PUMP: Power Under Multiplicity Project

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Slides available: github.com/kristenbhunter/presentations/tree/master/NCI2022

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Multiple outcomes

- The use of multiple testing procedures (MTPs) changes statistical **power**
- **Problem**: In some fields, current practice for determining statistical power for RCTs does not take the use of MTPs into account
- **Solution**: Easy-to-use software for calculating power, sample size, and minimum detectable effect size (MDES) for RCTs
- Easy exploration of power over different assumed parameter values

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Introducing PUMP

- **PUMP**: R package on CRAN
- Power Under Multiplicity Project
- Calculates power for multiple hypotheses in multilevel **randomized controlled trials** (RCTs)
- **Multilevel**: hierarchical structure, such as patients nested within hospitals nested within hospital systems
- Assumes frequentist **mixed effects** models

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Multilevel models

$$
\begin{aligned}
\underbrace{Y_{ijkm}}_{\text{Outcome}} = \; & \underbrace{\psi_{1,m}}_{\text{Tx effect}} \; \underbrace{T_{jk}}_{\text{Tx asst}} \\
& + \underbrace{\mu_{0,km}}_{\text{Level 2 Grand mean}} \\
& + \sum_{r=1}^{g_{2,m}} \delta_{mr} \underbrace{X_{jkmr}}_{\text{Level 2 covariate}} \\
& + \sum_{p=1}^{g_{1,m}} \gamma_{mp} \underbrace{C_{ijkmp}}_{\text{Level 1 covariate}} \\
& + \underbrace{u_{0,jkm}}_{\text{Level 2 random effect}} \\
& + \underbrace{r_{ijkm}}_{\text{Level 1 random effect}}
\end{aligned}
$$

Example

I have 3 outcomes, with a 2-level blocked design. My power to detect the effect for any individual outcome:

- Without any adjustment (no MTP): 0.81.
- Using Bonferroni adjustment: 0.67.

Having multiple outcomes has reduced my power...or has it? Stay tuned!

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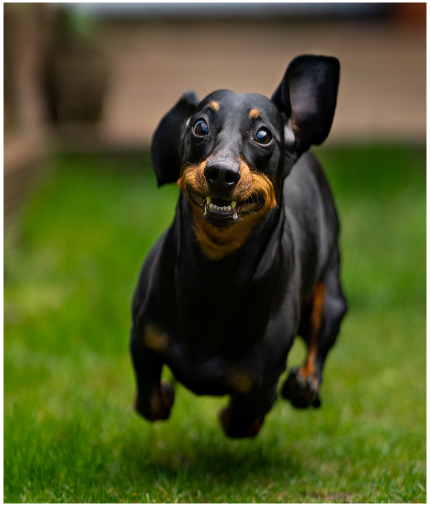

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Factors affecting power in RCTs

With at least one outcome:

- design of the study and assumed model
- $\bar{n}$, J, K: number of level 1/2/3 units
- $\bar{T}$: proportion of units treated
- number of covariates
- R^2: explanatory power of covariates
- ICC: intraclass correlation (ratio of variance at level to overall variance)
- Treatment impact heterogeneity

Note: terminology varies across fields!

Unique to **multiple** outcomes:

- definition of power
- M: number of outcomes/tests
- ρ: correlation between test statistics
- proportion of outcomes for which there are truly effects
- multiple testing procedure (MTP)

Define the experimental setup

How to **design** the experiment

- Levels: 1, 2, 3
- Randomization level: 1, 2, 3

How to **model** the experiment

- Assumes mixed effects regression models
- Intercepts: fixed or random
- Treatment effects: constant, fixed, or random

Supported designs and models:

- d1.1_m1c
- d2.1_m2fc
- d2.1_m2ff
- d2.1_m2fr
- d2.1_m2rr
- d2.2_m2rc
- d3.1_m3rr2rr
- d3.2_m3fc2rc
- d3.2_m3ff2rc
- d3.2_m3rr2rc
- d3.3_m3rc2rc

Definitions of power

How do we define power if we have *multiple* hypotheses/outcomes?

- **Individual** power: probability of rejecting a particular null hypothesis
- **1-Minimal** power: probability of rejecting at least one null hypothesis
- **D-Minimal** power: probability of rejecting at least d null hypotheses
- **Complete** power: probability of rejecting all the null hypotheses

All valid options--the choice depends on how we want to define success!

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Multiple testing procedures

- **Bonferroni**
  - simple
  - most conservative
- **Holm**
  - step down version of Bonferroni
  - less conservative for larger p-values than Bonferroni
- **Benjamini-Hochberg**
  - step up procedure
  - controls the false discovery rate (less conservative)
- **Westfall-Young** (single step and step down versions)
  - permutation-based approach
  - takes into account correlation structure of outcomes
  - computationally intensive
  - not overly conservative

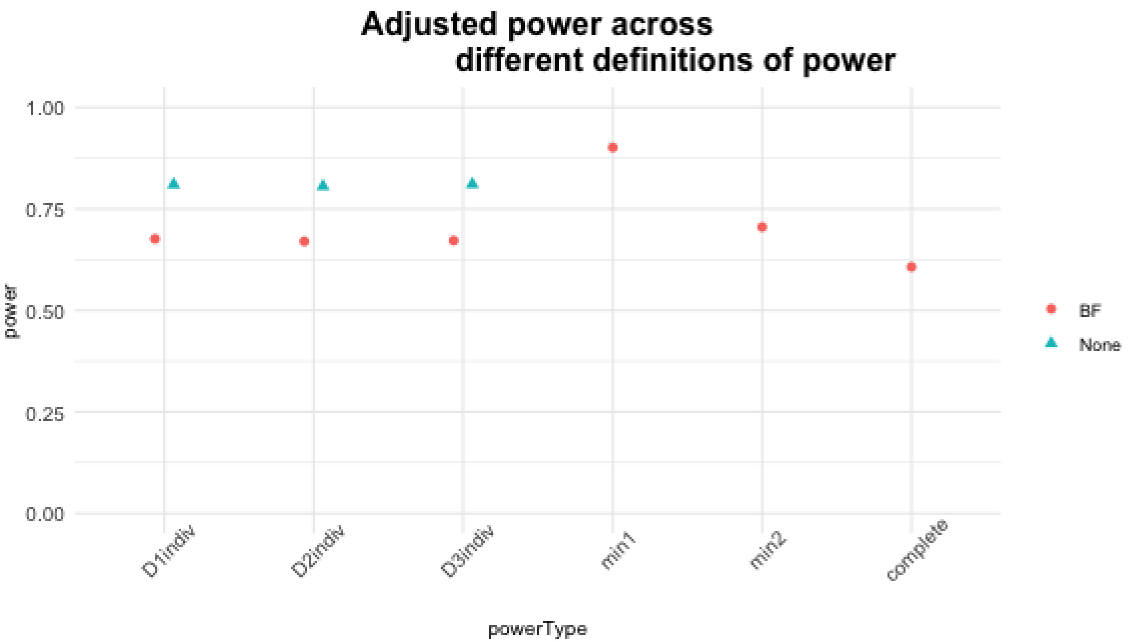
Diving in!

```
library( PUMP )

pow <- pump_power(
  d_m =  "d2.1_m2fc",     # choice of design and model
  MTP = "BF",             # multiple testing procedure
  MDES = rep( 0.10, 3 ), # assumed effect size
  M = 3,                  # number of outcomes
  J = 10,                 # number of schools/blocks
  nbar = 275,             # average number of students per school
  Tbar = 0.50,            # proportion of students treated per school
  alpha = 0.05,           # significance level
  numCovar.1 = 5,         # number of covariates at level 1
  R2.1 = 0.1,             # assumed R^2 of level 1 covariates
  ICC.2 = 0.05,           # intraclass correlation
  rho = 0.4               # test statistic correlation
)
```

Power results

MTP	D1indiv	D2indiv	D3indiv	indiv.mean	min1	min2	complete
None	0.81	0.81	0.81	0.81	NA	NA	NA
BF	0.68	0.67	0.67	0.67	0.9	0.71	0.61



How it works

- For simple designs and one outcome, we often have a formula for power
- It would be difficult (in some cases impossible) to derive explicit formulas for every design, model, number of outcomes, MTP, and definition of power

Instead, we use **simulation**! A full simulation approach would be:

1. *Simulate data* according to the alternative hypotheses
2. *Calculate test statistics* under the alternative hypotheses
3. Use these test statistics to calculate p-values
4. Calculate power using the distribution of p-values

How it works

- We can simplify this approach by skipping step 1
- Given:
  - design and model
  - correlation between test statistics for different hypotheses
- We know the joint alternative distribution of test statistics!
- Results in **simpler** and **faster** power calculations

Simulation approach to calculating power:

1. *Sample test statistics* under the alternative hypotheses.
2. Use these test statistics to calculate p-values.
3. Calculate power using the distribution of p-values.

Note: because we use simulations to calculate power, estimates are approximate, but the user can increase the number of test statistic draws to increase precision.

Sample size and MDES

We can also calculate:

- `pump_mdes()`: minimum detectable effect size (MDES) for a particular target power
- `pump_sample()`: sample size for a given target power and MDES

Types of sample size calculations:

- K: number of level 3 units (hospital systems)
- J: number of level 2 units (hospitals)
- nbar: number of level 1 units (patients)

Sample size example

```r
ss <- pump_sample(
  target.power = 0.8,         # target power
  power.definition = "min1", # power definition
  typesample = "J",          # type of sample size procedure
  tol = 0.01,                # tolerance
  d_m =  "d2.1_m2fc", MTP = "BF",
  MDES = 0.1, M = 3, nbar = 350, Tbar = 0.50, alpha = 0.05,
  numCovar.1 = 5, R2.1 = 0.1, ICC.2 = 0.05, rho = 0.4
)
```

MTP	Sample.type	Sample.size	min1.power
BF	J	7	0.81

Assessing sensitivity

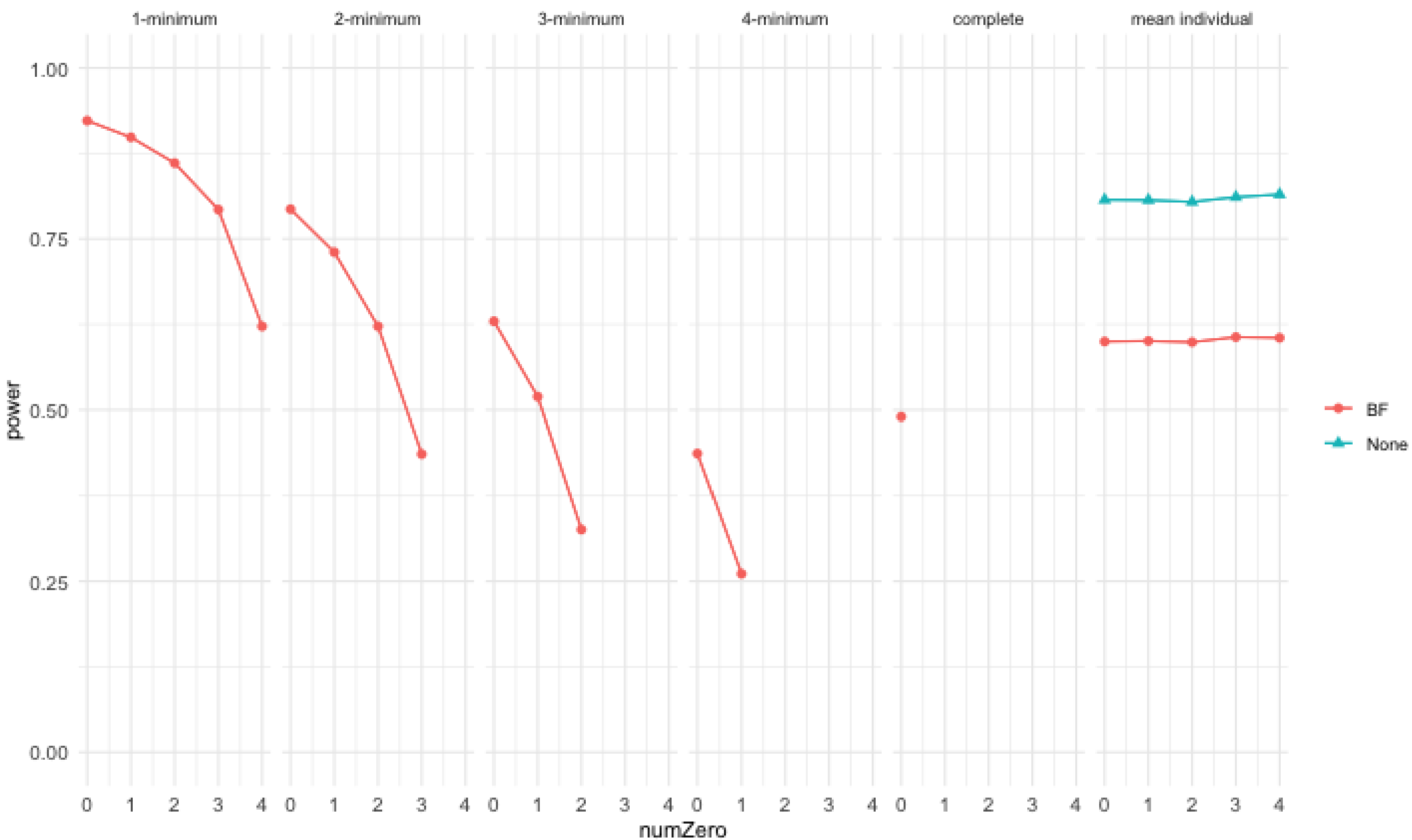
We can use the grid function to assess sensitivity to different model and design parameters.

Example: how many outcomes are assumed to have zero effect?

```
gridZero <- update_grid(
  pow,
  # vary parameter
  numZero = 0:4,
  # update number of outcomes
  M = 5
)
```

Assessing sensitivity

```
plot( gridZero, nrow = 1 )
```



Features for ease of use

Update function allows you to just update certain parameter values:

```
p_d <- update( pow,
               M = 5,
               R2.1 = c( 0.1, 0.3, 0.1, 0.2, 0.2 ))
```

Update grid:

```
gridICC <- update_grid( pow,
                        ICC.2 = seq( 0, 0.3, 0.05 ))
```

Bonus features

- Functions to simulate data from multilevel RCTs
- Function to estimate the approximate correlation between *test statistics* based on the correlation between *outcomes* (using a simulation approach)

```
covariate.corr.matrix <- gen_corr_matrix(M = 3, rho.scalar = 1)
cor.tstat <- check_cor(
  pow,
  rho.C = covariate.corr.matrix,
  n.sims = 500
)
est.cor <- mean(cor.tstat[lower.tri(cor.tstat)])
print( est.cor )
```

```
## [1] 0.374517
```

Summary: PUMP R package

- Estimates power for multiple outcomes for multilevel RCTs
- Takes into account multiple testing procedures
- Calculates minimum detectable effect size (MDES) and sample size
- Allows user to assess sensitivity of power to different parameter choices

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Available now!

- CRAN: CRAN.R-project.org/package=PUMP
- Shiny app: mdrc.shinyapps.io/pump
- Github: github.com/MDRCNY/PUMP
- arXiv: arxiv.org/abs/2112.15273
- Slides: github.com/kristenbhunter/presentations/tree/master/NCI2022
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