Robust Tests for Trials with Recurrent Events Occuring Over Multiple Treatment Periods

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Outline

- Introduction
- Relative Efficiency Considerations
- Semiparametric Methods
- Simulation Studies
- Application
- General Remarks

Joint work with Wei Wei (University of Michigan)

BACKGROUND

Trials are increasingly often designed based on counts or recurrent events.

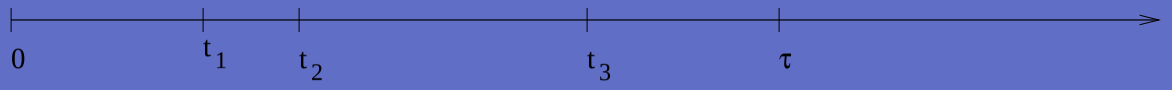
- premature ventricular contractions [Farewell and Sprott, 1988]
- episodes of transient myocardial ischemia [ACIP Investigators, 1992]
- seizures in epilepsy patients [Thall and Vail, 1988]
- asthma exacerbations [Sears et al, 1992]
- vasovagal syncope [Connelly et al, 2002]

Analyses are typically based on robust marginal methods.

- Wei, Lin Weissfeld (1989)
- Andersen and Gill (1982)
- Lawless and Nadeau (1995)

OBJECTIVE : To consider whether more powerful robust tests for treatment effects can be developed in settings with multiple treatment periods.

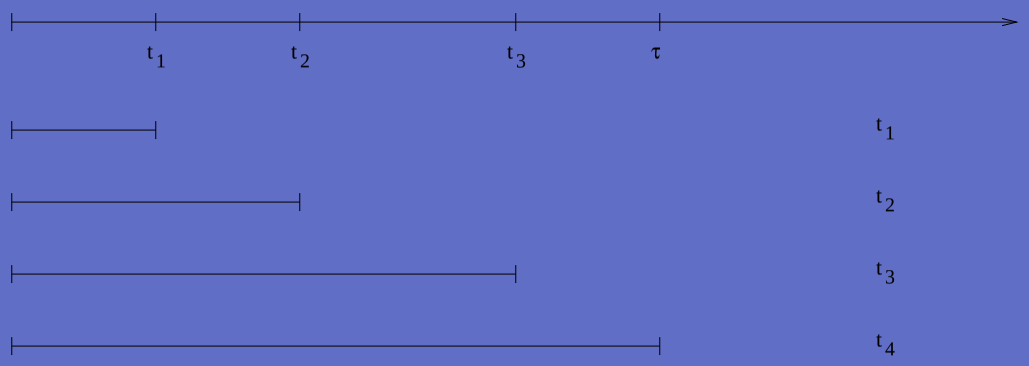
TIMELINE DIAGRAM WITH RECURRENT EVENTS



With recurrent events:

- events are all of the same type and hence of "equal importance"
- examples include
  - epileptic attacks
  - asthma attacks
  - respiratory exacerbations in cystic fibrosis
- $t_1 =$ time of 1st event; $t_2 =$ time of 2nd event; $t_3 =$ time of 3rd event . . .
- subsequent event times are right censored

METHODS BASED ON MULTIVARIATE FAILURE TIME DATA (Wei, Lin and Weissfeld, 1989)



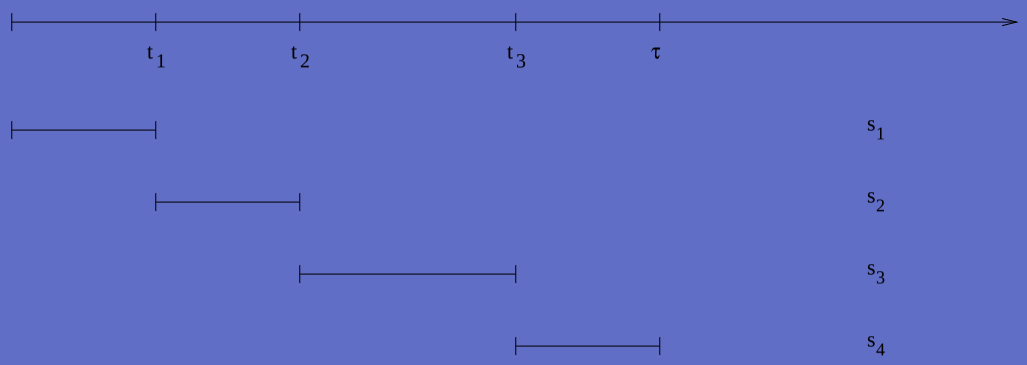
Developed for settings in which

- correlated failure times with events different in nature
- No ordering among event types

EXAMPLES

- t_1 = vertebral compression
- t_1 = infection
- t_2 = vertebral fracture
- t_2 = graft rejection episode
- t_3 = non-vertebral fracture
- t_3 = graft versus host disease

ANALYSES BASED ON INTER-EVENT TIMES (Aalen and Husebye, 1991)

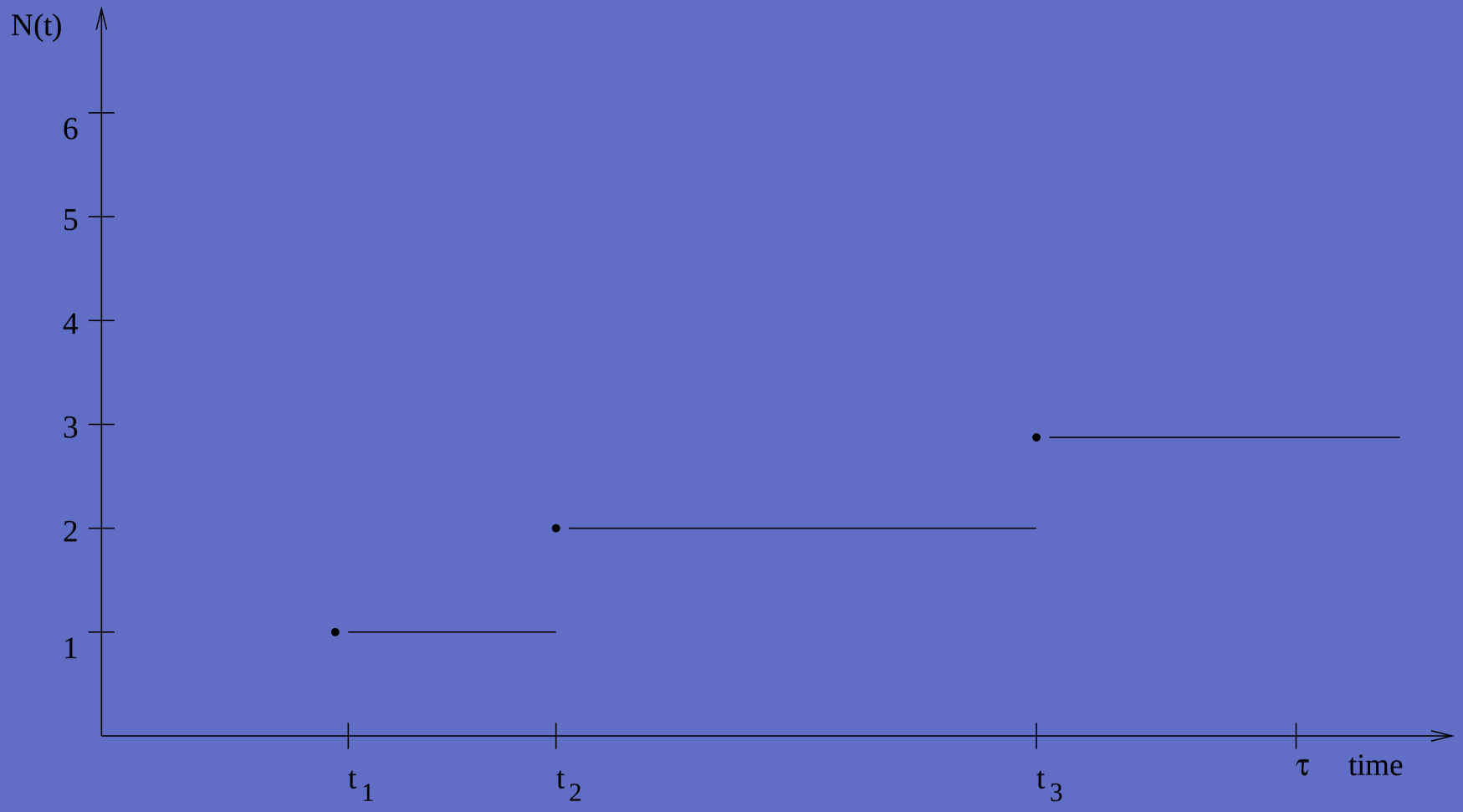


QUESTION: Under what model assumptions should analyses based on the inter-event times be carried out in the context of randomized controlled trials?

ANSWER: Never.

- Dependent censoring arises for second and subsequent gaps
- Selection effects arise for second and subsequent gaps.
- Randomization does not protect inferences for second and subsequent gaps.

COUNTING PROCESS REPRESENTATION OF RECURRENT EVENTS



METHODS BASED ON RATE FUNCTIONS (Andersen and Gill, 1982; Lawless and Nadeau, 1995)

- τ_i denotes the duration of follow-up for subject i, $i = 1, \ldots, I$
- $\{N_i(s), 0 \leq s\}$ is the counting process for events
- $Y_i(s) = I(s < \tau_i)$ is the "at risk" indicator
- Let $\lambda(t)dt = E(dN(t)) = P(dN(t) = 1)$ be the rate function evaluated at time t
- $\lambda(t)$ is a marginal quantity (i.e. unlike and intensity function, it is not conditional on the process history)
- For Poisson processes, the rate function is the same as the intensity function
- An unbiased estimate of $\lambda(t)$ is given by

$$\hat{\lambda}(t)dt = \frac{dN_.(t)}{Y_.(t)}$$

where

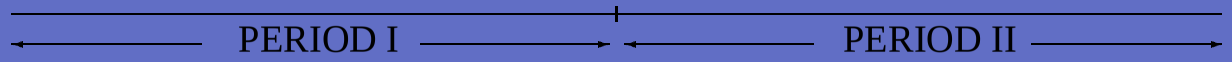
$dN_.(t) = \sum_{i=1}^{I} dN_i(t)$ is the total number of events at t

$Y_.(t) = \sum_{i=1}^{I} Y_i(t)$ is the size of the risk set at t

SET-UP OF INTEREST

Frequently baseline data are available on the incidence of events for a fixed period prior to the start of therapy.

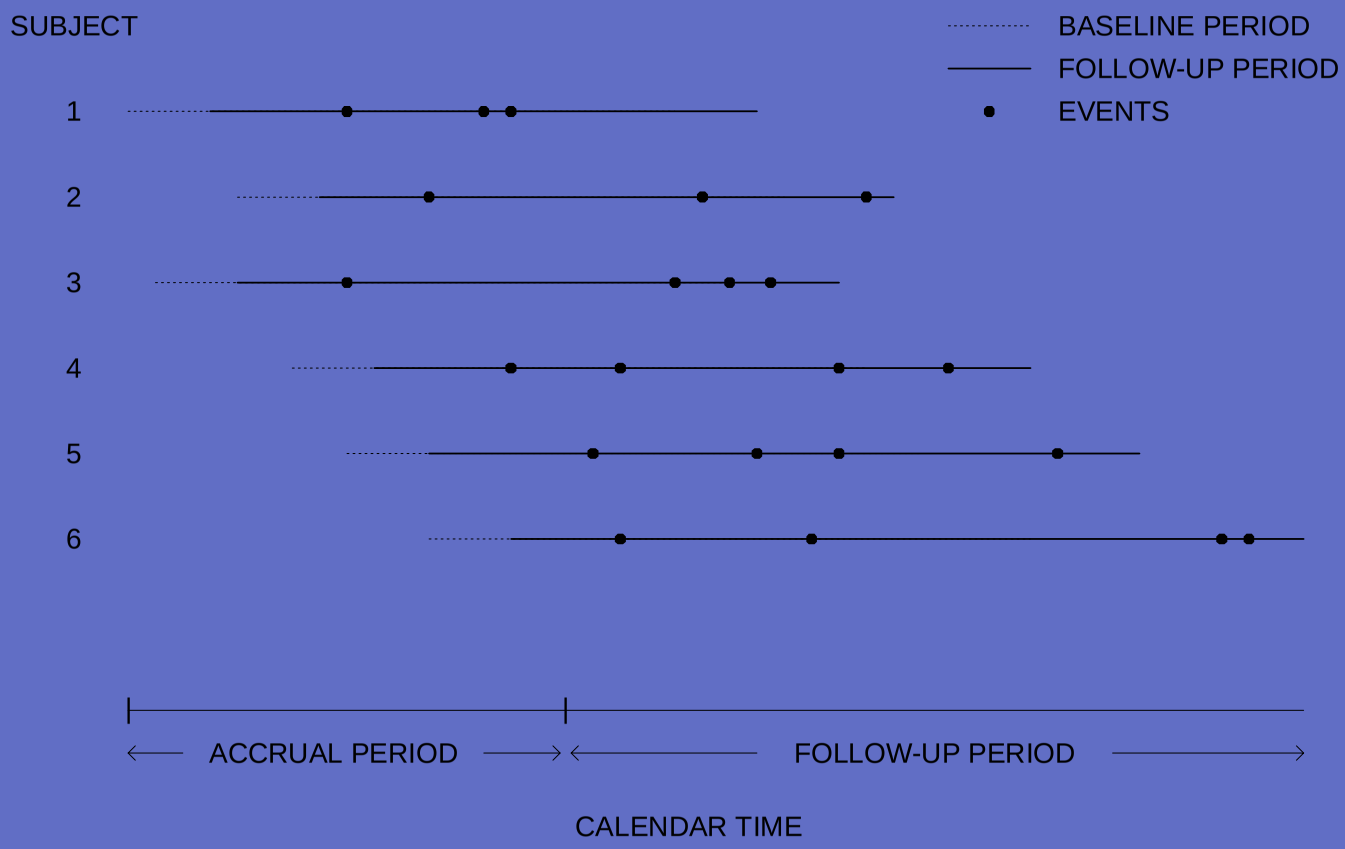
Alternatively, subjects may be observed over multiple treatment periods involving different medications or interventions.



Here we focus on the first scenario.

- We adopt a working assumption of mixed Poisson processes.
- Robust variance estimates will be developed.

RECURRENT EVENT DATA WITH BASELINE COUNTS



NOTATION

	Baseline Period $(-\tau_B, 0]$	Follow-up Period $(0, \tau_i]$
Data	$M_i, i = 1, \ldots, I$	$t_{i1} < \cdots < t_{iN_i},\ N_i(\tau_i), i = 1, \ldots, I$
Conditional Mean/Rate	$E(M_i \mid u_i) = u_i \mu$	$\lambda_i(s \mid u_i) = u_i \lambda_0(s) \exp(\beta x_i)$
Population Mean	$E(M_i) = \mu$	$\Lambda_i(t) = \int_0^t \lambda_0(s) \exp(\beta x_i) ds = \Lambda_0(t) \exp(\beta x_i)$
Random Effect	$u_i \sim$ Gamma with $E(u_i) = 1, \quad \text{var}(u_i) = \phi$	

Marginal Negative Binomial Model (Lawless, 1987)

$$P(N_i = n_i; \beta, \lambda_0(\cdot), \phi) = \frac{\Gamma(\phi^{-1} + n_i)}{\Gamma(\phi^{-1}) n_i!} \left(\frac{1}{1 + \Lambda_i \phi}\right)^{\phi^{-1}} \left(\frac{\Lambda_i \phi}{1 + \Lambda_i \phi}\right)^{n_{i2}} \prod_{j=1}^{n_i} \frac{\lambda_0(t_{ij})}{\Lambda_0(\tau_i)} \tag{1}$$

Conditional Negative Binomial Model (Cook and Wei, 2003)

$$P(\boldsymbol{t_i}, N_i = n_i \mid m_i; \beta, \mu, \lambda_0(\cdot), \phi) = \frac{\Gamma(\phi^{-1} + m_i + n_i)}{\Gamma(\phi^{-1} + m_i) n_i!} \frac{(1 + \mu\phi)^{\phi^{-1} + m_i} (\Lambda_i \phi)^{n_i}}{(1 + (\mu + \Lambda_i)\phi)^{\phi^{-1} + m_i + n_i}} \cdot \prod_{j=1}^{n_i} \frac{\lambda_0(t_{ij})}{\Lambda_0(\tau_i)} \tag{2}$$

AN ALTERNATIVE CONDITIONING ARGUMENT

$$\begin{aligned} P(m_i, \boldsymbol{t}_i, n_i | u_i; \beta, \mu, \lambda_0(\cdot)) &= \frac{(u_i\mu)^{m_i} \exp(-u_i\mu)}{m_i!} \cdot \frac{(u_i\Lambda_i(\tau_i))^{n_i} \exp(-u_i\Lambda_i(\tau_i))}{n_i!} \prod_{j=1}^{n_i} \frac{\lambda_0(t_{ij})}{\Lambda_0(\tau_i)} \\ &= \frac{u_i^{m_i+n_i} \mu^{m_i} (\Lambda_i(\tau_i))^{n_i} \exp(-u_i(\mu + \Lambda_i(\tau_i)))}{m_i!\, n_i!} \prod_{j=1}^{n_i} \frac{\lambda_0(t_{ij})}{\Lambda_0(\tau_i)} \end{aligned}$$

Since the Poisson distribution is in the exponential family

1. $m_i + n_i$ is sufficient for u_i
2. If we condition on $m_i + n_i$, we will eliminate u_i

If we let $\boldsymbol{\theta} = (\beta, \mu, \lambda_0(\cdot))'$, we obtain a conditional binomial model

$$P(m_i, n_i | m_i + n_i; \boldsymbol{\theta}) = \begin{pmatrix} m_i + n_i \\ m_i \end{pmatrix} \left(\frac{\mu}{\mu + \Lambda_i(\tau_i)}\right)^{m_i} \left(\frac{\Lambda_i(\tau_i)}{\mu + \Lambda_i(\tau_i)}\right)^{n_i} \tag{3}$$

QUESTIONS

1. What is the efficiency compared to marginal and conditional/joint analyses for mixed Poisson processes?
2. Can this approach be made robust?

ASYMPTOTIC VARIANCES

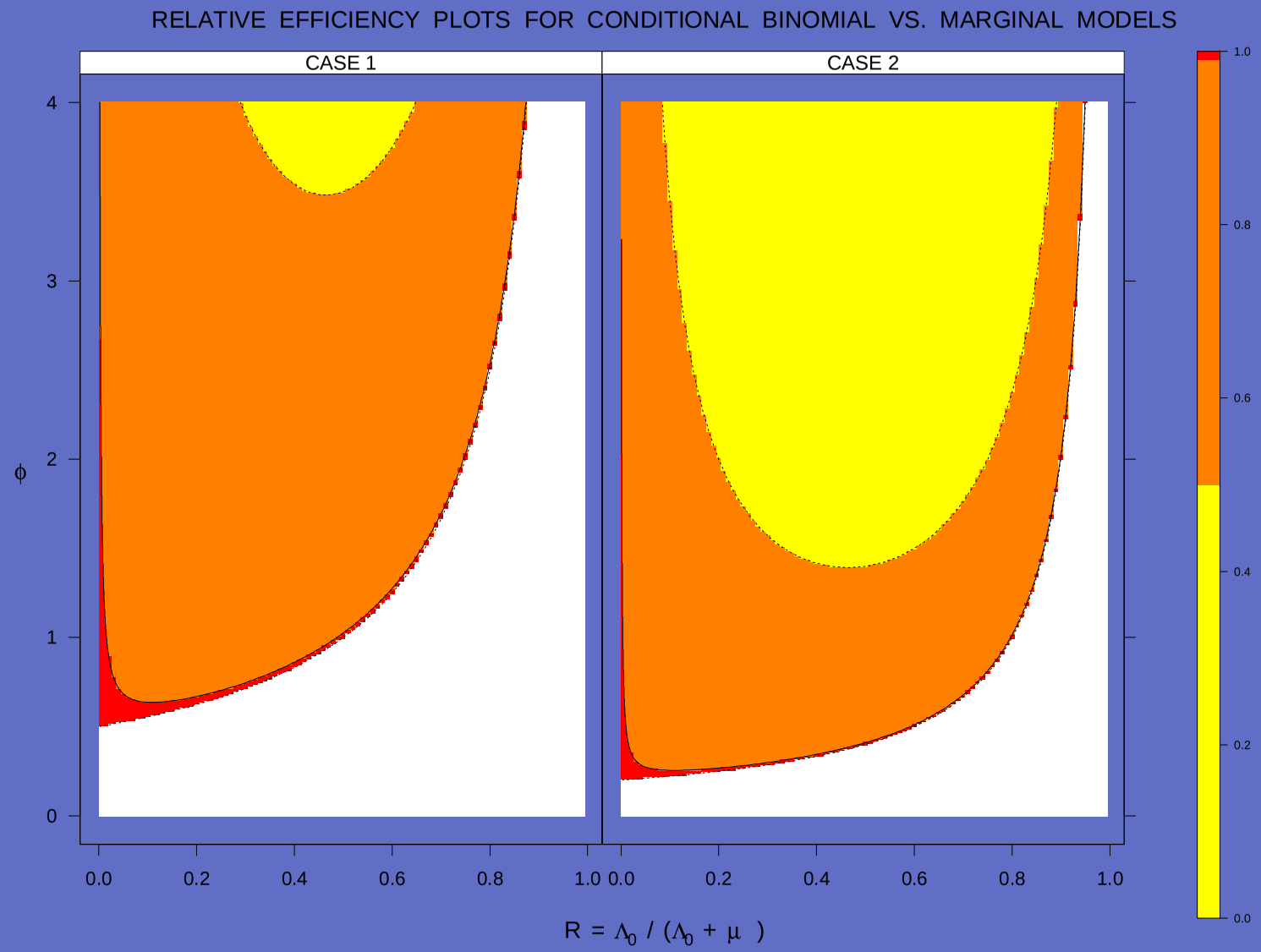
Suppose $\tau_B = \tau_i = \tau = 1, i = 1, \ldots, I$, and denote $\Lambda_0(\tau) = \Lambda_0$.

Then, based on the Fisher information matrices, we find

Marginal Negative Binomial	$\text{asvar}(\widehat{\beta}) = \frac{2}{m}(2\phi + \Lambda_0^{-1}(1 + \exp(\beta))^{-1})$
Conditional Negative Binomial	$\text{asvar}(\widehat{\beta}) = \frac{2}{m}\frac{(\mu\phi(1 + \exp(\beta)) + 1 + (2\Lambda_0\phi + 1)\exp(\beta))}{\lambda_0(1 + \mu\phi)\exp(\beta)}$
Conditional Binomial	$\text{asvar}(\widehat{\beta}) = \frac{2}{m}(2\mu^{-1} + \Lambda_0^{-1}(1 + \exp(\beta))^{-1})$

- From these expressions we can derive asymptotic relative efficiencies.
- Here we consider mixed Poisson processes and the following parameter configurations
  - $\Lambda_0 + \mu = 2$ (CASE 1) and 5 (CASE 2)
  - $0 \leq \phi \leq 4$
  - Define $R = \Lambda_0/(\Lambda_0 + \mu)$ and let $0 \leq R \leq 1$
  - Examine RE contours 50%, 99% 100%

RELATIVE EFFICIENCY PLOTS



NOTATION

- $\{N_i(s), 0 \leq s\}$ is the counting process for events after treatment
- $Y_i(s) = I(s < \tau_i)$ is "at risk" indicator

A ROBUST PSEUDO-SCORE STATISTIC (Andersen and Gill, 1982; Cook, Lawless and Nadeau, 1996)

$$\sum_{i=1}^{I} \int_0^{\tau} Y_i(s) \{dN_i(s) - d\Lambda_0(s) \exp(\beta x_i)\} x_i$$

Inserting the Breslow estimate

$$d\hat{\Lambda}_0(s) = \frac{\Sigma_{i=1}^{I} Y_i(s) dN_i(s)}{\Sigma_{i=1}^{I} Y_i(s) \exp(\beta x_i)}$$

for $d\Lambda_0(s)$ gives

$$U(\beta) = \sum_{i=1}^{I} \int_0^{\tau} Y_i(s) W_i(\beta, u) dN_i(u) \tag{4}$$

where

$$W_i(\beta, u) = x_i - \frac{\Sigma_{j=1}^{I} Y_j(u) \exp(x_j \beta) x_j}{\Sigma_{j=1}^{I} Y_j(u) \exp(x_j \beta)}$$

A robust sandwich type variance estimate can be obtained.
A robust test statistic ($H_0 : \beta = 0$) can be derived from (4) by noting that

$$\frac{\sqrt{I}^{-1} U(0)}{\widehat{\text{var}}(\sqrt{I}^{-1} U(0))} \sim N(0,1) \text{ asymptotically under } H_0.$$

ANOTHER ROBUST PSEUDO-SCORE STATISTIC (Cook, Wei and Yi, 2003)

Let $\boldsymbol{\theta} = (\beta, \psi)'$ and $\psi = (\mu, \lambda_0)'$

$$\begin{aligned}
\ell(\boldsymbol{\theta}) &= \sum_{i=1}^{I} n_i \log(\Lambda_i(\tau_i)/\mu) + (m_i + n_i \log(1/(1+\Lambda_i(\tau_i)/\mu)) \\
U_1(\boldsymbol{\theta}) &= \sum_{i=1}^{I} (n_i - (m_i + n_i)\left(\frac{\Lambda_i(\tau_i)}{\mu + \Lambda_i(\tau_i)}\right)) x_i \\
U_{21}(\boldsymbol{\theta}) &= \sum_{i=1}^{I} (m_i - \mu) \\
U_{22}(\boldsymbol{\theta}) &= \sum_{i=1}^{I} \int_0^t Y_i(s)(dN_i(s) - d\Lambda_i(s))
\end{aligned}$$

Then,

$$\frac{\sqrt{I}^{-1} U_1(\beta^0, \tilde{\psi})}{\sqrt{\widehat{var}(\sqrt{I}^{-1} U_1)}} \sim N(0,1) \quad \text{asymptotically}$$

where (Breslow, 1990),

$$\widehat{Var}(\sqrt{I}^{-1} U_1) = B_{11} - A_{12}[A_{22}]^{-1} B_{21} - B_{12}[A_{22}^{-1}]^t[A_{12}]^t + A_{12}[A_{22}]^{-1} B_{22}[A_{22}^{-1}]^t[A_{12}]^t$$

$$B_{11} = \sum_{j=1}^{I} U_{1j}^2(\beta^0, \psi) \quad B_{12} = \Sigma_{j=1}^{I} U_{1j}(\beta^0, \tilde{\psi}) \mathbf{U}_{2j}(\beta^0, \tilde{\psi}) = (B_{21})^t \quad B_{22} = \sum_{j=1}^{I} \mathbf{U}_{2j}(\beta^0, \tilde{\psi}) \mathbf{U}_{2j}^t(\beta^0, \tilde{\psi})$$

$$A_{12} = \Sigma_{j=1}^{I} \partial U_{1j}/\partial\psi\Big|_{(\beta^0, \tilde{\psi})} \qquad A_{22} = \sum_{j=1}^{I} \partial \mathbf{U}_{2j}/\partial\psi\Big|_{(\beta^0, \tilde{\psi})}$$

MIXED POISSON PROCESSES

- Randomize subjects to treatment or control conditions such that

$$x_i = 1 \text{ w.p. } 0.5 \text{ and } x_i = 0 \text{ otherwise.}$$

- $u_i \sim$ Gamma with $E(u_i) = 1$ and $\text{var}(u_i) = \phi$ $[\phi = 0.5, 1, 2, 4]$
- Simulate baseline counts and follow-up event times with $\tau_1 = \tau_2 = 1$, according to
  - $M_i|u_i \sim$ Poisson with mean $u_i\mu$ $[\mu = 1, 4]$
  - $\{N_i(u), u > 0\}\,|u_i \sim$ Poisson process with rate $\lambda_i(s|u_i) = u_i\lambda_0 \exp(\beta x_i)$ $[\lambda_0 = 1, 4]$
  - small, moderate and large treatment effects $[\exp(\beta) = 0.50, 0.70, 0.90]$

- Subjects are censored according to an exponential distribution to give 0 or 10% censoring.

Empirical Type I error rates of robust marginal and conditional pseudo-score statistics under mixed Poisson models ($\mu = 1$)

			$I = 100$				$I = 200$				$I = 400$			
λ_0	ϕ	% CENS	R_1	R_2	M	CB	R_1	R_2	M	CB	R_1	R_2	M	CB
1	0.5	10%	0.048	0.057	0.068	0.057	0.041	0.042	0.059	0.05	0.046	0.046	0.058	0.055
1	0.5	0%	0.05	0.053	0.074	0.052	0.049	0.052	0.048	0.056	0.061	0.063	0.054	0.064
1	1	10%	0.051	0.058	0.08	0.056	0.054	0.057	0.069	0.051	0.052	0.054	0.058	0.048
1	1	0%	0.053	0.057	0.073	0.047	0.05	0.053	0.064	0.047	0.055	0.055	0.051	0.05
1	2	10%	0.057	0.061	0.089	0.053	0.049	0.05	0.07	0.054	0.051	0.052	0.065	0.046
1	2	0%	0.046	0.051	0.085	0.051	0.044	0.045	0.073	0.059	0.044	0.044	0.061	0.05
1	4	10%	0.052	0.058	0.103	0.044	0.05	0.052	0.083	0.05	0.047	0.048	0.062	0.047
1	4	0%	0.046	0.053	0.114	0.053	0.047	0.05	0.081	0.045	0.059	0.059	0.071	0.051

- R_1 - robust, pooled variance estimates
- R_2 - robust, unpooled variance estimates.
- M - semiparametric marginal
- CB - semiparametric conditional binomial

Empirical power of robust marginal and conditional pseudo-score statistics under mixed Poisson models ($\mu = \lambda_0 = 1$)

			$I = 100$				$I = 200$				$I = 400$			
$\exp(\beta)$	ϕ	% CENS	R_1	R_2	M	CB	R_1	R_2	M	CB	R_1	R_2	M	CB
0.70	0.5	10%	0.263	0.275	0.148	0.215	0.463	0.469	0.256	0.355	0.763	0.763	0.384	0.650
0.70	0.5	0%	0.273	0.284	0.169	0.223	0.464	0.47	0.26	0.371	0.774	0.774	0.446	0.653
0.70	1	10%	0.195	0.209	0.148	0.218	0.371	0.379	0.207	0.35	0.652	0.652	0.342	0.626
0.70	1	0%	0.196	0.21	0.14	0.225	0.368	0.377	0.219	0.405	0.669	0.669	0.352	0.661
0.70	2	10%	0.146	0.159	0.147	0.203	0.262	0.269	0.175	0.344	0.489	0.489	0.261	0.624
0.70	2	0%	0.153	0.164	0.163	0.216	0.27	0.276	0.182	0.387	0.506	0.506	0.277	0.649
0.70	4	10%	0.094	0.102	0.135	0.197	0.183	0.187	0.155	0.348	0.314	0.314	0.203	0.610
0.70	4	0%	0.085	0.09	0.151	0.193	0.176	0.178	0.164	0.365	0.343	0.343	0.205	0.657

- R_1 - robust, pooled variance estimates
- R_2 - robust, unpooled variance estimates.
- M - semiparametric marginal
- CB - semiparametric conditional binomial

MIXED RENEWAL PROCESSES

- Randomize subjects to treatment or control conditions such that

$$x_i = 1 \text{ w.p. } 0.5 \text{ and } x_i = 0 \text{ otherwise.}$$

- $u_i \sim$ Gamma with $E(u_i) = 1$ and $\text{var}(u_i) = \phi$ $[\phi = 0.10, 0.20]$
- Let V_{ij} denote the inter-arrival time between the (j-1)st and jth event for subject i
  - $V_{ij}|u_i \sim \text{Gamma}(\text{shape} = \theta, \text{scale} = \pi_i)$ where $\pi_i = u_i \pi_0 \exp(\beta x_i)$ $[\theta = 2]$
  - Here, $E(V_{ij}|u_i) = \theta \pi_i$ $[\pi_0 = 1/2, 1/8]$
  - small, moderate and large treatment effects $[\exp(\beta) = 0.70, 0.80, 0.90]$
- Again we consider no censoring and light (10%) censoring

Empirical type I error rates of robust marginal and conditional pseudo-score statistics under mixed renewal models ($\theta = 2$)

			$m = 100$			$m = 200$			$m = 400$		
π_0	ϕ	% CENS	R_1	R_2	CB	R_1	R_2	CB	R_1	R_2	CB
0.5	0.1	10%	0.052	0.055	0.055	0.056	0.056	0.053	0.054	0.057	0.052
0.5	0.1	0%	0.055	0.06	0.05	0.055	0.055	0.046	0.057	0.059	0.046
0.5	0.2	10%	0.049	0.054	0.059	0.037	0.037	0.047	0.044	0.044	0.054
0.5	0.2	0%	0.058	0.062	0.048	0.062	0.062	0.046	0.048	0.05	0.051
0.125	0.1	10%	0.051	0.057	0.064	0.046	0.047	0.051	0.053	0.055	0.042
0.125	0.1	0%	0.046	0.052	0.053	0.048	0.05	0.056	0.055	0.058	0.049
0.125	0.2	10%	0.044	0.05	0.053	0.05	0.051	0.044	0.048	0.048	0.048
0.125	0.2	0%	0.049	0.053	0.049	0.057	0.061	0.046	0.058	0.059	0.05

- R_1 - robust, pooled variance estimates
- R_2 - robust, unpooled variance estimates.
- CB - semiparametric conditional binomial

Empirical power of robust marginal and conditional pseudo-score statistics under mixed renewal processes ($\theta = 2$, $\pi_0 = 1/2$, mean inter-event time is 1)

			$I = 100$			$I = 200$			$I = 400$		
$\exp(-\beta)$	ϕ	% CENS	R_1	R_2	CB	R_1	R_2	CB	R_1	R_2	CB
0.90	0.1	10%	0.102	0.11	0.073	0.153	0.16	0.101	0.24	0.242	0.174
0.90	0.1	0%	0.096	0.104	0.077	0.151	0.154	0.117	0.237	0.24	0.184
0.90	0.2	10%	0.089	0.096	0.081	0.127	0.129	0.114	0.215	0.218	0.184
0.90	0.2	0%	0.092	0.098	0.08	0.13	0.133	0.90	0.225	0.228	0.198
0.80	0.1	10%	0.248	0.261	0.167	0.447	0.456	0.309	0.738	0.742	0.55
0.80	0.1	0%	0.255	0.267	0.196	0.45	0.453	0.317	0.761	0.764	0.582
0.80	0.2	10%	0.219	0.237	0.2	0.385	0.394	0.353	0.666	0.67	0.604
0.80	0.2	0%	0.209	0.228	0.215	0.394	0.405	0.38	0.684	0.688	0.627
0.70	0.1	10%	0.505	0.519	0.397	0.81	0.816	0.642	0.984	0.984	0.914
0.70	0.1	0%	0.525	0.543	0.386	0.839	0.846	0.678	0.986	0.986	0.913
0.70	0.2	10%	0.431	0.444	0.416	0.752	0.761	0.702	0.958	0.96	0.93
0.70	0.2	0%	0.47	0.484	0.441	0.751	0.76	0.709	0.96	0.96	0.941

- R_1 - robust, pooled variance estimates
- R_2 - robust, unpooled variance estimates.
- CB - semiparametric conditional binomial

Empirical power of robust marginal and conditional pseudo-score statistics under mixed renewal processes ($\theta = 2$, $\pi_0 = 1/8$, mean inter-event time is 0.25)

			$I = 100$			$I = 200$			$I = 400$		
$\exp(-\beta)$	ϕ	% CENS	R_1	R_2	CB	R_1	R_2	CB	R_1	R_2	CB
0.90	0.1	10%	0.174	0.188	0.171	0.306	0.315	0.284	0.546	0.551	0.547
0.90	0.1	0%	0.185	0.197	0.203	0.343	0.349	0.341	0.571	0.575	0.585
0.90	0.2	10%	0.117	0.125	0.19	0.211	0.218	0.337	0.361	0.366	0.584
0.90	0.2	0%	0.121	0.125	0.192	0.215	0.221	0.365	0.369	0.373	0.612
0.80	0.1	10%	0.566	0.582	0.581	0.864	0.869	0.868	0.993	0.993	0.992
0.80	0.1	0%	0.589	0.606	0.591	0.87	0.874	0.897	0.992	0.992	0.996
0.80	0.2	10%	0.367	0.386	0.603	0.624	0.634	0.884	0.919	0.923	0.994
0.80	0.2	0%	0.404	0.417	0.654	0.664	0.674	0.918	0.918	0.918	0.996
0.70	0.1	10%	0.916	0.925	0.926	0.999	0.999	0.997	1	1	1
0.70	0.1	0%	0.925	0.933	0.938	0.999	0.999	0.998	1	1	1
0.70	0.2	10%	0.745	0.757	0.932	0.951	0.953	0.998	0.999	0.999	1
0.70	0.2	0%	0.75	0.766	0.957	0.964	0.966	1	0.999	0.999	1

- R_1 - robust, pooled variance estimates
- R_2 - robust, unpooled variance estimates.
- CB - semiparametric conditional binomial

ANALYSIS OF AN ASTHMA TRIAL (Ng and Cook, CJS, 1999)

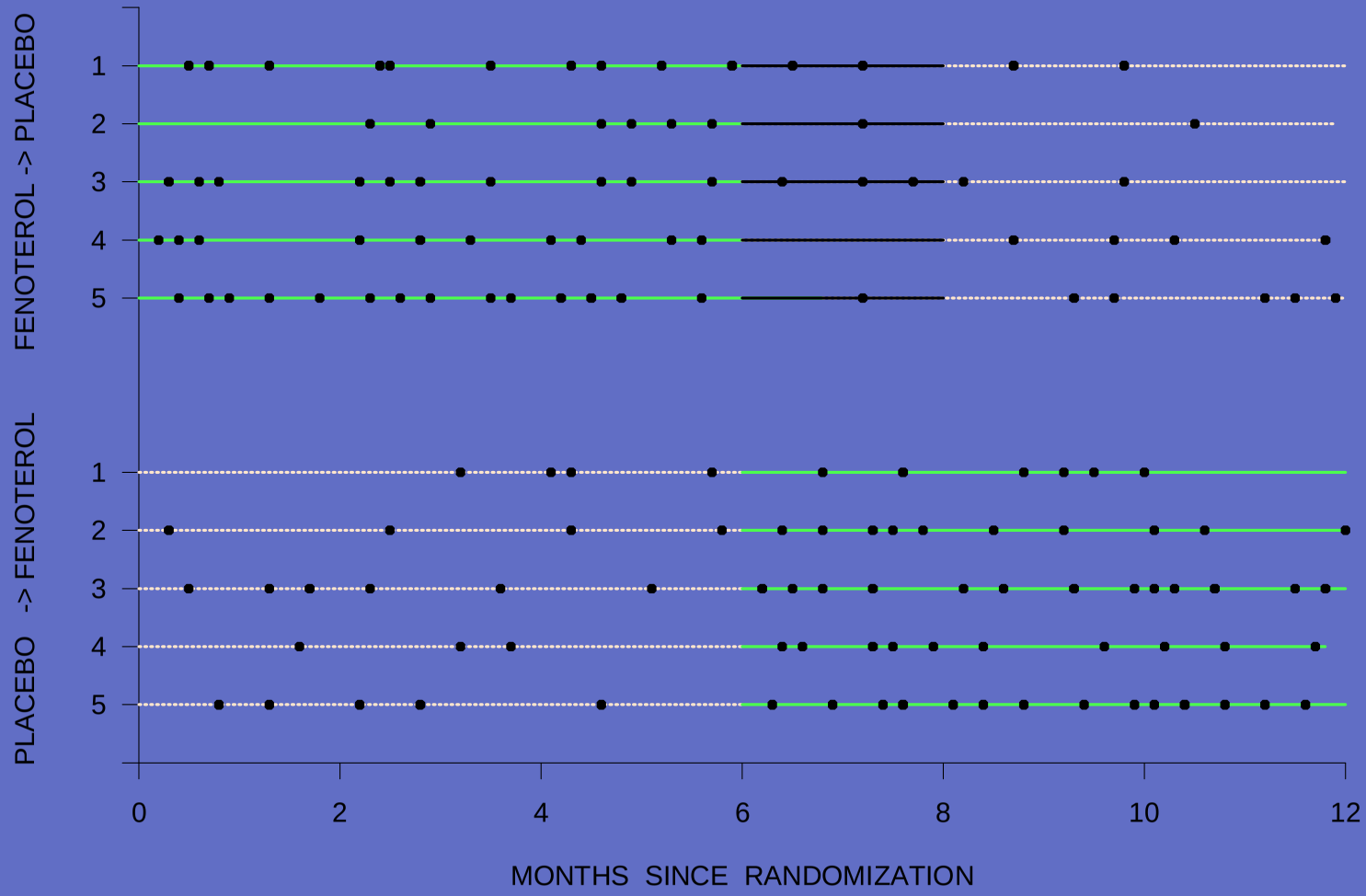
- Crossover trial of fenoterol versus placebo in patients with asthma.
- Intended follow-up for 12 months
  - Period I - six months
  - Period II - six months
  - Possible carry-over effect?
- Evening episodes of coughing are recorded by daily diary
- Carry-over effect modeled for 8 weeks.

Sequence Group	Period I (0,6M)	Wash-out	Period II (6M-12M)	n
A	Fenoterol	NA	Placebo	35 patients
B	Placebo	NA	Fenoterol	29 patients
				64 patients

CHALLENGES

- Cross-overs do not occur exactly on schedule.
- Patients are lost to follow-up leading to variable τ_i's

TIMELINE DIAGRAM FOR ASTHMA CROSSOVER TRIAL



SEMIPARAMETRIC MODEL SPECIFICATION

- τ_i^C is time from trial entry to cross-over
- Δ is duration of time influenced by carry-over
- τ_i is total duration on study
- Let

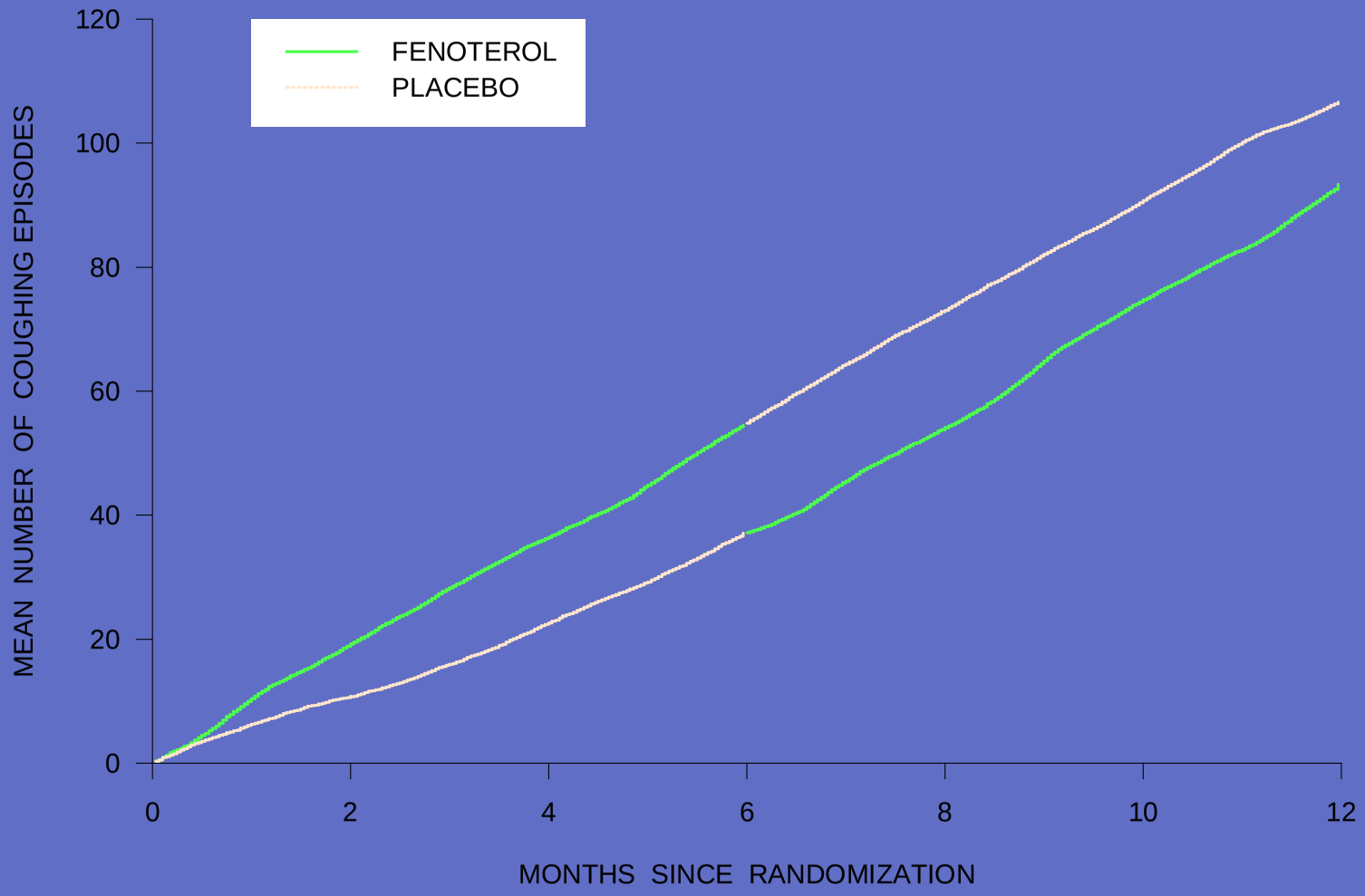
$$x_1(t) = \begin{cases} 1 & \text{if on Fenoterol at time t} \\ 0 & \text{o.w.} \end{cases} \qquad x_2(t) = \begin{cases} 1 & \text{if in Group A and } \tau_i^C < t \leq \tau_i^C + \Delta \\ 0 & \text{o.w.} \end{cases}$$

RATE FUNCTION

$$E(dN(t)|\boldsymbol{x}(t), u) = u\lambda_0(t)\exp(\beta_1 x_1(t) + \beta_2 x_2(t))$$

where

- β_1 denotes the direct treatment effect
- β_2 denotes the carry-over effect


FENOTEROL
PLACEBO
MEAN NUMBER OF COUGHING EPISODES
120
100
80
60
40
20
0
0
2
4
6
8
10
12
MONTHS SINCE RANDOMIZATION

RESULTS FROM MARGINAL AND CONDITIONAL ANALYSES OF ASTHMA DATA

	Andersen-Gill			Our Approach		
	Est.	s.e.	$p-$value	Est.	s.e.	$p-$value
Treatment	-0.2041	0.1267	0.107	-0.2810	0.1075	0.009
Carry-over	-0.0386	0.3283	0.906	-0.2094	0.1550	0.177

GENERALIZATIONS REQUIRED FOR THIS CROSSOVER TRIAL

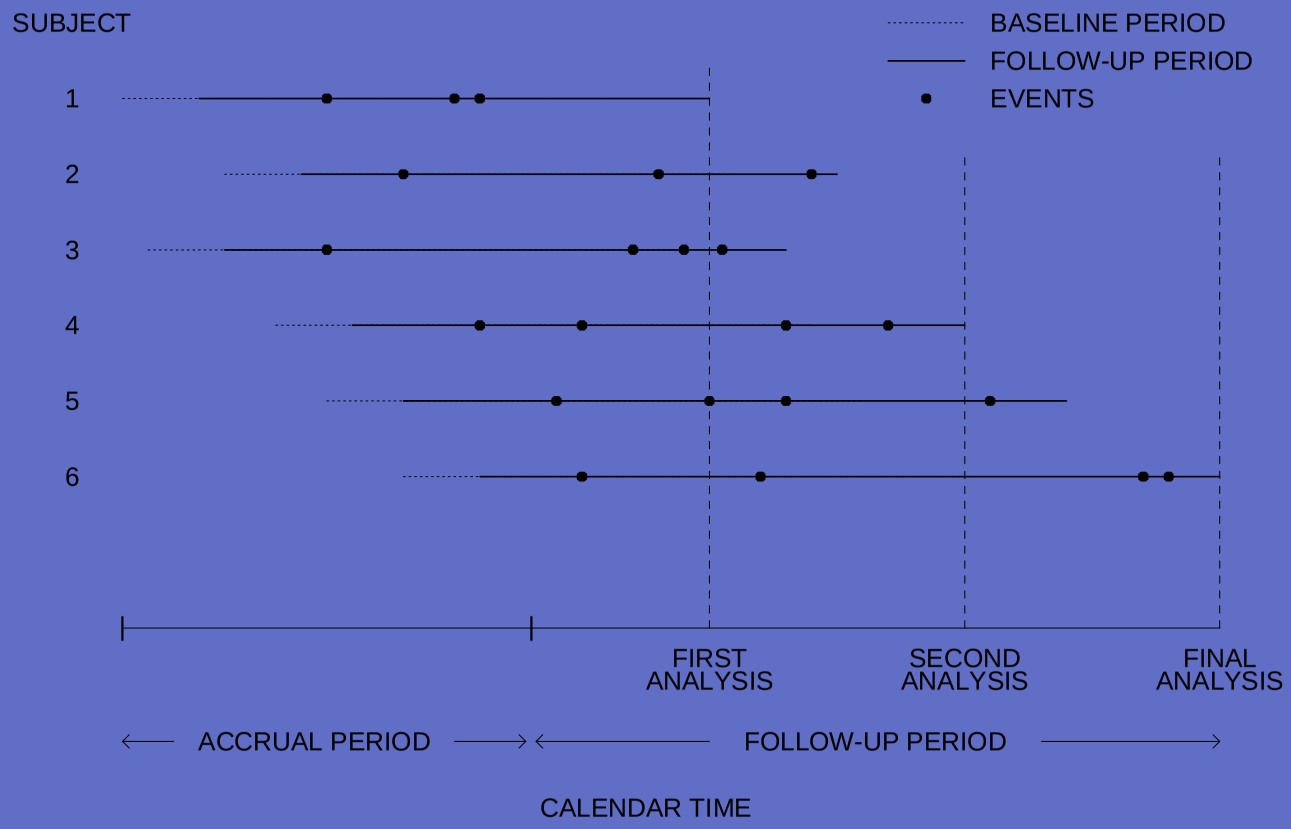
- Dealt with time-varying covariates
- Focus on estimation rather than simply testing due to carry-over effect
- Resulting estimating equations of a conditional "trinomial" form due to three time intervals in Group A

SUMMARY

- In settings with baseline counts and considerable between-patient variability in event rates, gains in efficiency can be realized when conditioning on the total number of events
- Robust variance estimates of pseudo-score statistics provide test statistics with good control of type I error under mixed renewal processes
- Gains in power can be realized over marginal tests in some settings
- Variable follow-up handled under semiparametric models for post-randomization response

FUTURE WORK

- Extensions to cross-over trials with possible carry-over
- Interim monitoring
- Design


SUBJECT
BASELINE PERIOD
FOLLOW-UP PERIOD
EVENTS
1
2
3
4
5
6
FIRST ANALYSIS
SECOND ANALYSIS
FINAL ANALYSIS
ACCRUAL PERIOD
FOLLOW-UP PERIOD
CALENDAR TIME