill Fit

```
Cox regression -- Breslow method for ties

No. of subjects =          645                  Number of obs   =        956
No. of failures =          361
Time at risk    =        99779
                                                LR chi2(1)      =       7.80
Log likelihood  =   -2296.4756                  Prob > chi2     =     0.0052

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .7441653   .0791329    -2.78   0.005     .6041636    .9166094
------------------------------------------------------------------------------
```

AG Model with FEV1

```
No. of subjects =          645                  Number of obs   =        956
No. of failures =          361
Time at risk    =        99779
                                                LR chi2(2)      =     137.09
Log likelihood  =    -2231.831                  Prob > chi2     =     0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .8032687   .0857086    -2.05   0.040     .6516852    .9901111
        fev1 |   .8261597   .0147089   -10.73   0.000      .797828    .8554975
------------------------------------------------------------------------------
```

AG with FEV1 and # Prior Events

```
No. of subjects =          645                   Number of obs   =        956
No. of failures =          361
Time at risk    =        99779
                                                 LR chi2(3)      =     144.59
Log likelihood  =   -2228.0807                   Prob > chi2     =     0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .8201676   .0877713    -1.85   0.064     .6649825    1.011568
        fev1 |   .8621718   .0198325    -6.45   0.000     .8241641    .9019324
        enum |   1.391863   .1618172     2.84   0.004     1.108246    1.748061
------------------------------------------------------------------------------
```

Andersen and Gill

- Good
  - Very easy inference and theory
- Bad
  - Assumes no subject-to-subject variation
  - Assumes no dependence across time

`Poisson' Regression

- Full intensity approach

$$\lambda(t|\mathcal{H}(t)) = \lambda \exp(\beta^T Z(t))$$

- Prior events don't affect future risk
- *Homogenous* Poisson process
- Can allow some history or frailty

Poisson for rhDNase

```
No. of subjects =          645                 Number of obs   =        956
No. of failures =          361
Time at risk    =        99779
                                               LR chi2(1)      =       7.90
Log likelihood  =   -850.12638                 Prob > chi2     =     0.0050

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .7428512   .0789871    -2.80   0.005     .6031064    .9149761
------------------------------------------------------------------------------
```

Poisson for rhDNase, FEV, prev events

```
No. of subjects =          645                  Number of obs   =        956
No. of failures =          361
Time at risk    =        99779
                                                LR chi2(3)      =     142.37
Log likelihood  =   -782.89139                  Prob > chi2     =     0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .8122218   .0868262    -1.95   0.052     .6586907    1.001539
        fev1 |   .8611953   .0197892    -6.50   0.000     .8232696    .9008682
        enum |    1.27625   .1408942     2.21   0.027     1.027935     1.58455
------------------------------------------------------------------------------
```

Poisson with frailty

```
No. of subjects =          645                    Number of obs    =       956
No. of failures =          361
Time at risk    =        99779
                                                  LR chi2(3)       =    148.04
Log likelihood  =   -780.05455                    Prob > chi2      =    0.0000

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.       z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .7309785   .1018049    -2.25   0.024     .5563602    .9604022
        fev1 |   .8251568    .026938    -5.89   0.000     .7740129    .8796801
        enum |   1.526471   .3015999     2.14   0.032     1.036354    2.248375
-------------+----------------------------------------------------------------
     /ln_the |  -.7857436   .3950768    -1.99   0.047     -1.56008   -.0114073
-------------+----------------------------------------------------------------
       theta |   .4557806   .1800684                      .2101193    .9886576
------------------------------------------------------------------------------
Likelihood-ratio test of theta=0: chibar2(01) =     5.67 Prob>=chibar2 = 0.009
```

Poisson Regression

- Good
  - Very, very easy inference and theory
  - Very easy to incorporate a frailty
- Bad
  - Hard to model dependence across time
  - Assumes homogeneous risk over time

Marginal Failure Rates

- Marginal failure rate $\alpha(t)$
- Simply, the overall incidence of events
- No incorporation of failure history

$$\alpha(t|Z(t)) := \lim_{\Delta \downarrow 0} \frac{\mathrm{pr}\{\text{event in } (t+\Delta, t]|Z(t)\}}{\Delta}$$

$$\alpha(t|Z(t)) = \alpha_0(t)\exp(\beta^T Z(t))$$

Marginal Failure Idea

- Idea by Pepe
- Condition only on covariates
  - model depends only on covariates
- Doesn't assume past is irrelevant
  - just doesn't incorporate it
- Partially specified model

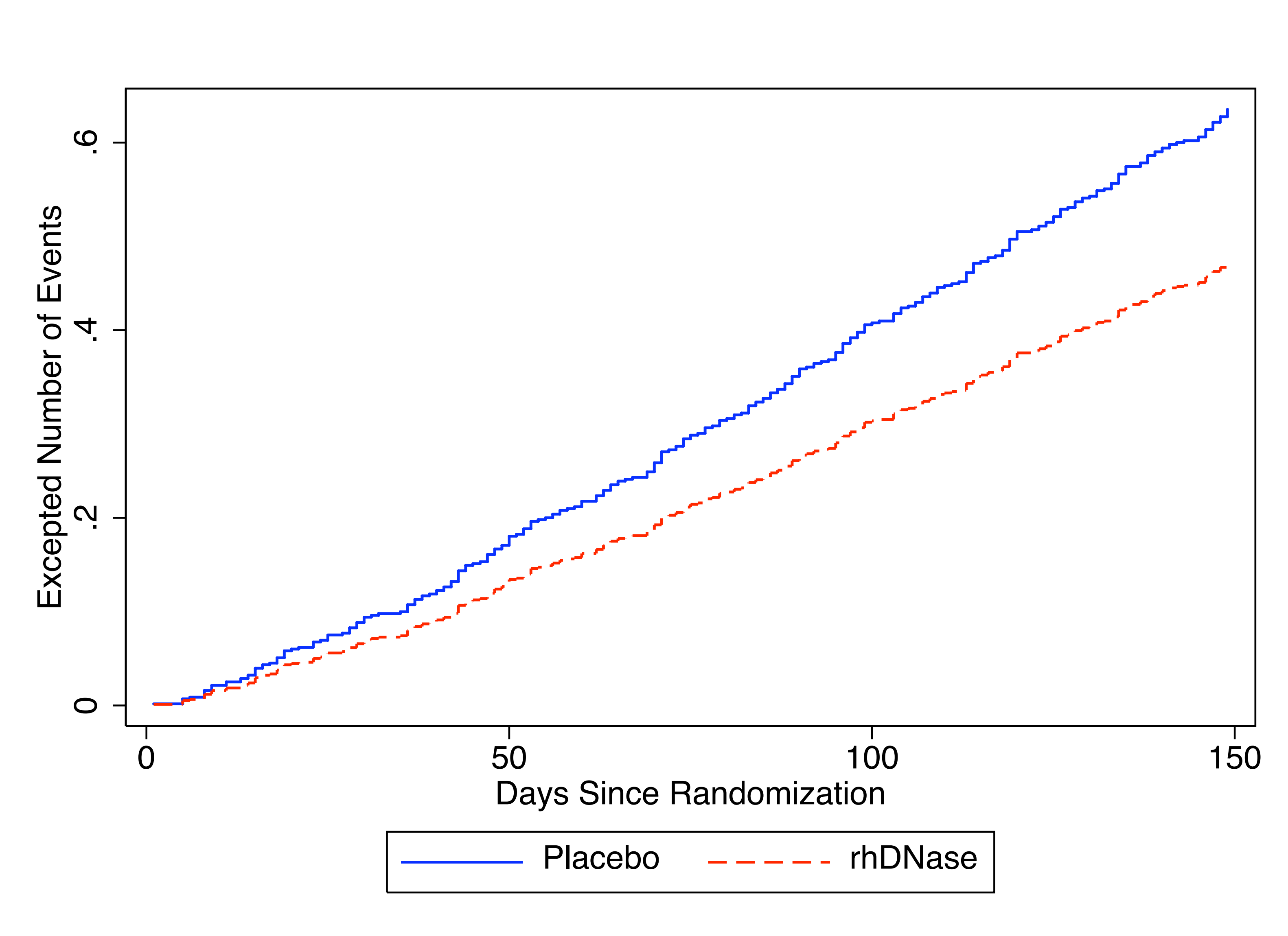
Robust model with rhDNase

```
No. of subjects      =          645                Number of obs   =        956
No. of failures      =          361
Time at risk         =        99779
                                                   Wald chi2(1)    =       4.89
Log pseudo-likelihood =   -2296.4756               Prob > chi2     =     0.0270

                              (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .7441653   .0994231    -2.21   0.027     .5727248    .9669252
------------------------------------------------------------------------------
```

Robust model with rhDNase and FEV

```
No. of subjects       =          645                Number of obs   =        956
No. of failures       =          361
Time at risk          =        99779
                                                    Wald chi2(2)    =     111.74
Log pseudo-likelihood =    -2231.831                Prob > chi2     =     0.0000

                               (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          rx |   .8032687   .0912557    -1.93   0.054     .6429241    1.003603
        fev1 |   .8261597    .015506   -10.17   0.000     .7963208    .8571167
------------------------------------------------------------------------------
```

Mean Events Graph



Another Approach

- Examine Gap Times $(S_1, \ldots, S_k)$
- Look at covariate effects
- Similar in spirit to WLW
  - $S_k = T_k - T_{k-1}$ (gap times)
  - T_k (WLW)

One approach

- Build separate Cox models

$$\lambda_S(t|Z(t)) = \lim_{\Delta \downarrow 0} \frac{\text{pr}\{t + \Delta > S_k \geq t | S_k \geq t, Z(t)\}}{\Delta}$$

$$\lambda_S(t|Z(t)) = \exp(\beta^T Z(t))$$

- This has biiiig problems

The rub

- Typically
- $(S_1, \ldots, S_k)$ are correlated
- Suppose subject is followed over $[0, \tau]$
- Censoring time for S_2 is $\tau - \min(S_1, \tau)$
- Censoring not independent of failure
- Lin proposes some approaches

I’ve neglected

- Prentice, Williams, Petersen
  - Full intensity approach with stratification
- Renewal models for dealing with gaps
- Panel count data
  - periodic measures of total events
- Left truncation

Dealing with Death

- Observation could be cut short by death
- A reasonable framework is to model
  - death hazard &

    $E\{N(U \wedge \tau)\}$
  - where τ is some maximum time
  - Ghosh and Lin (2000)

Some Advice

- Marginal intensity model
  - Interpretable
  - Easy to fit
  - Well-attuned to clinical trials
  - very GEE like
- Identical to model for $E\{N(t)|Z\}$
  - when covariates are time-fixed

More Advice

- Full intensity model
  - Difficult to model dependence
  - Not ideal for clinical trials
- WLW
  - Parameters hard to interpret
  - Uses total time for all events

Partly Conditional Models

- Interesting alternative by Pepe and Cai
- Models rate conditional on some hx
  - Not all history
  - Avoids model mispecification
- Sandwich estimator for variance

Some Good References

- Cook & Kalbfleisch. *Statist Meth in Med Research* 11:141-66, 2002.
- Wei & Glidden. *Statist Med.* 16: 833-9, 1997
- Hougaard. *Analysis of Multivariate Survival Data*, 2000

Thanks to

- Estie
- Tor