Dynamic borrowing of historical data:

Performance and comparison of existing methods based on a case study

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Outline

Introduction: Antibiotic development

- Number of antibiotics under development low
  - Traditionally large programs required for approval
  - Lack of return on investment
- Growing concerns on antibiotic resistance
  - Unmet medical need (high mortality)
  - Small target population
- Evolving regulatory context
  - Pre-clinical evidence accepted
  - Use of historical data mentioned (FDA guidance for industry 2013)
  - Bayesian methods accepted for devices (FDA guidance for industry 2010)

Introduction: Case study

- Design of phase III comparative study of new agent against pseudomonas aeruginosa (p.a.)
- Target population: Ventilator associated and hospital acquired pneumonia
- Rare condition:
  - 5-10 VAH/HAP per 1,000 hospital admissions
  - 20% caused by p.a.
- Maximum enrollment: 300 subjects total
- Endpoint: 14 days mortality rate (binomial)
- Non-inferiority combo design (maximize safety database)

Motivation for use of historical control

- Subjects are rare
- Need to maximize safety database
  $\Rightarrow$ unbalanced randomization
- Subjects infected, diagnosed, treated, followed up in hospital
  $\Rightarrow$ hope for detailed medical record for historical data

Historical Control

Pocock criteria

1. Treatment in historical control same as randomized control
   $\Rightarrow$ **Met**
2. Historical control form control CT is recent and identical inclusion criteria
   $\Rightarrow$ **Not met**
3. Evaluation of endpoint is the same
   $\Rightarrow$ **Met**
4. Distribution of important subject characteristics are the same
   $\Rightarrow$ **Met**
5. Historical control must be treated in same institution and same investigators
   $\Rightarrow$ **Met**
6. No other indications to expect different outcome
   $\Rightarrow$ **Met**

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- **Very strict criteria**
- **No guaranty that prior match**

Historical control and randomized control

- Concern: Uncontrolled factors may impact validity of historical control

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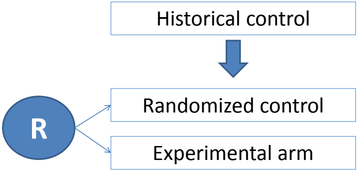
- Use Small randomized control to check compatibility of historical control



Dynamic Bayesian Borrowing

Goal of methods

Increase precision when compatible, control bias when not compatible

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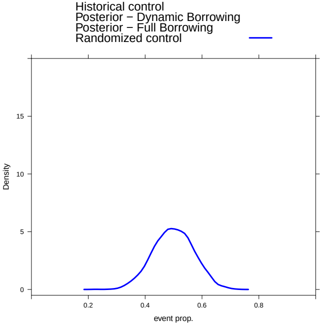
Compatible historical data



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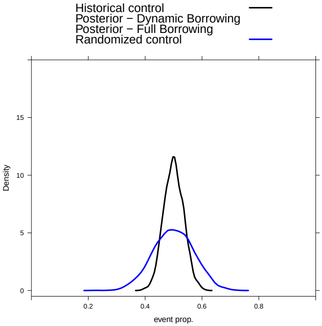

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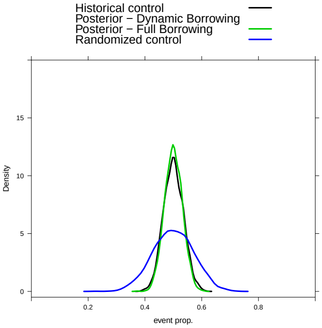

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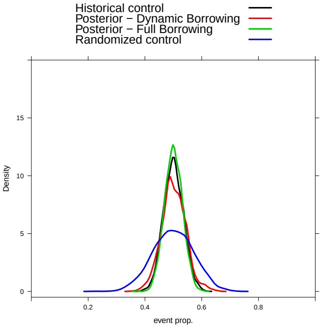

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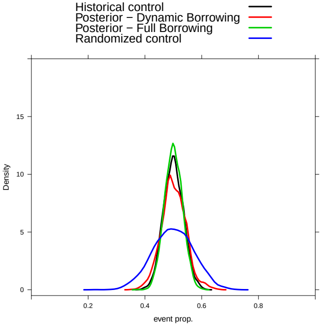
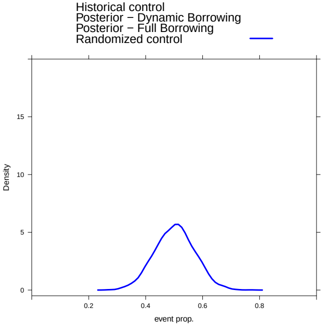


Incompatible historical data



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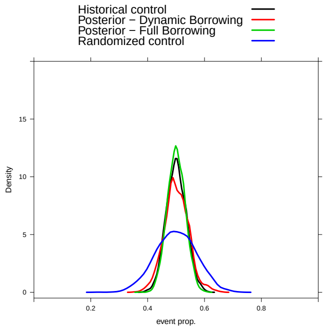

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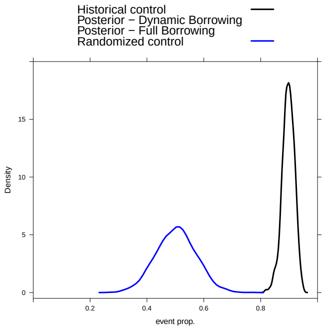

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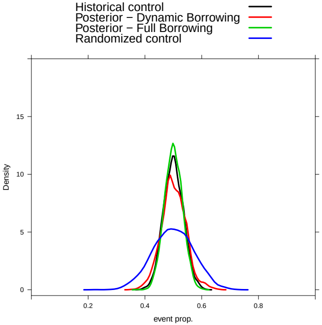

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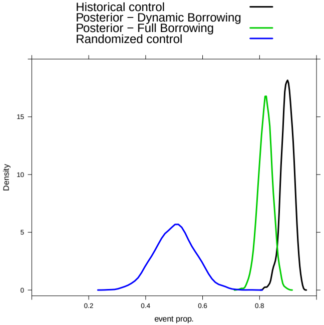


Full Borrowing

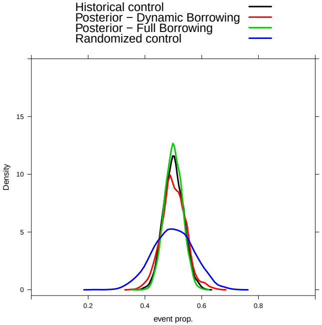
- Increase in Bias

Dynamic Bayesian Borrowing

Goal of methods

Increase precision when compatible, control bias when not compatible

Compatible historical data



- Increase in precision

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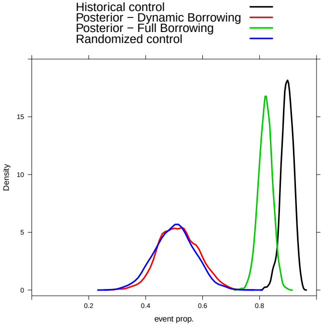


Dynamic Borrowing

- Bias controlled

Methods

- **Normalized power prior**
- **Robust mixture prior**
- **Commensurate prior**

Normalized power prior

Prior for event rate p:

$$\pi^P(p,\theta|H) \propto \underbrace{\frac{1}{C(\theta)}}_{\text{Normalizing cst}} \Big[\underbrace{L^H(p)}_{\text{Historical data}} \Big]^{\theta} \underbrace{\pi_v(p)}_{\text{vague prior}} \underbrace{\pi_v(\theta)}_{\text{vague prior for } \theta}$$

- Historical data (H) prior raised to power θ
- $\theta \in [0,1] =$ measure of compatibility
    - $\theta = 0 \Rightarrow$ No Borrowing
    - $\theta = 1 \Rightarrow$ FULL Borrowing
- θ jointly estimated with p

Robust Mixture prior

Prior for event rate p:

$$\pi^{mx}(p|H) = w \underbrace{\pi^{H}(p)}_{\text{Historical data}} + (1-w) \underbrace{\pi^{v}(p)}_{\text{vague prior}}$$

- Weights w are pre-specified
- Determined through simulations
- Weights are updated in posterior
- Random weights possible, but do not depend on data

Commensurate prior

$$\pi^C(p, p_h, \sigma | H) \propto \underbrace{L^H(p_h)}_{\text{Historical data}} \underbrace{\psi(p, p_h, \sigma)}_{\text{link function}} \underbrace{\pi_v(p_h, \sigma)}_{\text{vague prior}}$$

- Separate parameters for randomized (p) and historical (p_h)
- Connected through a link function (distribution)
  - Mean of link distribution $= p_h$
  - Variance $= \sigma =$ measure of compatibility
    - High variance $\Rightarrow$ Low compatibility
    - Low variance $\Rightarrow$ high compatibility

Note on method

All methods depend on parameters : Need for calibration

- Robust Mixture Prior: pre-specified weight w
- Commensurate prior: Prior for variance $\pi_v(\sigma)$
- Normalized power prior: Prior for power parameter $\pi_v(\theta)$
  $\Rightarrow$ Natural choice: Jeffreys' prior Beta(1/2,1/2)

$\Rightarrow$ **All methods calibrated on NPP**
$\Rightarrow$ **On maximum type I error**

Simulations

Goal of simulations

Compare methods:

- Impact of drift on type I error
- Increase in power
- Against
  - Frequentist test: No borrowing, just randomized data
  - Full borrowing: Simple Bayesian analysis (pooled analysis)

Here:

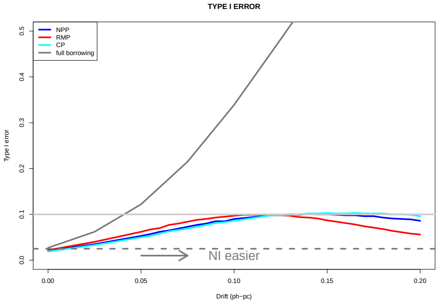
- Design stage: Best assumptions on control and experimental mortality rate
- Control collected at site opening:
  - Unknown historical rate
  - Historical rate to be simulated as well

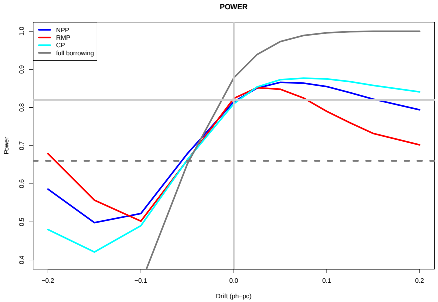
Simulation settings

- Non-inferiority test for mortality rate ($\searrow$ better)
- Rate in randomized control: $p_c = 25\%$
- Non inferiority margin $= 12.5\%$

  Positive test if 95% CI of difference $p_e - p_c < 12.5\%$
- Rate in Incompatible historical control: $p_h = 37.5\%$
- Rate in compatible historical control: $p_h = 25\%$
- Sample size:
  - Historical control : 200
  - Randomized control: 100
  - Experimental arm: 200

Results





- Maximum α set to 10% (following calibration)
- Power gain: 12% (Power = 82%)
- All methods similar

Comparison with frequentist

- Previous plot: All methods calibrated to max(α)$=$ 0.10

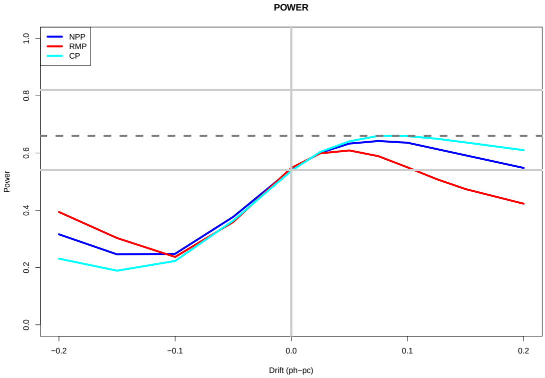
  Except "Frequentist" α=0.025

- 2 options align α

  1. Lower Dynamic borrowing to maximum $\alpha \leq 0.025$
  2. Allow frequentist to have $\alpha = 10\%$

Option 1

- **Dynamic borrowing to maximum** $\alpha \leq 0.025$
- Change width of CI (methods use 95% CI):
  Width: 95% $\Rightarrow$ 99%



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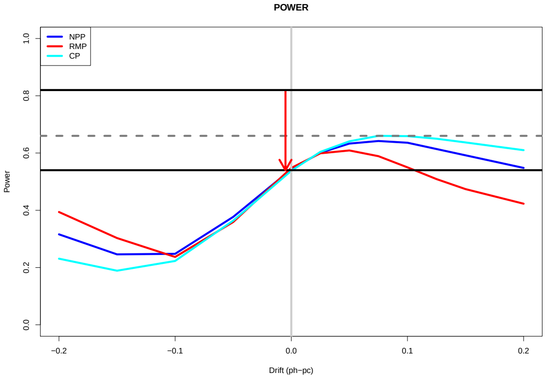

- Power reduced from 0.82 to 0.54

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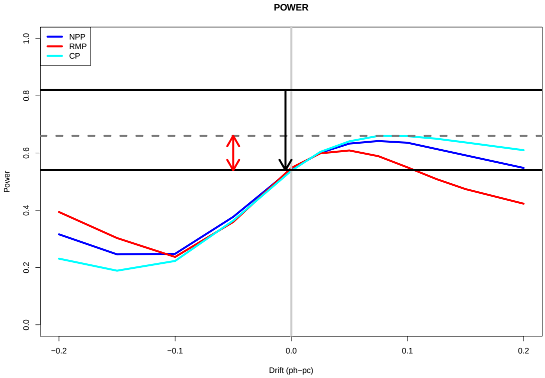
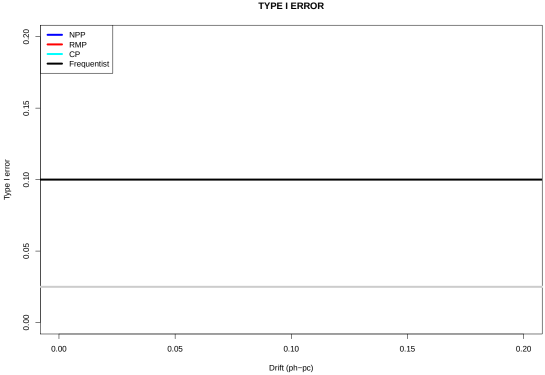


- Power reduced from 0.82 to 0.54
- Power of dynamic borrowing (0.54) lower than no historical data (0.66)

Option 2

- **Frequentist** $\alpha = 10\%$
- Power of frequentist method increases $\rightarrow 0.87$
- **Frequentist higher power than Dynamic borrowing (0.82)**



- Frequentist α constant $= 0.1$ over drift

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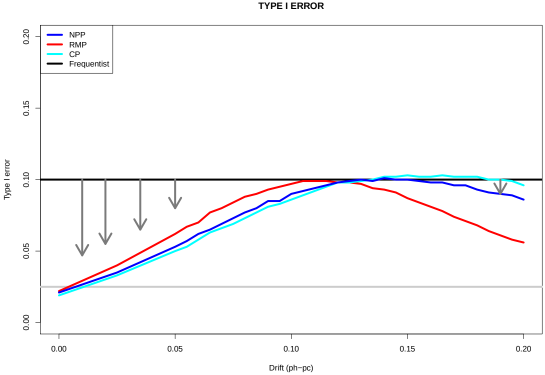

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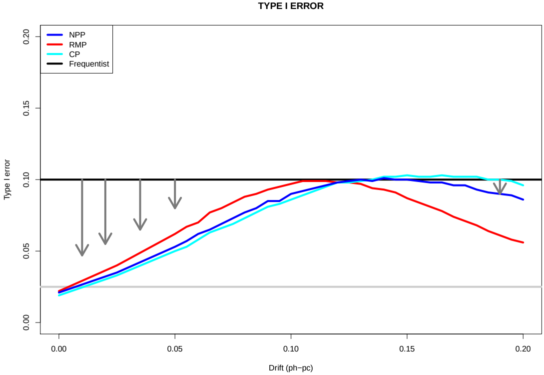

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$\Rightarrow$ **Dynamic borrowing methods have lower** α

Discussion

- **Can Dynamic borrowing replace a frequentist analysis (gain power)**
  - **NO,** when strict control of α required
  - **YES** , if some increase is allowed
    - Makes sense: Historical data = trustworthy source of data
    - Type I error inflation depends on historical data
    - Risk (α/power) of historical data is limited but not suppressed!
- **Benefits of Dynamic borrowing**
  - Limit bias, type I error compared to full borrowing in case incompatible data
  - Mixture prior is best (Simple - needs optimization - fast)
  - Commensurate difficult to implement
    Linked to variance parameter controlling for compatibility

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