Statistical Modeling of Carryover Effects After Cessation of Treatments

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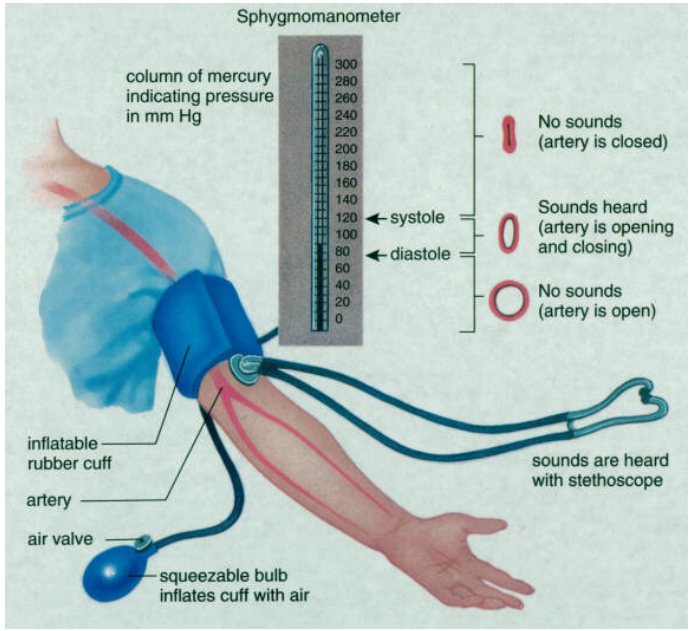
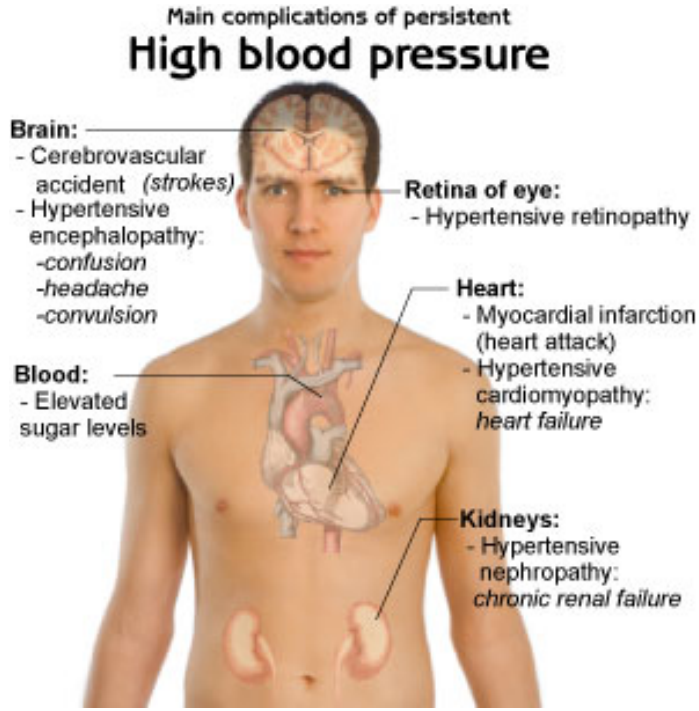
Hypertension



For our purposes high blood pressure (BP) is defined:

- having systolic BP above 140 mm Hg
- top measurement

Dangers and Solutions of Hypertension



- Lifestyle interventions - ineffective
- Medication - effective

Medications

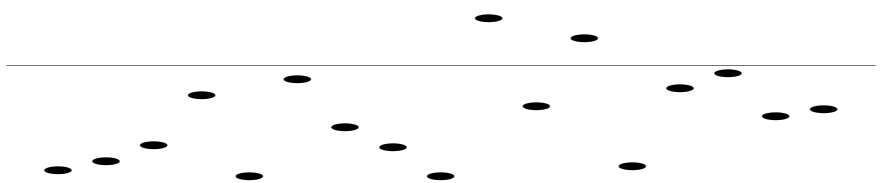
- Lower systolic blood pressure (BP) by about 10 mm Hg
- Sales are approximately $35 billion per year
- When BP is lowered through medication you generally stay on these for life
- Do the drugs have benefits after they have lowered your BP?

AstraZeneca's TRial Of Preventing HYpertension (TROPHY) examined this question — Do the effects of candesartan continue after treatment has ceased?

TROPHY

Trial Of Preventing HYpertension

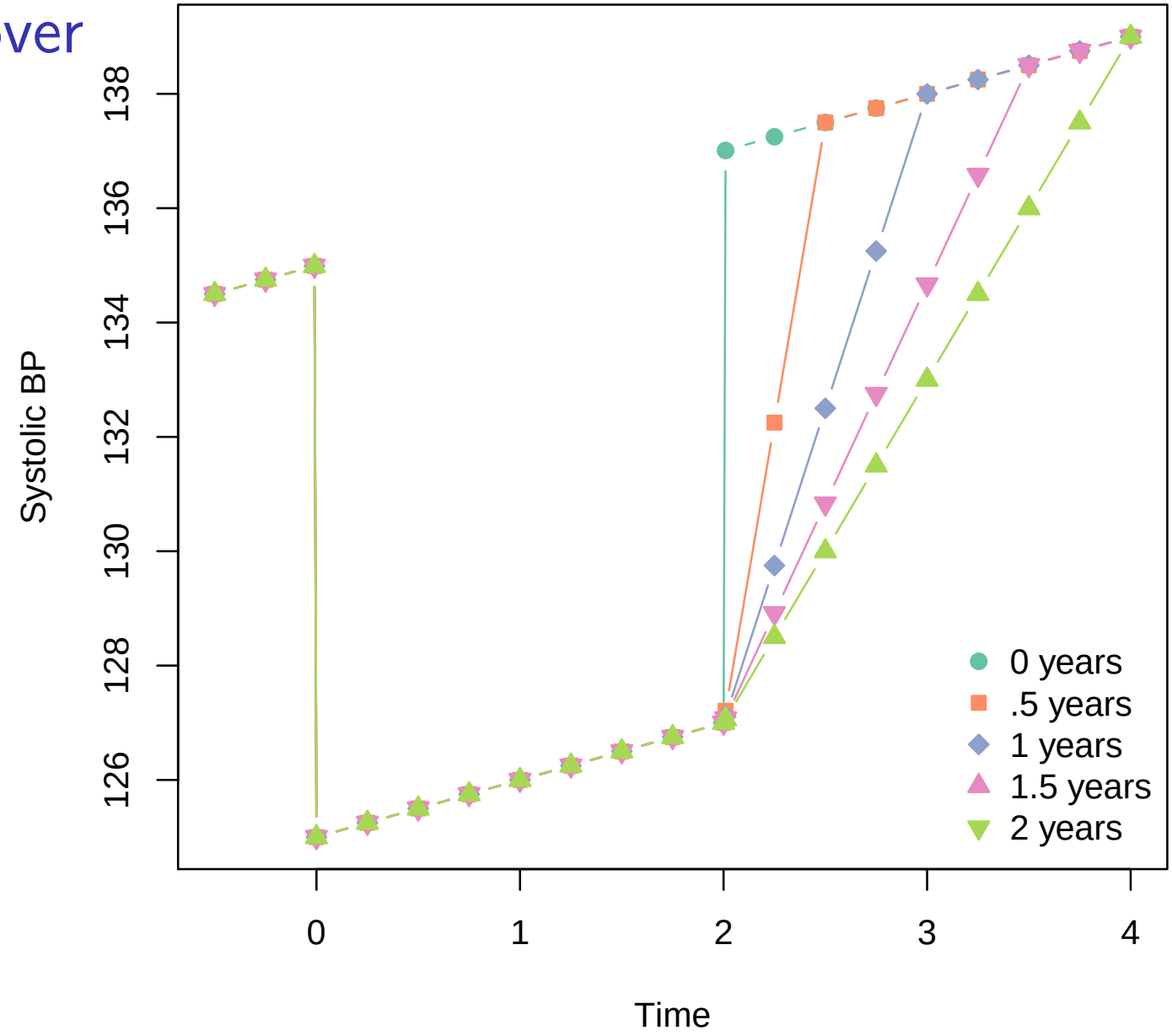
- 809 participants with systolic blood pressure (BP) 130 - 139 mm Hg randomised
- Treatment - two years, then two year follow up
- Placebo - 4 years of monitoring
- Measurements every 3 months
- 69% of those diagnosed with hypertension did so by having 3 measurements above 140 mm Hg
- Treatment 53.2%, Placebo 63.0% cumulative diagnosis

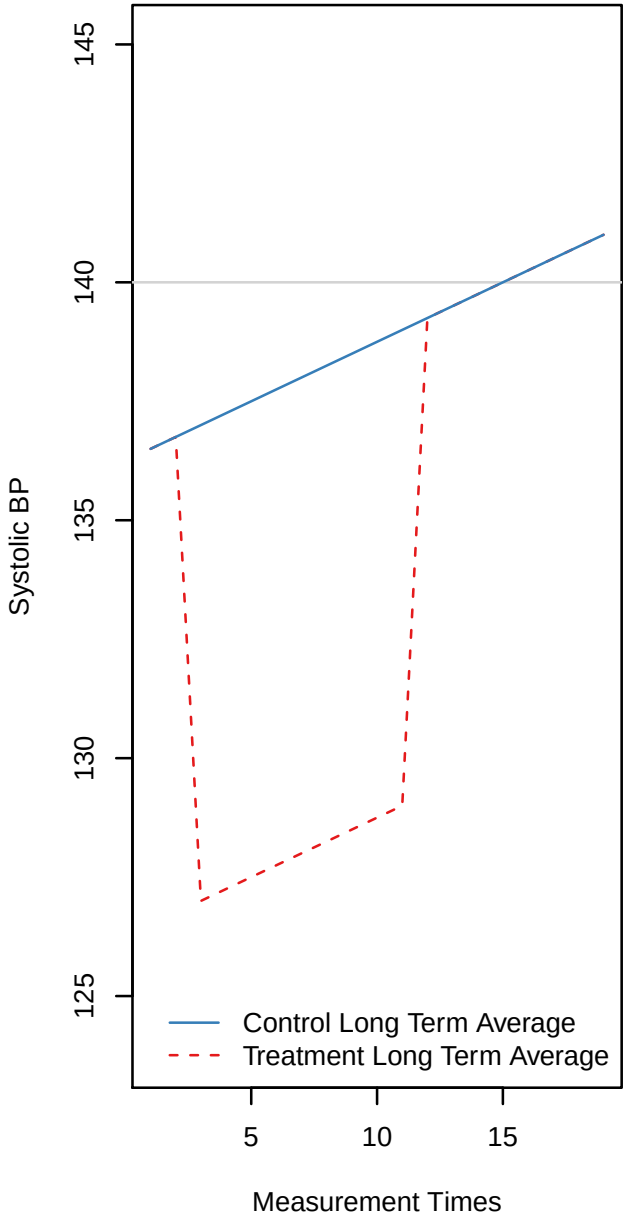


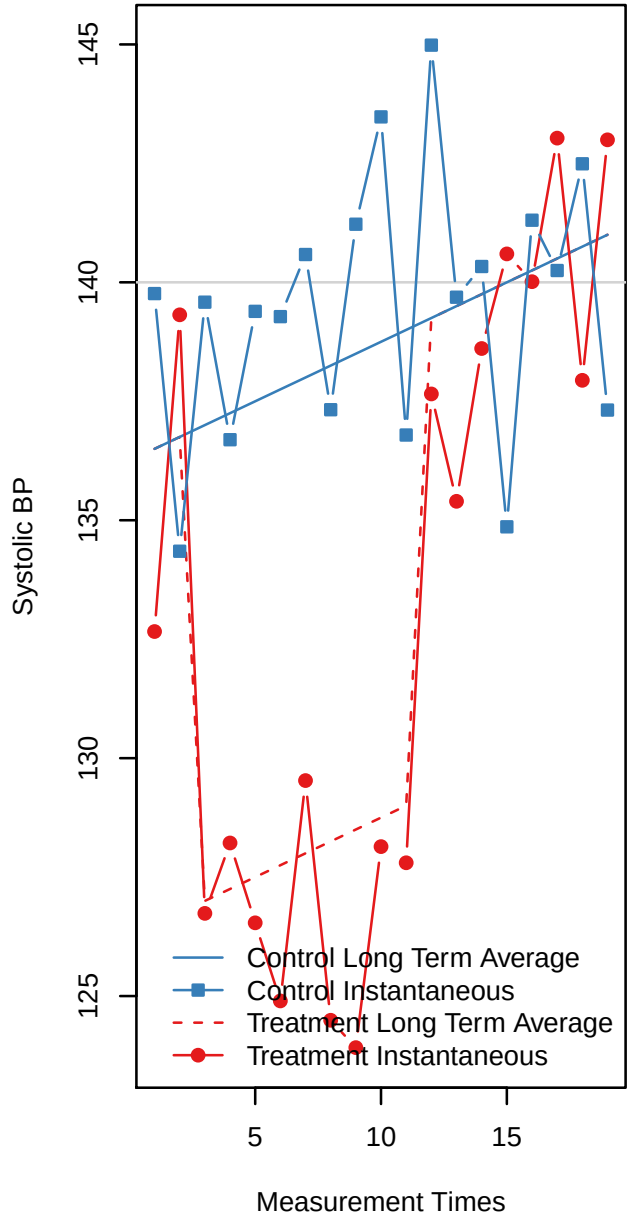
Concluded that "...the effect of active treatment on delaying the onset of hypertension can extend up to 2 years after the discontinuation of treatment. "
High-impact paper with the conclusions:

- Control group had 240 participants develop hypertension while the candesartan group had 208 $P < .0007$
- Treatment of prehypertensives is beneficial

Carryover


Systolic BP
126
128
130
132
134
136
138
0
1
2
3
4
Time
0 years
.5 years
1 years
1.5 years
2 years


Systolic BP
145
140
135
130
125
5
10
15
Measurement Times
Control Long Term Average
Treatment Long Term Average


Systolic BP
145
140
135
130
125
5
10
15
Measurement Times
Control Long Term Average
Control Instantaneous
Treatment Long Term Average
Treatment Instantaneous

Criticisms of TROPHY's analysis

Meltzer (2006)

- "idiosyncratic primary endpoint seriously impairs external applicability"

Persell and Baker (2006)

- Cumulative diagnosis rates would differ even with identical underlying BP

Lumley, Rice and Psaty (2008)

- Simulations conducted to replicate TROPHY outcomes
- Without carryover, similar cumulative incidences of hypertension were found in 80% of studies

Complications

Our modeling must consider the following:

- Noisy measurement
- Exceeding a threshold
- Treatment after diagnosis - measurements no longer used

Approaches for developing methodologies which test a carryover hypothesis:

- Attempt to remedy TROPHY design
  - Parallel design
  - Crossover design
  - A 3 arm study with both parallel, crossover, and control
- Potential ways to do an analysis
  - Linear mixed model
  - Discrete survival analysis

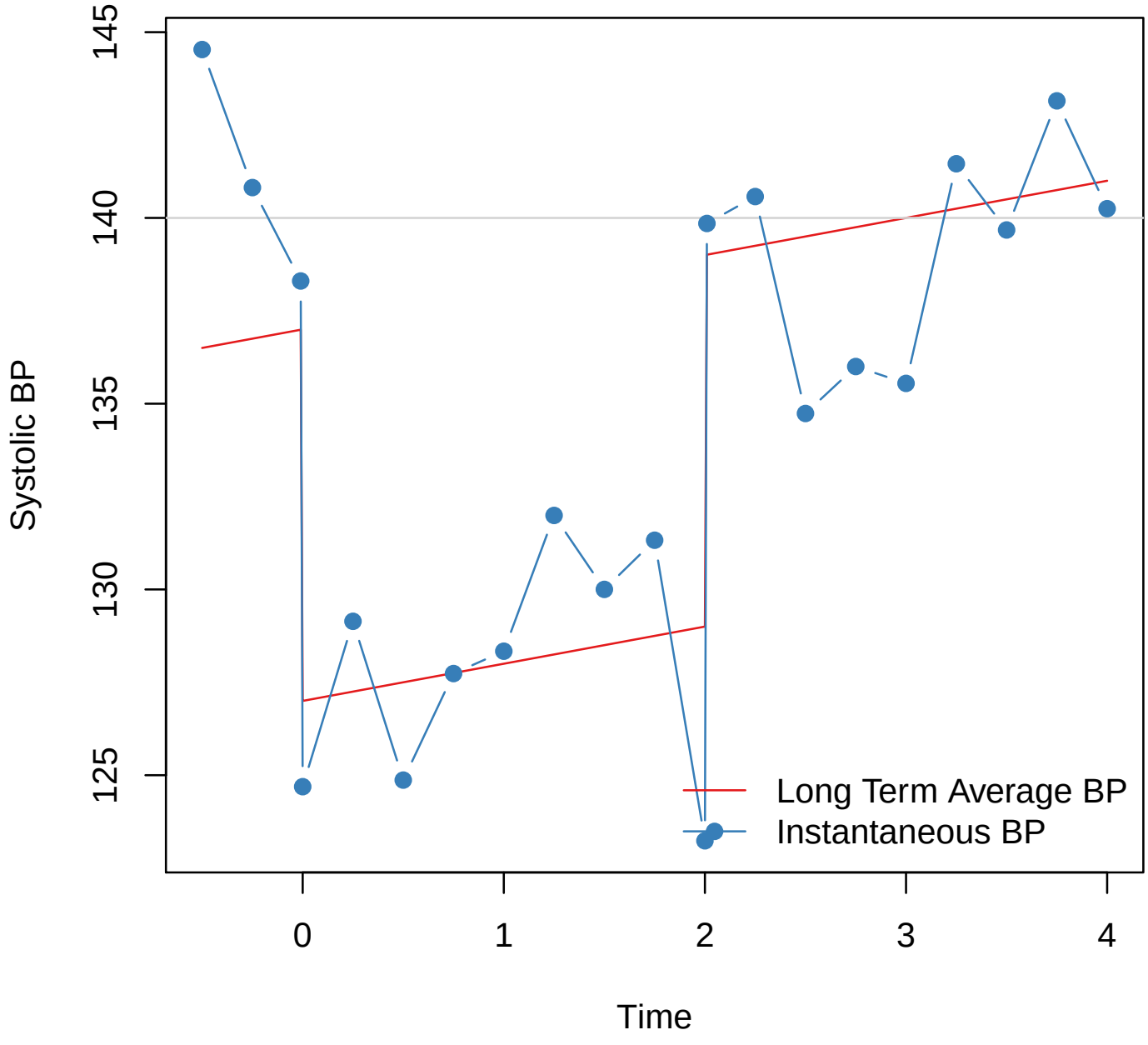
Rules for Diagnosis

Six Rules

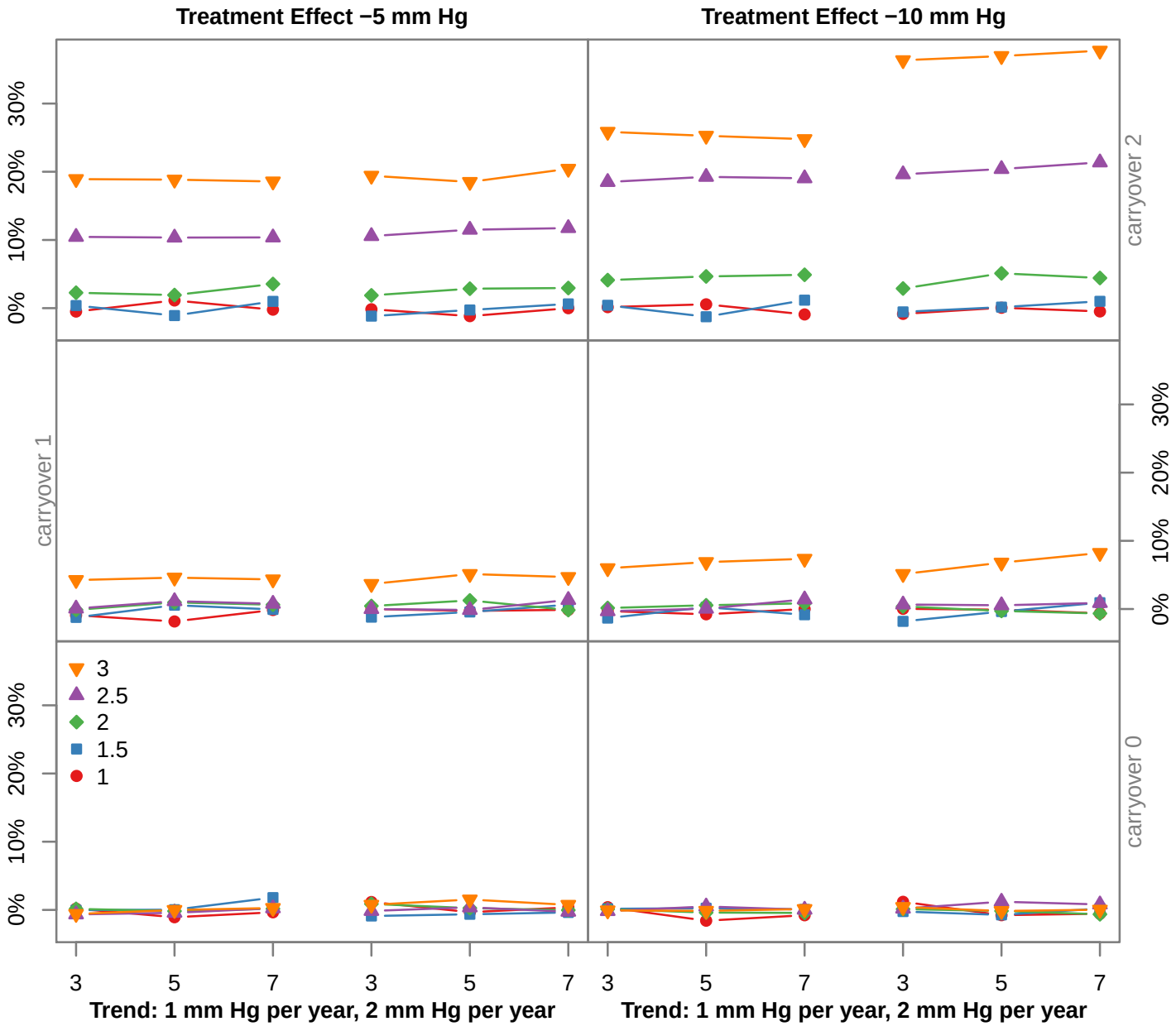
- 1 Over
- 1 Over Then Check
- 2 Consecutive
- Average of 2 Consecutive Measurements
- 3 Measurements Over
- Average of 3 Consecutive Measurements Over

We tested the rules to see which have might have appropriate differences and powers.

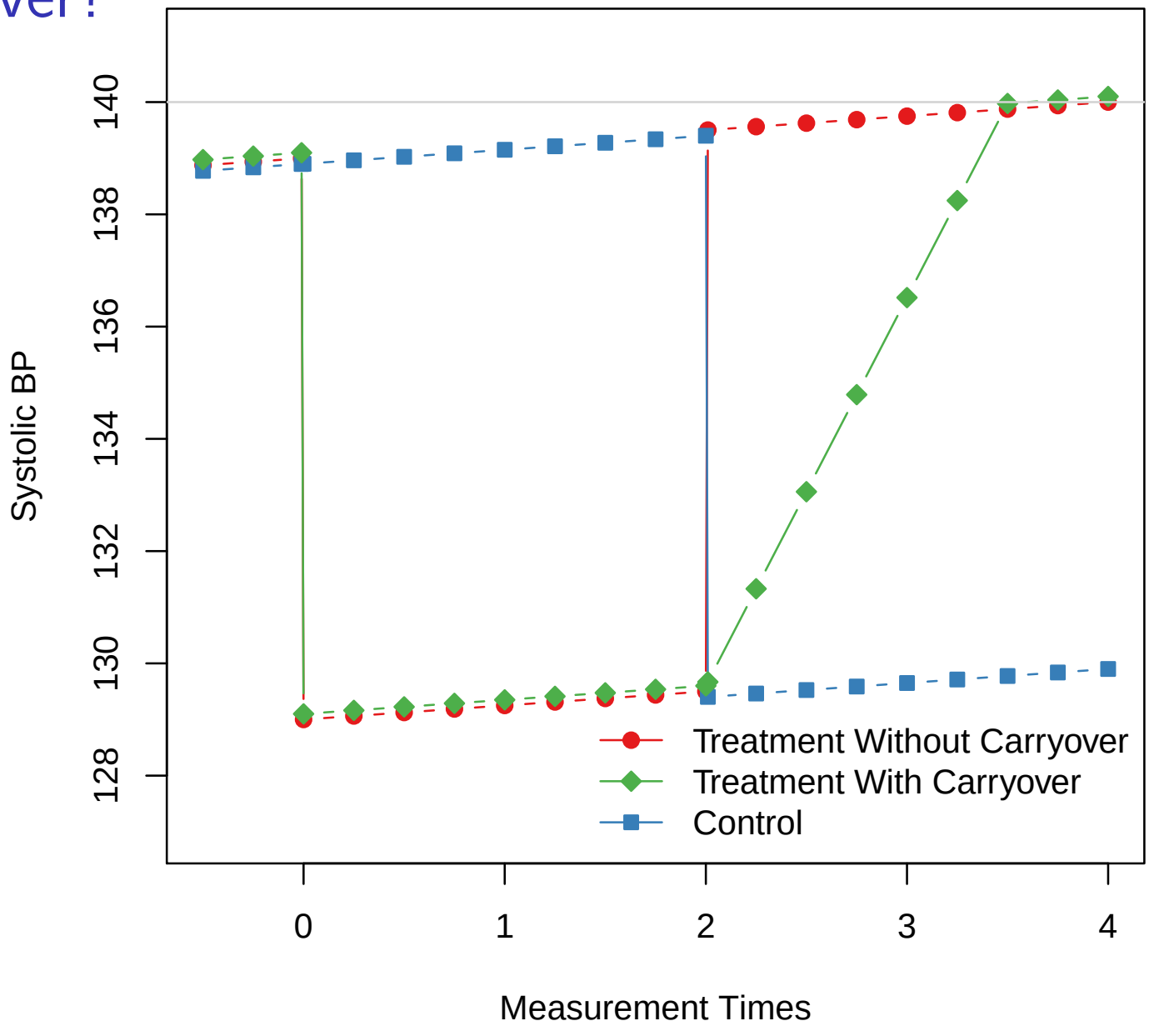
Rules


Systolic BP
145
140
135
130
125
0
1
2
3
4
Time
Long Term Average BP
Instantaneous BP

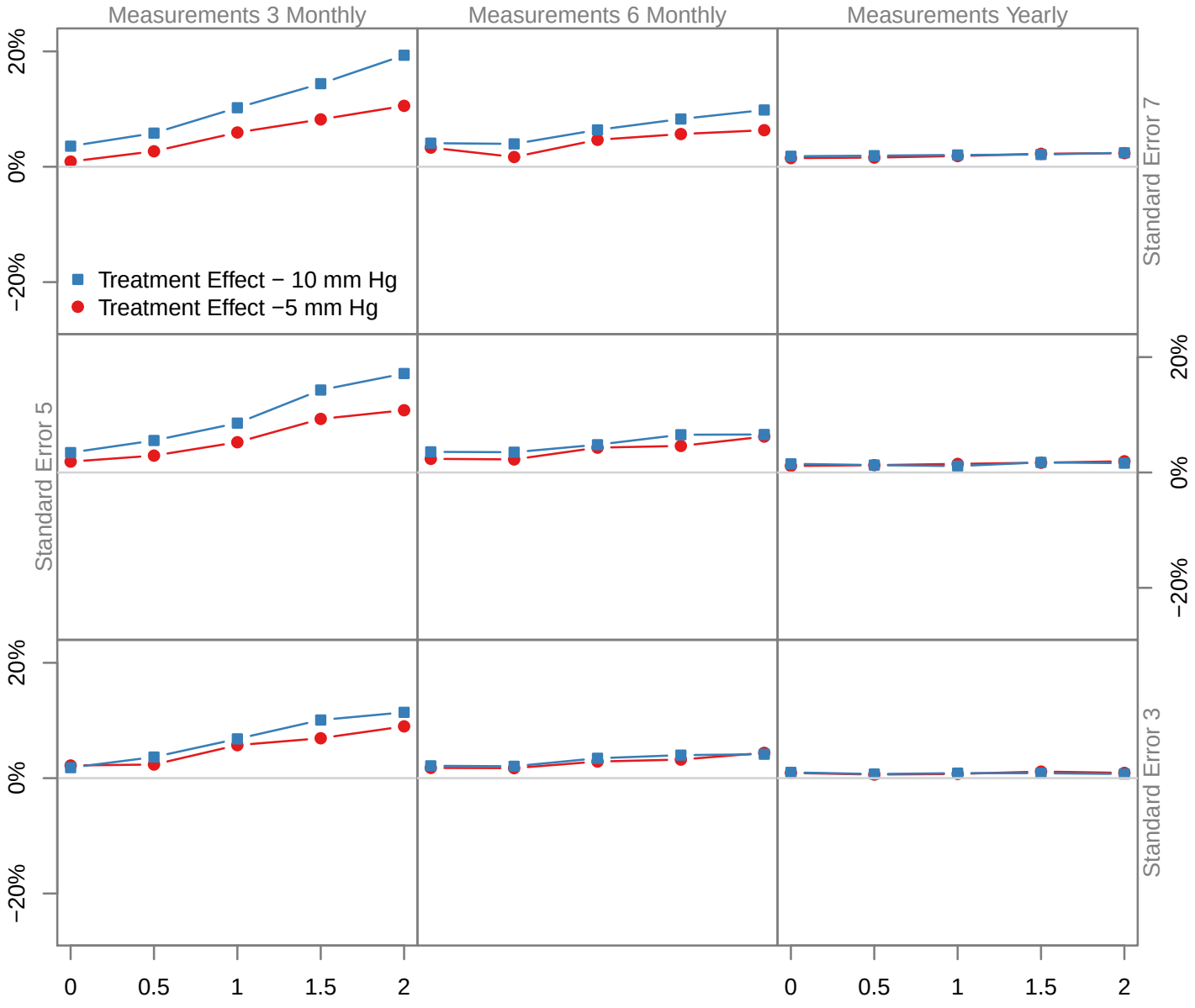
Apparent Treatment Effects − Rule 1 Over Then Check Measurements 3 Monthly



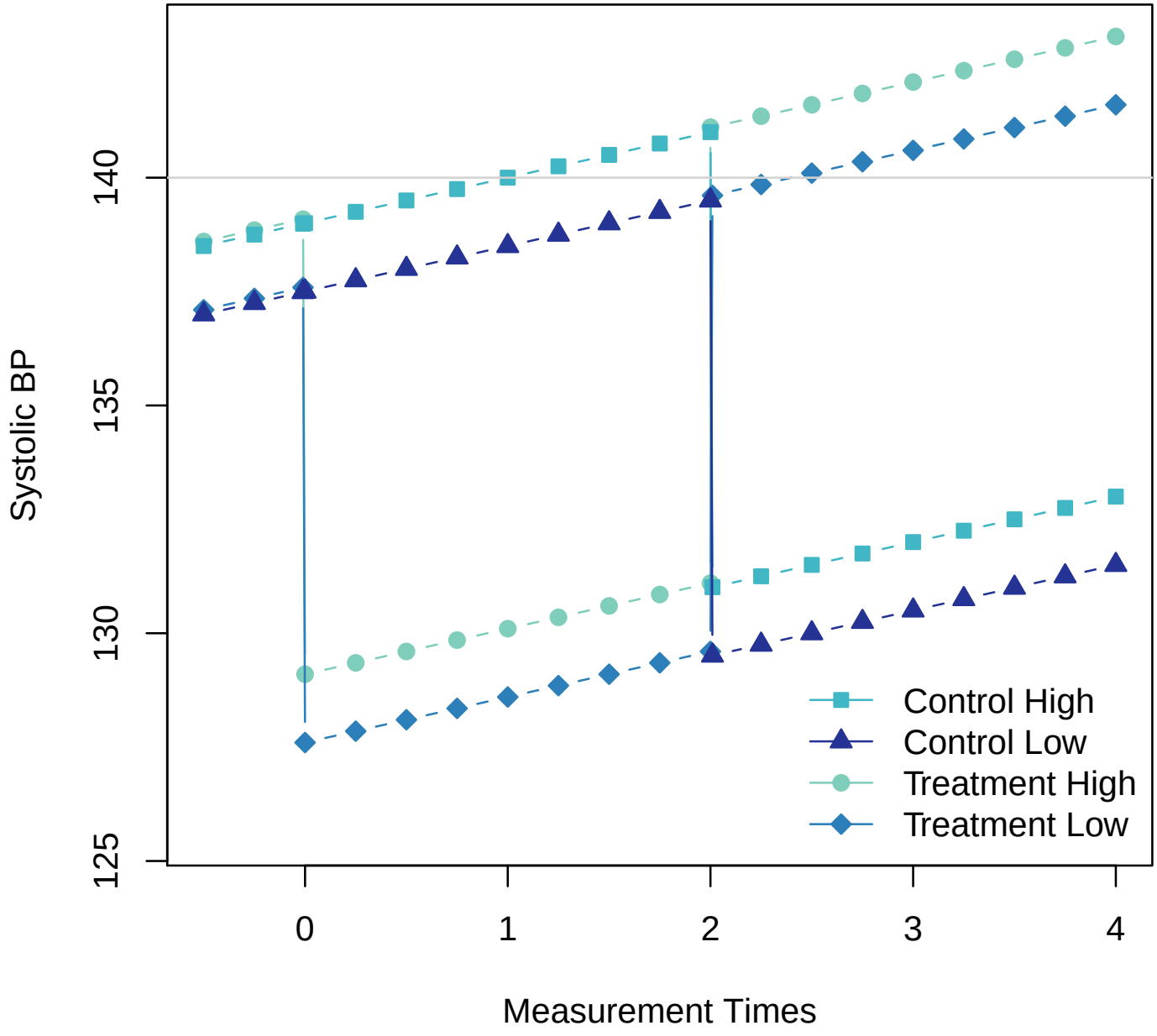
Crossover?


Systolic BP
128
130
132
134
136
138
140
0
1
2
3
4
Measurement Times
Treatment Without Carryover
Treatment With Carryover
Control

Apparent Treatment Effects − Rule 3 Over Trend 0 mm Hg per Year



Crossover Faults



It appears that design methodologies to test for carryover are not useful. Analytic methods must be developed to test a carryover hypothesis.

Linear Mixed Model

Justification:

- Longitudinal data (correlated)
- Diagnosis results in treatment in a way that we understand
- Our data is *missing at random*: probability of dropout depends on past observed values

Linear Mixed Model

We model BP using: $Y_i = a_i + b_i t + c_i X_{it} + d_i Z_{it} + \epsilon_{it}$

- Y_i is the blood pressure (BP) measurement
- $a_i \sim b_i \sim N(0, \Sigma)$, c_i estimates the treatment effects
- d_i estimates the carryover
- X_{it} is 1 if person i is on treatment at time t and 0 otherwise
- Z_{it} starts at 1 when someone stops treatment and decreases linearly to 0 over the carryover period.

We use a linear mixed model for continous BP to find the maximum likelihood estimate (MLE) of:

$$\begin{pmatrix} a_i \\ b_i \\ c_i \\ d_i \end{pmatrix} \sim N \left[\begin{pmatrix} \alpha \\ \beta \\ \gamma \\ \delta \end{pmatrix}, \mathbf{\Sigma} \right]$$

where $\mathbf{\Sigma}$ is the covariance matrix. From here we model hypertension analytically using a probit model, and computationally using a parametric bootstrap.

Discrete Survival Analysis

- Time to event - when long term average BP is above 140 mm Hg
- Impossible - measurement error
- Diagnosis to estimate

This is similar to "Discrete Proportional Hazards Models for Mismeasured Outcomes"

Acknowledgements:

- Thomas
- Ross
- Ken
- My mom

For further reading

A. S. Meier, B. A. Richardson, and J. P. Hughes.
Discrete proportional hazards models for mismeasured outcomes.
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S. D. Persell and D. W. Baker.
Studying interventions to prevent the progression from prehypertension to hypertension: Does TROPHY win the prize?
American Journal of Hypertension, 19(11):1095–7, 2006.

J. I. Meltzer.
A specialist in clinical hypertension critiques the TROPHY trial.
American Journal of Hypertension, 19(11), 2006.

More reading

T. Lumley, K. M. Rice, and B. M. Psaty.
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S. Julius, S. D. Nesbitt, B. M. Egan, M. A. Weber, E. L. Michelson, N. Kaciroti, H. R. Black, R. H. Grimm, F. H. Messerli, and S. Oparil.
Feasibility of treating prehypertension with an angiotensin-receptor blocker.
New England Journal of Medicine, 354(16):1685–97, 2006.

Close to submission

- "Testing for Carryover Effects After Cessation of Treatments: A Parallel Design Approach does not work." by S. Gwynn Sturdevant and Thomas Lumley to be submitted to Journal of Clinical Epidemiology
- "Testing for Carryover Effects After Cessation of Treatments: A Crossover Design Approach does not work" by S. Gwynn Sturdevant and Thomas Lumley to be submitted to Contemporary Clinical Trials

Discrete Survival Analysis

Research based on "Discrete Proportional Hazards Models for Mismeasured Outcomes" by Meier et al. (2003) with a differing model for measurement error. Her notation:

- $t_i(t_i^0)$ is the true (observed) time the ith subject has the event
- $d_i(d_i^0)$ is the true (observed) event status (1 = failure, 0 = censoring)
- $\mathbf{X_i}$ is the vector of covariates for subject i

Our likelihood function with true event status (d_i) and failure or censoring times (t_i) is:

$$f(t_i, d_i; \mathbf{X_i}, \beta, \boldsymbol{\lambda_0}) = \prod_{j=1}^{t_i-1} \left\{ (1 - \lambda_{0j})^{e^{\mathbf{x_i'}\beta}} \right\} \times \left\{ 1 - (1 - \lambda_{0t_i})^{e^{\mathbf{x_i'}\beta}} \right\}^{d_i} \times \left\{ (1 - \lambda_{0t_i})^{e^{\mathbf{x_i'}\beta}} \right\}^{1-d_i}$$

with baseline hazard $\boldsymbol{\lambda_0} = (\lambda_{01}, \lambda_{02}, ..., \lambda_{0T})$. Our objective is to estimate $\boldsymbol{\Omega} = \begin{pmatrix} \boldsymbol{\lambda_0} \\ \beta \end{pmatrix}$ which is not possible due to the measurement error in d_i and t_i.

So that boundaries are not placed on the hazard vector $\boldsymbol{\lambda_0}$ we reparameterize the baseline hazard by letting $\gamma_{0j} = log(\frac{\lambda_{0j}}{1-\lambda_{0j}})$, for $j = 1, \ldots T$. Using this parametrization we have:

$$f(t_i, d_i; \mathbf{X_i}, \beta, \boldsymbol{\gamma_0}) = \prod_{j=1}^{t_i-1} \left\{ (1 + e^{\gamma_{0j}})^{-e^{\mathbf{x_i'}\beta}} \right\} \times \left\{ 1 - (1 + e^{\gamma_{0j}})^{-e^{\mathbf{x_i'}\beta}} \right\}^{d_i} \times \left\{ (1 + e^{\gamma_{0j}})^{-e^{\mathbf{x_i'}\beta}} \right\}^{1-d_i}.$$

As d_i and t_i are unknown we estimate them using d_i^0 and t_i^0. We then multiply to find the joint density:

$$f(t_i, d_i, t_i^0, d_i^0) = f(t_i, d_i) \times f(t_i^0, d_i^0 | t_i, d_i).$$

Now, we derive $f(t_i^0, d_i^0 | t_i, d_i)$ assuming sensitivity θ, and specificity ϕ. The derivation is as follows:

Variable								
T_i	1,	2,	...,	$t_i - 1$,	t_i,	...,	$t_i^0 - 1$,	t_i^0
d_i^0	0,	0,	...,	0,	0,	...,	0,	1
d_i	0,	0,	...,	0,	1			

The probability of these outcomes given failure at time t_i is:

$$f(t_i^0, d_i^0 | t_i, d_i) = \phi^{t_i - 2}(1 - \theta)^{t_i^0 - t_i - 1}\theta.$$

Discrete Survival Analysis - Our notation

The following notation is for observed data based upon simulations:

- Let BP be measured at times t_i for each $i = 1, ..., n$ subjects
- Based upon BP measurements, we have a resultant binary vector of length t_i where I_{it} is 1 if BP is above 140 mm Hg and 0 otherwise.
- Using our rules, defined above, we have the vector D_{it} where 0 denotes that our subject has yet to be diagnosed as hypertensive and 1 upon diagnosis and thereafter
- We define the vector Z_{it} to be 1 when diagnosis takes place and 0 otherwise.

The unobserved vectors of important follow:

- H_{it} is 1 when the true value of BP is above 140 mm Hg, and 0 otherwise and
- Y_{it} is 1 at the first t_i where H_{it} is above 140 mm Hg.
- $p_t(x_{it,\theta})$ is the probability of the ith person being diagnosed with hypertension at time t_i and the probability of this not occuring $q(x_{it,\theta})$

Without measurement error our likelihood function would be:

$$L_y = \prod_i [\prod_t p_t(x_{it_i,\theta})^{Y_{it}}][q(x_{it_i,\theta})^{1-Y_i}]$$

We can only estimate Y_{it} using Z_{it} and thus find $Pr(Y_{it})$ using $Pr(Z_{it}/Y_{is}, I_{it})$ where $s \leq t$ and Bayes' Theorem. The rules will again be pertinent at this stage. From here we use the Expecatation Maximization (EM) algorithm to iteratively find the value of Y which maximizes the probability of the data.