META-ANALYSIS WORKSHOP

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National Animal Nutrition Program (NANP) Workshop
2023 American Dairy Science Association Meetings
June 25, 2023

https://github.com/Tempelman/Meta_analysis

Introduction to Meta Analysis

- Growing in popularity in animal science at apparently 15% per year (Sauvant et al. 2020; *Animal*).

- Likely to keep being important, especially if supplemental electronic submissions of raw data/summary statistics increases in the future.

- “The statistical analysis of a large *collection* of analysis *results* from individual studies for the purpose of integrating the findings” - Glass (1976)

- There are many important issues (publication bias, GIGO, etc.) that will go beyond the scope of a 2 hour workshop.

Strategy used in today's workshop

- Simulated Data (including some from St. Pierre, 2001)
- Why?
  - Truth is "known" -> so meta-analysis methods could be assessed relative to not only the truth but also to analyses based on raw data (versus using summary statistics from individual studies).
  - Raw data typically not available for meta-analysis (but that will change!)
  - Avoids problems with workshop participants trying to read in data.
- For the vast majority of cases, meta-analysis of original raw data should closely agree with meta-analysis of summary statistics!

Case #1: A good starting point

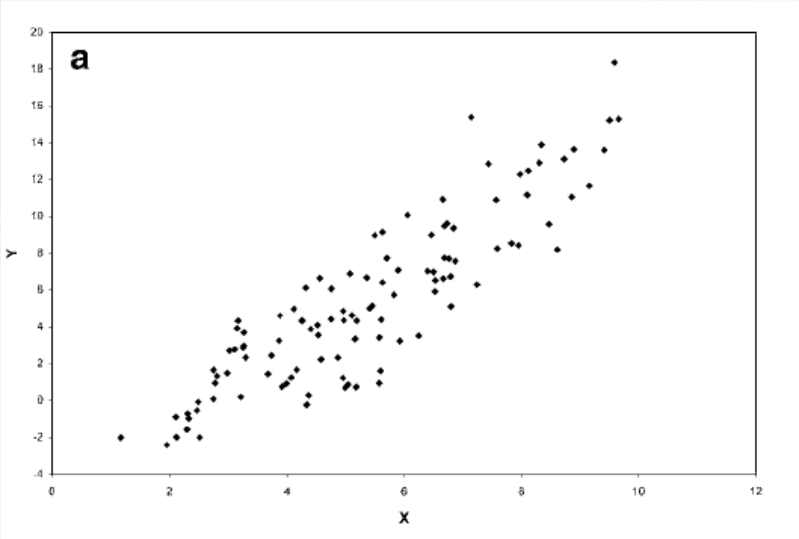
J. Dairy Sci. 84:741–755

Invited Review: Integrating Quantitative Findings from Multiple Studies Using Mixed Model Methodology[1]

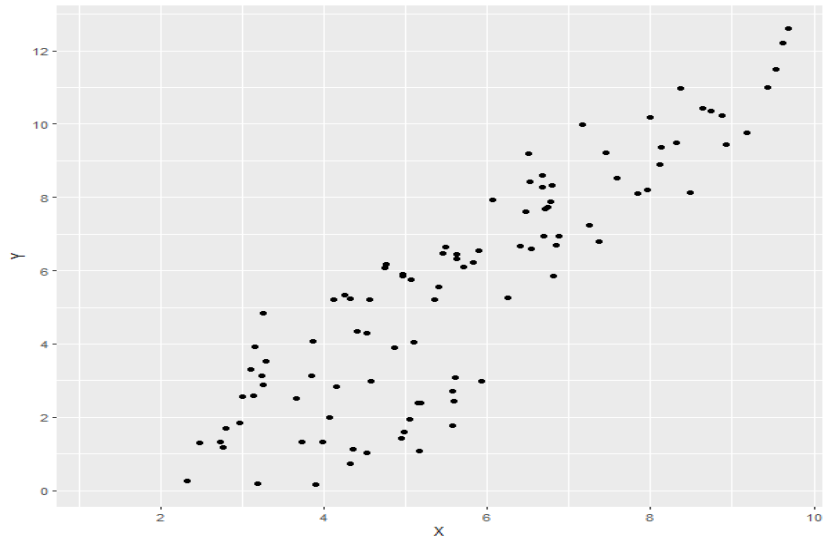
N. R. St-Pierre
Department of Animal Sciences
The Ohio State University
Columbus, OH 43210

Y vs X

Figure 2a in St-Pierre (2001)



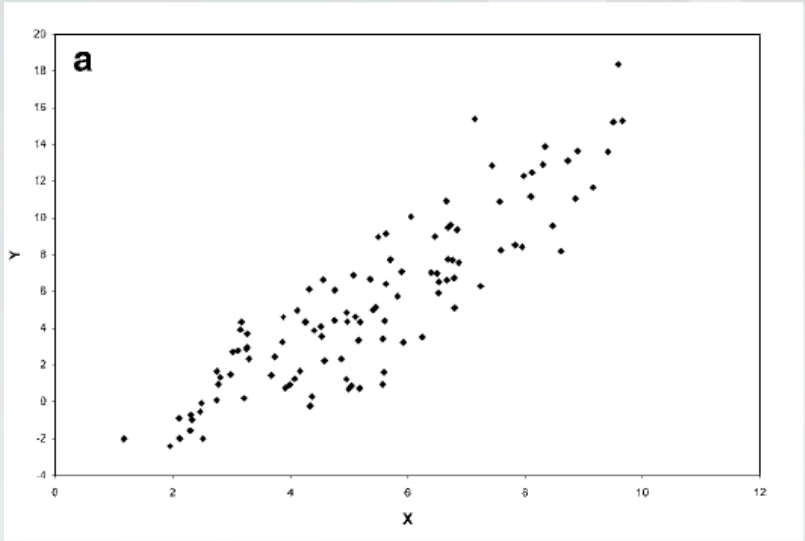
Graph created from data provided at Appendix St-Pierre (2001) (see lab)



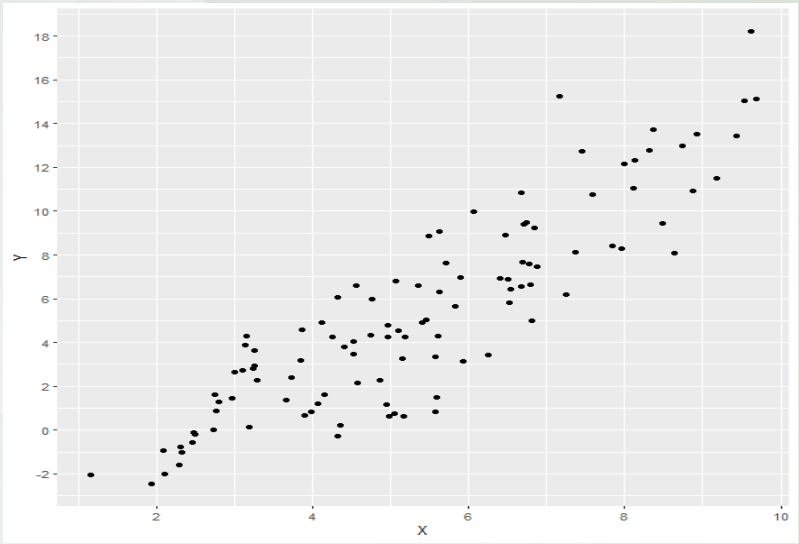
- Wrong data was seemingly provided

Corrected data provided by Dr. White (forwarded by Dr. St-Pierre)

Figure 2a in St-Pierre (2001)



Corrected data (see lab)



Data generation

- St-Pierre (2001) simulated data with *study-specific heterogeneity*:

$$y_{ij} = \beta_0 + s_i + (\beta_1 + b_{1i})\, x_{ij} + e_{ij};\quad i=1,2,\ldots\ n_{study} = 20,\quad j = 1,2\ldots,\ n_i$$

Study-specific intercept — *Study-specific slope*

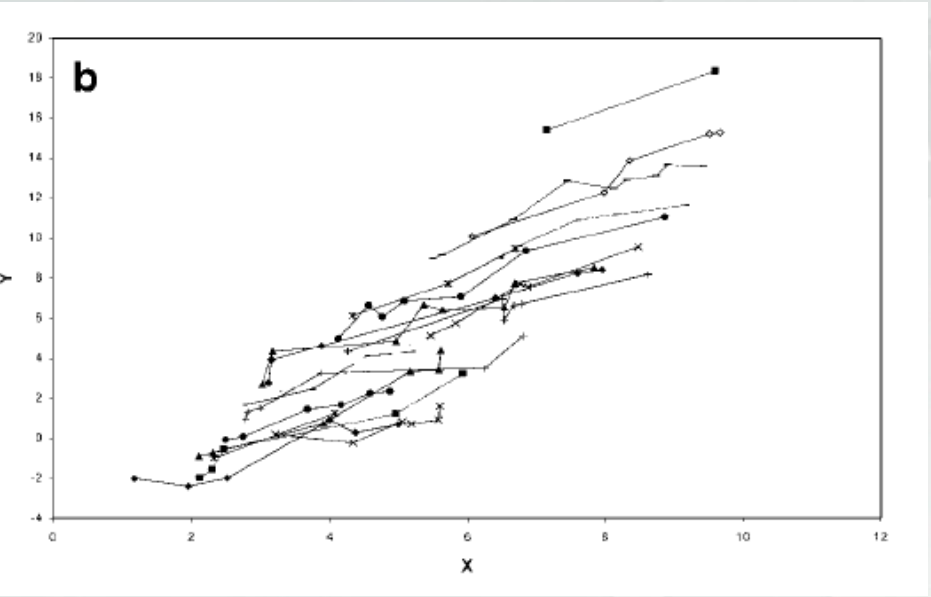
- St-Pierre choose $\beta_0 = 0$ and $\beta_1 = 1$, Furthermore,

$$\begin{bmatrix} s_i \\ b_{1i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 4 & 0.5\sqrt{4}\sqrt{0.04} \\ 0.5\sqrt{4}\sqrt{0.04} & 0.04 \end{bmatrix} \right);\ e_{ij} \sim N(0, 0.25)$$

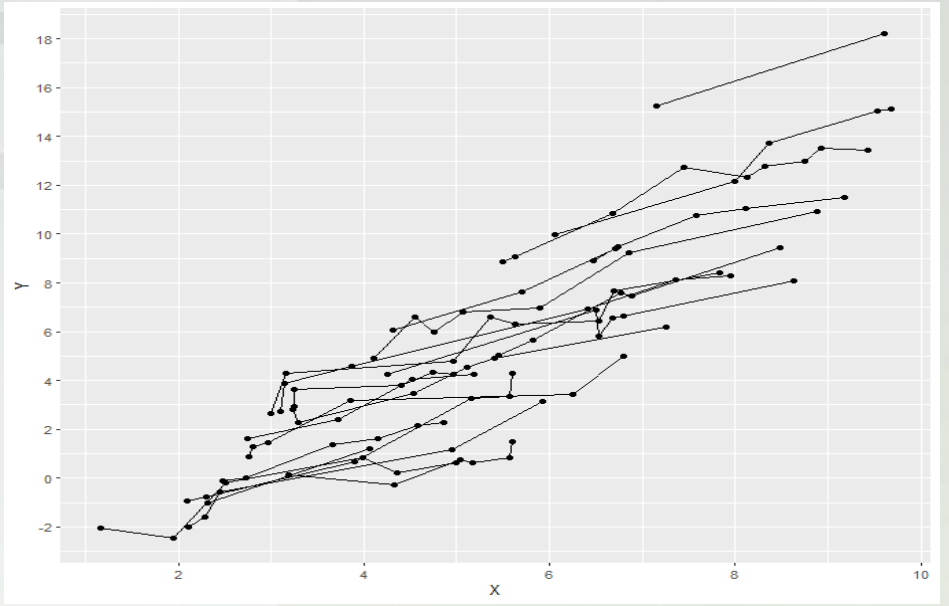
Correlation = 0.5 across studies

- Translation:
  - Study specific intercepts have an overall average expected value of 0 with a variance of 4 (sd =2) across studies
  - Study specific intercepts have an overall average expected value of 1 with a variance of 0.04 (sd =0.2) across studies
  - Residual variability about each study-specific line has sd = 0.5.

Figure 2b



Generated in R lab



Each line above corresponds to a different study

Goal: to *meta*-estimate the overall intercept (β_0) and slope (β_1) !

Meta-analysis

EFFECT SIZE (z_i)

- Suppose we only had the study-specific slopes and estimates alongside with the standard errors (St-Pierre did not pursue this)
  - Each meta-analysis "data point" would be a duplet of (1) estimate and (2) std.error

	Study	term	estimate	std.error	t.statistic	p.value	nrec
1	A	Intercept	-3.07734838	0.76656078	-4.01448711	1.593713e-02	6
2	A	X	0.81671421	0.22252478	3.67021698	2.138706e-02	6
3	B	Intercept	-4.15298434	0.63281610	-6.56270335	7.195518e-03	5
4	B	X	1.17586084	0.16301208	7.21333571	5.492902e-03	5
5	C	Intercept	-4.07597045	0.61009504	-6.68087785	2.609649e-03	6
6	C	X	1.39429265	0.13995723	9.96227671	5.702866e-04	6
7	D	Intercept	-1.80848842	1.09619111	-1.64979300	1.743302e-01	6
8	D	X	0.50088152	0.22415810	2.23450111	8.916425e-02	6
9	E	Intercept	-3.97906524	NaN	NaN	NaN	2
10	E	X	1.27253453	NaN	NaN	NaN	2

- Let's focus entirely on the slope estimates

Can't include Study E…only 2 datapoints!! No se!

Sampling variances and weights

- Instead of std.error, these are more commonly used in meta-analysis software
- Sampling variance = std.err^2 (s_i^2)
- Weight = (1/std.err^2) (w_i)
- So a duplet data point might be either one of the following:
  - estimate,sampling variance (z_i, s_i^2) popular in meta-analysis software (`metafor`)
  - estimate, weight (z_i, w_i) useful in mixed model analysis

s_i^2 :Not to be confused with variance of data or residuals!

w_i : "precision"

Common effects (CE) analysis

- **Ignores study heterogeneity!** → Assumes that variability between studies is simply due to sampling error!

- Working model:
  - $z_i = \zeta + \varepsilon_i$

  Unknown true effect size

  Residual (within-study) variation

  $\varepsilon_i \sim N(0, s_i^2 = \frac{1}{w_i})$

- Weighted least squares estimate $\hat{\zeta} = \frac{\sum_{i=1}^{n_{study}} w_i z_i}{\sum_{i=1}^{n_{study}} w_i}$

  with standard error $se(\hat{\zeta}) = \sqrt{\left(\sum_{i=1}^{n_{study}} w_i\right)}$

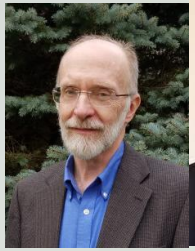
Common effects (CE) analysis

- Three different sets of R codes provided to compute CE estimate:
  - 1. WLS estimate on previous slide.
  - 2. Using linear (mixed) models software
  - 3. Using `metafor` (popular R meta-analysis software package)
    - Option `method = EE`

    - **THIS SHOULD NOT BE YOUR FIRST OPTION!**

Using linear models software to do CE analysis

(see Madden, LV, H-P Piepho and P.A. Paul. 2016. Statistical models and methods for network meta-analysis. Phytopathology 106:792-806)




- Common effect model $z_i = \zeta + \varepsilon_i$ $\quad \varepsilon_i \sim N(0, s_i^2 = \frac{1}{w_i})$

"Trick:" Same as fitting $z_i = \zeta + \frac{e_i}{w_i}$ $\quad e_i \sim N(0, \mathbf{1})$ Hold constant to 1 in software

Then specify w_i as a known weight function in the software (R or SAS)

- SAS is especially friendly for fixing variance components to constant values.
- `glmmTMB` seems to be the only R package that easily does this…but doesn't have as many covariance modeling options as SAS.

Mixed effects **univariate** meta-analysis

Meta-analysis statisticians bicker as to whether study is fixed or random

- Accomodates study heterogeneity!

- Working model:
  - $z_i = \zeta + u_i + \varepsilon_i$

Unknown true effect size

Residual (within-study) variation

$\varepsilon_i \sim N(0, s_i^2 = \frac{1}{w_i})$

Between –study heterogeneity:

$u_i \sim N(0, \tau^2)$

In other words:

- $z_i \sim N(0, \tau^2 + s_i^2)$

ONE SHOULD ALMOST ALWAYS EXPECT STUDY HETEROGENEITY!!

Mixed effects **multivariate** meta-analysis

- Jointly model study heterogeneity on two (or more) parameters.
  - e.g. intercept and slope…TOGETHER
- $$\begin{bmatrix} z_{i1} \\ z_{i2} \end{bmatrix} = \begin{bmatrix} \zeta_1 + u_{i1} + \varepsilon_{1i} \\ \zeta_2 + u_{i2} + \varepsilon_{2i} \end{bmatrix}$$

Study specific squared standard errors

$$\begin{bmatrix} u_{i1} \\ u_{i2} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \mathbf{G} = \begin{bmatrix} \tau_1^2 & \tau_{12} \\ \tau_{12} & \tau_2^2 \end{bmatrix} \right) \qquad \begin{bmatrix} \varepsilon_{1i} \\ \varepsilon_{2i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} s_{i1}^2 & 0 \\ 0 & s_{i2}^2 \end{bmatrix} \right)$$

- Meta-analysis software (e.g. `metafor` in R) having multivariate estimation capabilities will facilitate different specifications for **G**.
  - Above **G** is said to be “unstructured” (**UN**).

Mixed effects (ME) analysis

- Workshop will generally present different sets of R codes provided to estimate ζ
  - 1. Using linear (mixed) models software
  - 2. Using `metafor` (popular meta-analysis software package)
    - Option method = REML
- Will demonstrate influence/outlier diagnostics with St-Pierre example.
  - Follows closely typical linear model applications.
- How do I know if ME is better than CE? -> Likelihood ratio test/AIC/BIC

Recap on estimates of ζ (β_1 in St-Pierre)

- Using mixed model (random coefficients) analysis of raw data (deleting two studies with 2 datapoints each)

```
##             Estimate Std. Error t value
## (Intercept) -0.78266    0.50278  -1.557
## X            1.08502    0.05775  18.787
```

Random coefficient ("random regression") model

- Using CE analysis (`metafor`) on summary stats

```
## estimate      se     zval    pval   ci.lb   ci.ub
##   1.0864  0.0317  34.3165  <.0001  1.0244  1.1485  ***
```

- Using mixed model analysis (`metafor` univariate) on summary stats

```
## estimate      se     zval    pval   ci.lb   ci.ub
##   1.0810  0.0586  18.4410  <.0001  0.9661  1.1959  ***
```

- Using mixed model analysis (`metafor` multivariate) on summary stats

```
##                estimate      se     zval    pval   ci.lb   ci.ub
## termIntercept   -0.7954  0.4894  -1.6252  0.1041  -1.7546  0.1638
## termX            1.0820  0.0582  18.5847  <.0001   0.9679  1.1961  ***
```

Validating meta-analytic models

- A good meta-analysis should lead to nearly the same estimates and standard errors as one would get using the correct model on the raw data.
  - Being able to simulate various experimental designs might be pedagogically helpful in that regard (we do that today!)
- Various R packages (`metafor`, `netmeta`) also provide example datasets that are useful to work through as well.
- Linear mixed models allow diagnostic checks as well.
  - **Should be based on studentized residuals**. Regular estimated residuals are not comparable between different studies with different sample sizes/designs.

The completely randomized design

- We'll go through a similar exercise there!

$$y_{ijk} = \mu + Study_i + Trt_j + Study * Trt_{ij} + e_{ijk};$$

i =1,2,…, n_{study}, j = 1,2,…, n_{Trt}, $k = 1,2,\ldots, n_{cow_{ij}}$

- $Study_i \sim N(0, \sigma^2_{Study})$; $Study * Trt_{ij} \sim N(0, \sigma^2_{Study*Trt})$

  Study heterogeneity — Treatment effect heterogeneity

- $e_{ijk} \sim N(0, \sigma^2_e)$ between and within cow variability
  - Depending upon trait, one might actually anticipate extensive heterogeneity in VC across studies. Bayesian analyses on raw data then would be ideal

Fit simple CRD for each study

- Two different options for analyses determining which summary statistics to save from each study.
- Contrast-based:
  - Trt A vs Trt B mean difference ($\hat{\mu}_1$ - $\hat{\mu}_2$) ± standard errors (SED= SE($\hat{\mu}_1$ - $\hat{\mu}_2$))
  - **Most popular in the meta-analysis methodology literature**.

- Mean-based ("Arm-based")
  - Trt A mean $\hat{\mu}_1$ ± standard errors (SEM = SE($\hat{\mu}_1$))
  - Trt B mean $\hat{\mu}_2$ ± standard errors (SEM = SE($\hat{\mu}_2$))

Commonly pursued in animal/dairy science

Contrast-based analyses (i.e., on $\hat{\mu}_1$ - $\hat{\mu}_2$)

- Recommendation: **accommodate study-specific heterogeneity!**
- Same as shown previously for univariate analysis on slope (St-Pierre's example)
  - $z_i = \zeta + u_i + \varepsilon_i$

In other words:

- $z_i \sim N\left(0, \tau^2 + s_i^2\right)$

Residual (within-study) variation

$\varepsilon_i \sim N(0, s_i^2 = SED^2 = \frac{1}{w_i})$

Between –study heterogeneity:

$u_i \sim N\left(0, \tau^2\right)$

A comprehensive arm-based analysis (i.e., on $\hat{\mu}_1$ and $\hat{\mu}_2$ separately)

Popular R software (`netmeta`, `metafor`) converts arm-based to contrast based information before analyses

- Modeling extension needed relative to contrast-based analysis.
- $z_{ij} = \zeta_j + u_i + u\zeta_{ij} + \varepsilon_{ij}$

Between –study heterogeneity: $u_i \sim N(0, \tau^2)$ (or fixed?)

Between –study inconsistency: $u\zeta_{ij} \sim N(0, \omega^2)$

Unfortunately, many scientists don't consider this but most statisticians agree this is required

Residual (within-study) variation

$$\varepsilon_{ij} \sim N(0, s_{ij}^2 = SEM_{ij}^2 = \frac{1}{w_{ij}})$$

Recall the "trick"

Specify $e_{ij} \sim N(0, \mathbf{1})$ and weight by w_{ij}

An equivalent model to that on previous slide

$Combine\ u_i + u\zeta_{ij}$ as u_{ij}

- Multivariate specification…typically used in software packages

$$\begin{bmatrix} z_{i1} \\ z_{i2} \end{bmatrix} = \begin{bmatrix} \zeta_1 + u_{i1} + \varepsilon_{i1} \\ \zeta_2 + u_{i2} + \varepsilon_{i2} \end{bmatrix}; \qquad \begin{bmatrix} \zeta_1 \\ \zeta_2 \end{bmatrix} = \begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}$$

CS

$$\begin{bmatrix} u_{i1} \\ u_{i2} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \mathbf{G} = \begin{bmatrix} \tau^2 + \omega^2 & \tau^2 \\ \tau^2 & \tau^2 + \omega^2 \end{bmatrix} \right) \qquad \begin{bmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} s_{i1}^2 & 0 \\ 0 & s_{i2}^2 \end{bmatrix} \right)$$

CS (compound symmetry) "reasonable" but several others available using either mixed model analyses (SAS or R) or R meta-analysis packages (`metafor`).

A multivariate parameterization allows us to explore alternative specifications to CS (see Madden et al., 2016; Phytopathology)

Meta-analytic contrast versus arms-based analysis vs analysis of raw data

25 simulated CRD studies

- Should all give you (nearly) the same answers!!
- Using Raw Data:

```
##  contrast estimate    SE df t.ratio p.value
##  A - B       -1.92 0.475 24  -4.048  0.0005
```

- Contrast-based meta-analytic

```
##                Estimate Std. Error z value Pr(>|z|)
## (Intercept)  -1.9266     0.4752  -4.054 5.03e-05 ***
```

- Arms-based meta-analytic

```
##  contrast estimate    SE df t.ratio p.value
##  A - B       -1.93 0.475 48  -4.054  0.0002
```

`metafor` leads to same test statistic but uses z-test (infinite df). This is typical of meta-analysis software. See code. SAS is more flexible

Analyzing Latin square designs across studies

$$y_{ijkl} = \mu + Study_i + Trt_j + Study * Trt_{ij} + Cow(Study)_{ik} + Period(Study)_{il} + e_{ijkl};$$

i =1,2,…, n_{study} ; j = 1,2,…, n_{Trt}; $k = 1,2,\dots,n_{cow_{ij}}$; $l = 1,2,\dots,n_{period_{il}}$

$Study_i \sim N(0, \sigma^2_{Study})$; $Study * Trt_{ij} \sim N(0, \sigma^2_{Study*Trt})$

$Cow(Study)_{ik} \sim N\left(0, \sigma^2_{Cow(Study)}\right)$; $Period(Study)_{il} \sim N\left(0, \sigma^2_{Period(Study)}\right)$

$e_{ijk} \sim N(0, \sigma^2_e)$ ***within*** cow variability

Contrast vs Arm based analysis

- Contrast-based analysis
  - With 3 or more treatments, more than one contrast then!
- Suppose focus was on A vs B contrast!
  - Two potential contrast-based strategies.
  1. Only consider univariate A vs B contrast analysis.
  2. Multivariate analysis considering ALL contrasts (or just “base contrasts” Piepho et al. (2012))

Contrast-based analysis.

Residual (within-study) variation

- Univariate: same as before: $z_i = \zeta + u_i + \varepsilon_i$

$\varepsilon_i \sim N(0, s_i^2 = SED^2 = \frac{1}{w_i})$

Between –study heterogeneity:

$u_i \sim N(0, \tau^2)$

- Multivariate: Include other contrasts.
  - Suppose a three-treatment replicated Latin square

CS

$$\begin{bmatrix} z_{1i} \\ z_{2i} \\ z_{3i} \end{bmatrix} = \begin{bmatrix} \zeta_1 + u_{1i} + \varepsilon_{1i} \\ \zeta_2 + u_{2i} + \varepsilon_{2i} \\ \zeta_3 + u_{3i} + \varepsilon_{3i} \end{bmatrix} \quad \begin{bmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{bmatrix} = \begin{bmatrix} \mu_1 - \mu_2 \\ \mu_1 - \mu_3 \\ \mu_2 - \mu_3 \end{bmatrix} \quad \begin{bmatrix} u_{1i} \\ u_{2i} \\ u_{3i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \mathbf{G} = \begin{bmatrix} \tau^2 & \tau_c & \tau_c \\ \tau_c & \tau^2 & \tau_c \\ \tau_c & \tau_c & \tau^2 \end{bmatrix} \right)$$

CS (compound symmetry) “reasonable” but several others available using either mixed model analyses (SAS or R) or R meta-analysis packages (`metafor`)

  - Basic versus functional contrasts (Piepho et al. 2012)

Arm-based analysis.

Multivariate: Suppose a three treatment replicated Latin square

$$\begin{bmatrix} z_{1i} \\ z_{2i} \\ z_{3i} \end{bmatrix} = \begin{bmatrix} \zeta_1 + u_{1i} + \varepsilon_{1i} \\ \zeta_2 + u_{2i} + \varepsilon_{2i} \\ \zeta_3 + u_{3i} + \varepsilon_{3i} \end{bmatrix} \qquad \begin{bmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{bmatrix} = \begin{bmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \end{bmatrix} \qquad \begin{bmatrix} u_{1i} \\ u_{2i} \\ u_{3i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \mathbf{G} = \begin{bmatrix} \tau^2 & \tau_c & \tau_c \\ \tau_c & \tau^2 & \tau_c \\ \tau_c & \tau_c & \tau^2 \end{bmatrix} \right)$$

Residual (within-study) variation

$$\varepsilon_{ij} \sim N(0, s_{ij}^2 = \frac{SED_{ii}^{\,2}}{2} = \frac{1}{w_{ij}})$$

Between –study heterogeneity: CS but many other options are available

Don't use SEM if cow treated as random because between-cow variation is "cancelled out" in treatment comparisons (see Piepho et al., 2012)

The arm-based analysis is “more correct” than the contrast based analyses given model on Slide 25 ((Piepho et al., 2012, Biometrics)).

- If $\begin{bmatrix} u_{1i} \\ u_{2i} \\ u_{3i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \mathbf{G} = \begin{bmatrix} \tau^2 & \tau_c & \tau_c \\ \tau_c & \tau^2 & \tau_c \\ \tau_c & \tau_c & \tau^2 \end{bmatrix} \right)$ for an arm-based analysis with $\begin{bmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{bmatrix} = \begin{bmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \end{bmatrix}$

- Then for a contrast-based analysis:

$$\begin{bmatrix} \zeta_1 \\ \zeta_2 \\ \zeta_3 \end{bmatrix} = \begin{bmatrix} \mu_1 - \mu_2 \\ \mu_1 - \mu_3 \\ \mu_2 - \mu_3 \end{bmatrix} = \begin{bmatrix} 1 & -1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \end{bmatrix}$$

such that $\begin{bmatrix} u_{1i} \\ u_{2i} \\ u_{3i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \mathbf{G} = \begin{bmatrix} 1 & -1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & -1 \end{bmatrix} \left\| \begin{bmatrix} \tau^2 & \tau_c & \tau_c \\ \tau_c & \tau^2 & \tau_c \\ \tau_c & \tau_c & \tau^2 \end{bmatrix} \right\| \begin{bmatrix} 1 & -1 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & -1 \end{bmatrix} \right)$

Moderator variables

- Effects of parity, lactation stage, 2nd treatment factor, etc.
  - Could add them as additional model factors, including interaction with primary treatment factor
- But more care is needed with Latin squares compared to CRD.
  - e.g. often split-plot-like arrangements -> cows are blocks for treatments but experimental units for parity

Network meta-analysis

- Suppose focus is on Treatment A vs B.
  - Some researchers will only focus on studies have both Treatments A and B.
  - Direct comparisons
- But suppose some studies include A vs C, some include B vs C.
  - Indirect comparisons between A and B: i.e. (A-C) – (B-C) = A-B.
- A network meta-analysis accommodates direct and indirect comparisons.
  - Particularly easier to do with arm-based rather contrast-based (see papers from Piepho and colleagues and provided code).
  - Systematic inconsistency: when direct ≠ indirect comparisons

Can I combine CRD and Latin square (and others) studies?

- Most certainly!
- Network-based arm analysis best suited to capture direct and indirect comparisons.
- Caution.
  - Sampling variances for CRD treatment means = $s^2 = 1/w = SEM^2/2$
  - For all other designs, use $s^2 = 1/w = SED^2/2$
    - Actually, simply just use $s^2 = 1/w = SED^2/2$ FOR ALL DESIGNS!
- Infer upon potential systematic inconsistencies!
  - i.e. infer effect of design (CRD or Latin Square) on treatment effects

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20502

August 25, 2022

MEMORANDUM FOR THE HEADS OF EXECUTIVE DEPARTMENTS AND AGENCIES

FROM: Dr. Alondra Nelson
Deputy Assistant to the President and Deputy Director for Science and Society
Performing the Duties of Director
Office of Science and Technology Policy (OSTP)

SUBJECT: Ensuring Free, Immediate, and Equitable Access to Federally Funded Research

This memorandum provides policy guidance to federal agencies with research and development expenditures on updating their public access policies. In accordance with this memorandum, OSTP recommends that federal agencies, to the extent consistent with applicable law:

1. Update their public access policies as soon as possible, and no later than December 31st, 2025, to make publications and their supporting data resulting from federally funded research publicly accessible without an embargo on their free and public release;
2. Establish transparent procedures that ensure scientific and research integrity is maintained in public access policies; and,
3. Coordinate with OSTP to ensure equitable delivery of federally funded research results and data.

My vision for the future

- Mature raw data repositories
  - Research reproducibility
  - Allow for Bayesian extensions.
    - Model distributions on variance components over studies. Better borrowing of information across studies on variance components.
    - Multivariate analyses involving multiple correlated traits over time.
  - Code also submitted with papers!!

Acknowledgements: *NCCC-170 Research Advances in Agricultural Statistics*

https://www.nimss.org/projects/view/mrp/outline/18798 supported by Hatch Multistate Research Fund (MRF) provided by the National Institute for Food and Agriculture (NIFA)