

Conducting Meta-analysis under Confidence Distribution Framework Using gmeta Package in R

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Outline of Today's Presentation

- Motivation
- Confidence distribution (CD)
- Meta-analysis under CD combining framework
- Demonstrations of gmeta package
- Conclusion and future work

Fusion Learning/Meta-analysis - not just a Buzz-word

- Advances of technologies \Rightarrow information explosion
 - data acquisition, storage and access
 - streaming media, cloud computing

need
 \Rightarrow efficient and meaningful processing
- **Meta-analysis: combining results from separate studies**
 - inferences from the combined results are typically **more reliable** than inferences from any single study
 - **enormous literature**: i.e. 281 references in a review by Sutton and Higgins (2008) on model based meta-analysis alone
 - important research: both in application and theoretical foundation

What is a Confidence Distribution?

- Characterization: a **sample-dependent distribution function on parameter space** that can represent **confidence intervals of all levels** for a parameter of interest.
- Θ - parameter space of the unknown parameter of interest θ ,
 \mathcal{X} - sample space corresponding to sample $\mathbf{x} = \{x_1, \dots, x_n\}$

DEFINITION: a function $H_n(\cdot) = H_n(\mathbf{x}, \cdot)$ on $\mathcal{X} \times \Theta \rightarrow [0, 1]$ is a CD for θ if

1. for each given $\mathbf{x} \in \mathcal{X}$, $H_n(\cdot)$ is a **continuous cumulative distribution function** on Θ
2. when $\theta = \theta_0$ (true), $H_n(\theta_0) \equiv H_n(\mathbf{x}, \theta_0) \sim U[0, 1]$
 \Rightarrow **provide confidence intervals of all levels for θ_0**

$$\Pr(\theta_0 \leq H_n^{-1}(\alpha)) = \alpha \quad \text{for all } 0 \leq \alpha \leq 1$$

- ensuring **unbiasedness, consistency, efficiency**

CD: the Past

- Long history
 - Fraser (2011) suggested the seed idea (alas, fiducial idea) can be traced back to Bayes (1763) and Fisher (1922).
 - the term “CD” appeared as early as 1937 in a letter from E.S. Pearson to W.S. Gosset (Student)
 - the first use of the term in a formal publication is Cox (1958).
- Little attention on CDs in the past
 - historic **connection to fiducial distribution** (considered as “Fisher’s biggest blunder” (Efron 1998))
 - **no important utilities of CDs in applications**

CD: the Present

- Recent developments
 - entirely within the frequentist school
 - with no attempt to derive a new “paradox free” fiducial theory
 - focus on providing frequentist inference tools for problems
 - unavailable/unknown solutions
- Renewed interest
 - cluster of important publications:
 - Schweder & Hjort 2002, 2014; Singh, Xie & Strawderman 2001, 2005, 2007; Xie, Singh & Strawderman 2011, Xie & Singh 2013, Liu et al. 2014a,b, etc.
 - focus on developing new inference tools
 - Efron (1998): “... but here is a safe prediction for the 21st century: ... something like fiducial inference will play an important role ...”
 - Efron (2013): The CD development is “a grounding process” to help solve “perhaps the most important unresolved problem in statistical inference....”

CD - the Content

- Provide meaningful answers for many questions in statistical inference: e.g., point estimate, CI, p-values, etc

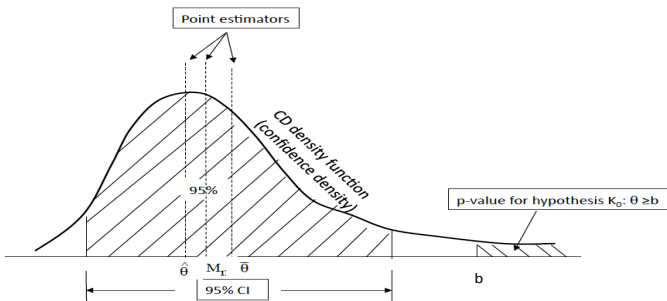


Figure 1. The plot is a graphical illustration on making inference using a CD, including examples of point estimators (mode $\hat{\theta}$, median M_n and mean $\bar{\theta}$), a level 95% confidence interval and a one-sided p-value.

Example 1: Normal CD function $N(\bar{x}, 1/n) \implies$ (i) Point estimator: \bar{x} ; (ii) level $(1 - \alpha)100\%$ CI: $\bar{x} \pm \Phi^{-1}(1 - \alpha/2)/\sqrt{n}$; (iii) p-value: $1 - \Phi(\sqrt{n}(b - \bar{x}))$, etc.

(cf., Xie & Singh 2013; Singh et al. 2007)

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- The idea of the CD approach is to **use a sample-dependent distribution (or density) function** to estimate the parameter of interest.

Example 1: normal mean and variance

- assume sample $x_1, \dots, x_n \stackrel{iid}{\sim} N(\mu, \sigma^2)$, then

$$H_n(y) = F_{t_{n-1}}\left(\frac{y - \bar{x}}{s_n/\sqrt{n}}\right) \text{ is a CD for } \mu$$

- \bar{x} : sample mean; s_n^2 : sample variance
- $F_{t_{n-1}}$: CDF of the Student t_{n-1} -distribution

** satisfying the two conditions for CD

(1). with a sample \mathbf{x} ,

$$H_n(y) \rightarrow 0 \text{ as } y \rightarrow -\infty \text{ and } H_n(y) \rightarrow 1 \text{ as } y \rightarrow \infty$$

(2). with $y = \mu$,

$$\begin{aligned} \Pr(H_n(\mu) \leq \alpha) &= \Pr\left(F_{t_{n-1}}\left(\frac{\mu - \bar{x}}{s_n/\sqrt{n}}\right) \leq \alpha\right) \\ &= \Pr(T_{n-1} \leq F_{t_{n-1}}^{-1}(\alpha)) \\ &= F_{t_{n-1}}(F_{t_{n-1}}^{-1}(\alpha)) = \alpha \end{aligned}$$

Example 2: CD from hypothesis test

- p -value for one-sided test: $H_0: \mu = \mu_0$ vs $H_a: \mu > \mu_0$

$$p(\mu_0) = P(\bar{X} > \bar{x}_n) = 1 - \Phi\left(\frac{\bar{x}_n - \mu_0}{1/\sqrt{n}}\right) = \Phi\left(\frac{\mu_0 - \bar{x}_n}{1/\sqrt{n}}\right)$$

p -value function $p(y) = \Phi\left(\frac{y - \bar{x}_n}{1/\sqrt{n}}\right)$ is a CD for μ

- with a sample \mathbf{x} ,

$$p(y) \rightarrow 0 \text{ as } y \rightarrow -\infty \text{ and } p(y) \rightarrow 1 \text{ as } y \rightarrow \infty$$

- with $y = \mu_0$, $\Pr(p(\mu_0) \leq \alpha) = \Pr\left(\Phi\left(\frac{\mu_0 - \bar{x}_n}{1/\sqrt{n}}\right) \leq \alpha\right) = \alpha$

- suppose $n = 100$ and we observe $\bar{x}_n = 0.3$

μ_0	$-\infty$	-0.1	0	0.1	0.1355	0.2	0.3	0.496
p -value	0	0.00002	0.0014	0.022	0.05	0.16	0.5	0.975

Example 3: CD from normalizing likelihood

- Likelihood function

$$\begin{aligned} L(\mu|x_1, \dots, x_n) &= \prod f(x_i|\mu) = C e^{-\frac{1}{2}(x_i - \mu)^2} \\ &= C e^{-\frac{n}{2}(\bar{x}_n - \mu)^2 - \frac{1}{2} \sum (x_i - \bar{x}_n)^2} \end{aligned}$$

- Normalized with respect to μ :

$$\frac{L(\mu|data)}{\int L(\mu|data)d\mu} = \dots = \frac{1}{\sqrt{2\pi/n}} e^{-\frac{n}{2}(\bar{x}_n - \mu)^2}$$

is a CD for μ

CD: Unifying Concept for Inference

- Wide range of examples (Xie and Singh 2013) :
 - bootstrap distribution
 - p-value functions
 - Bayesian posteriors
 - empirical likelihood
 -
- New methodology developments: e.g. Rutgers group
 - new prediction approaches
 - new testing methods
 - new simulation schemes
 - **combining information from diverse sources** through combining CDs (**meta analysis**, split & conquer, etc.)

Meta-analysis through Confidence Distributions

- Why combine CDs in meta-analysis?
 - **informative**: much more than a single point or an interval
 - **broad**: covering a broad range of examples
 - **supported by statistical theory**: e.g., ensuring frequentist coverage, etc
- Key points/steps:
 - **summarize** relevant data information **using a CD in each study**
 - **synthesize** information from diverse sources/studies **via combination** of the CDs from these studies

General framework on Combining CDs

- Suppose there are k independent studies to estimate θ - a common parameter of interest.
 - data \mathbf{x}_i of the i th study $\xrightarrow{\text{construct}}$ CD - $H_i(\cdot) = H_i(\mathbf{x}_i, \cdot)$ for θ
- A general recipe for combining these k independent CDs:

$$H^{(c)}(\theta) = \Pr\{g_c(U_1, \dots, U_k) \leq g_c(H_1(\theta), \dots, H_k(\theta))\} \quad (1)$$

$H^{(c)}(\cdot)$:

- a combined CD for θ the common true parameter
- contains information from all k samples

$g_c(u_1, \dots, u_k)$:

- a non-decreasing and continuous function in each coordinate
 - $U_1, \dots, U_k \stackrel{iid}{\sim} U[0, 1]$

Special Choices of $g(\cdot)$ Function

- Choice 1:

$$g_c(u_1, \dots, u_k) = w_1 a_0(\mu_1) + \dots + w_k a_0(\mu_k) \quad (2)$$

- $a_0(\cdot)$: continuous and monotonic function
 - often $a_0(\cdot) = F_0^{-1}(\cdot)$ where $F_0(\cdot)$ is a CDF (i.e. $a_0 = \Phi^{-1}$)
- w_i : generic weights (≥ 0) for the combination ($\sum w_i > 0$)
 - **fixed**: improve the efficiency of combination
 - **adaptive**: robust combination

- Choice 2:

$$g_c(u_1, \dots, u_k) = w_1 \mu_1 + \dots + w_k \mu_k \quad (3)$$

Case 1: Fisher p -value combination

- Conduct k clinical trials to study $H_0 : \theta \geq s$ vs $H_1 : \theta < s$
 - the p -value is a function of $s \Rightarrow p$ -value function
 - let $p_i(\cdot)$ be the p -value function for i th study \Rightarrow a CD function

- Set $w_i = 1$ and $a_0(\cdot) = \log(\cdot)$ in CD combining recipe:

$$g_c(u_1, \dots, u_k) = w_1 a_0(\mu_1) + \dots + w_k a_0(\mu_k)$$

$$\begin{aligned} \therefore H^{(c)}(s) &= \Pr\{g_c(U_1, \dots, U_k) \leq g_c(p_1(s), \dots, p_k(s))\} \\ &= \Pr\{\log U_1 + \dots + \log U_k \leq \log p_1(s) + \dots + \log p_k(s)\} \\ &= \Pr\left\{-2 \sum_{i=1}^k \log U_i \geq -2 \sum_{i=1}^k \log p_i(s)\right\} \\ &= \Pr\left\{\chi_{2k}^2 \geq -2 \sum_{i=1}^k \log p_i(s)\right\} \quad \Rightarrow \text{Fisher's method} \end{aligned}$$

- fact: $U_1, \dots, U_k \stackrel{iid}{\sim} U[0, 1] \Rightarrow -2 \sum_{i=1}^k \log U_i \sim \chi_{2k}^2$

Case 2: Stouffer (Normal) p -value Combination

- Use $g_c(u_1, \dots, u_k) = \Phi^{-1}(u_1) + \dots + \Phi^{-1}(u_k)$

$$\begin{aligned}
 \therefore H^{(c)}(s) &= P\{g_c(U_1, \dots, U_k) \leq g_c(p_1(s), \dots, p_k(s))\} \\
 &= \Pr\left\{\sum_{i=1}^k \Phi^{-1}(U_i) \leq \sum_{i=1}^k \Phi^{-1}(p_i(s))\right\} \\
 &= \Pr\left\{Z \leq \frac{1}{\sqrt{k}} \sum_{i=1}^k \Phi^{-1}(p_i(s))\right\} \quad (Z \sim N(0, 1)) \\
 &= \Phi\left\{\frac{1}{\sqrt{k}} \sum_{i=1}^k \Phi^{-1}(p_i(s))\right\} \quad \Rightarrow \text{Stouffer Method}
 \end{aligned}$$

– **fact:** $\Phi^{-1}(U_i) \sim N(0, 1) \Rightarrow \sum \Phi^{-1}(U_i) \sim N(0, k)$

Case 3: Fixed-effects Meta-Analysis

- Let Y_i be a summary statistic with known variance s_i^2

$$Y_i \stackrel{iid}{\sim} N(\theta, s_i^2) \quad \text{for } i = 1, \dots, k$$

– CD function $H_i(\theta) = \Phi[(\theta - Y_i)/s_i]$

- Use $g_c(u_1, \dots, u_k) = \Phi^{-1}(u_1)/s_1 + \dots + \Phi^{-1}(u_k)/s_k$

$$\therefore H^{(c)}(\theta) = P\{g_c(U_1, \dots, U_k) \leq g_c(H_1(\theta), \dots, H_k(\theta))\}$$

$$= P\left\{ \sum_{i=1}^k \Phi^{-1}(U_i)/s_i \leq \sum_{i=1}^k \Phi^{-1}(\Phi[(\theta - Y_i)/s_i])/s_i \right\}$$

$$= \Phi\left(\left(\sum_{i=1}^k \frac{1}{s_i^2} \right)^{1/2} (\theta - \hat{\theta}_c) \right) \Rightarrow \text{Normand 1999}$$

– $\hat{\theta}_c = (\sum_{i=1}^k Y_i/s_i^2)/(\sum_{i=1}^k 1/s_i^2)$ - weighted average

** estimate θ by a normal CD $N(\hat{\theta}_c, (\sum_{i=1}^k 1/s_i^2)^{-1})$

Unifying Framework for Combining Information

A unifying platform for almost all existing methods of information combination

Classical approaches of combining p-values (from Marden, 1991)	Fisher method Stouffer (normal) method Tippett (min) method Max method Sum method
Model-based meta-analysis approaches (from Normand, 1999, Table IV)	Fixed-effects model: MLE method Fixed-effects model: Bayesian method Random-effects model: Method of moment Random-effects model: REML method Random-effects model: Bayesian method (normal prior on θ and fixed τ)
(Xie, Singh & Strawderman, 2011)	
Others (2×2 tables)	Tian et al (2009, <i>Biostat.</i>) approach of combining intervals (risk difference) Mantel-Haenszel (MH) method (odds ratio) Peto method (odds-ratio)
(Yang et al, 2013; Yang, 2013)	
Combining functions	Multiplication of likelihood functions Bayesian formula

(Singh, Xie & Strawderma 2005; Xie et al 2013)

Case 4: robust meta-analysis of large studies

- Setting: k studies of the same treatment
 - sample sizes n_1, n_2, \dots, n_k - all very large
 - true value of parameter $\theta_i^{(0)}$ for i th study (extension of fixed-effects models)

$$Y_i \stackrel{ind}{\sim} N(\theta_i^0, s_i^2) \quad \text{for } i = 1, 2, \dots, k$$

- parameter of interest $\theta_0 = \text{median}\{\theta_1^{(0)}, \dots, \theta_k^{(0)}\}$
 - assume majority of studies with θ_0 , others are outlying studies
- Key ideas (Xie et al 2011):
 - use asymptotic CD - $\Phi\left(\frac{\theta - \bar{Y}_i}{s_i/\sqrt{n}}\right)$ for each study
 - down-weight studies far from the majorities by using adaptive weights

Case 5: robust meta-analysis of large # of studies

- **Setting:** true parameters of studies come from a population with a mixture of two components (mixture mean θ_*):
 - a regular (or “good”) part with mean of θ_0
 - a contaminated part (with a different distribution)
- Xie et al 2011 proposed a combined CD function:
 - using $H_i(\theta)$ - a CD function for θ_* in the mixed distribution

$$H^{(c)}(\theta) = \Phi\left(\frac{\sum_{i=1}^k w_i(H_i(\theta) - 0.5)}{\sqrt{k} \sum_{i=1}^k w_i^2/12}\right)$$

- median of $H^{(c)}$: a robust and consistent estimator of θ_* distribution
 - **protection against model mis-specification**
- extension of random-effects meta-analysis

Case 6: Exact Meta-Analysis for 2×2 Table

	events	non-events	total
treatment (drug)	x_i	$n_i - x_i$	n_i
control (placebo)	y_i	$m_i - y_i$	m_i

- Conventional meta-analysis - some with zero cell count
 - exclusion of tables with zero cell count
 - continuity correction
 - large sample approximation for distribution of summary statistic
- Exact meta-analysis (Liu et al 2014)
 - conduct an exact test study for each of the studies
 - obtain associated p -values
 - choose $a_0(\cdot)$ and weights to get a combined CD
 - ** achieve asymptotical efficiency & enhance finite sample efficiency

Computing Package - gmeta

- R package for CD combining (Yang, Cheng and Xie 2015)
 - mimicing the structure of the `glm()` function in R
 - “family” in `glm()` \Leftrightarrow “gc” in `gmeta()`
 - “link” in `glm()` \Leftrightarrow “weights” in `gmeta()`
 - a plot function to visualize individual and combined CDs through extended forest plots
- Functionalities:
 - classical p -value combination methods (such as methods of Fisher, Stouffer, Tip- pett, etc.)
 - meta-anlalysis with fixed-effects and random-effects models
 - robust meta-analysis
 - exact meta-analysis

Computing Package - gmeta

- Available at:
<http://cran.r-project.org/web/packages/gmeta>
- CRAN Page:

`gmeta`: Meta-Analysis via a Unified Framework of Confidence Distribution

An implementation of an all-in-one function for a wide range of meta-analysis problems. It contains a single function `gmeta()` that unifies all standard meta-analysis methods and also several newly developed ones under a framework of combining confidence distributions (CDs). Specifically, the package can perform classical p-value combination methods (such as methods of Fisher, Stouffer, Tippett, etc.), fit meta-analysis fixed-effect and random-effects models, and synthesizes 2x2 tables. Furthermore, it can perform robust meta-analysis, which provides protection against model-misspecifications, and limits the impact of any unknown outlying studies. In addition, the package implements two exact meta-analysis methods from synthesizing 2x2 tables with rare events (e.g., zero total event). A plot function to visualize individual and combined CDs through extended forest plots is also available.

Version: 2.2-6
 Depends: stats, [BiasedUrn](#), [binom](#)
 Published: 2016-02-23
 Author: Guang Yang, Jerry Q. Cheng, and Minge Xie
 Maintainer: Guang Yang <gyang.rutgers@gmail.com>
 License: [GPL-2](#) | [GPL-3](#) [expanded from: GPL (≥ 2)]
 NeedsCompilation: yes
 In views: [MetaAnalysis](#)
 CRAN checks: [gmeta results](#)

Arguments of gmeta()

```
gmeta <- function(gmi, gmi.type = c('pivot', 'cd', 'pvalue', '2x2'),
  method = c('fixed-mle', 'fixed-robust1', 'fixed-robust2',
    'fixed-robust2(sqrt12)', 'random-mm', 'random-reml', 'random-tau2',
    'random-robust1', 'random-robust2', 'random-robust2(sqrt12)',
    'fisher', 'normal', 'stouffer', 'min', 'tippett', 'max', 'sum',
    'MH', 'Mantel-Haenszel', 'Peto', 'exact1', 'exact2'),
  linkfunc = c('inverse-normal-cdf', 'inverse-laplace-cdf'),
  weight = NULL, study.names = NULL, gmo.xgrid = NULL, ci.level = 0.95,
  tau2 = NULL, mc.iteration = 10000, eta = 'Inf', verbose = FALSE,
  report.error = FALSE)
```

- key arguments

- method - assumption for a meta-analysis model
- linkfunc - how to handle information from individual studies

- other

- gmi - summary statistics
- gmo.xgrid - range and grid points to evaluate a combined CD

Demonstration of gmeta - the Ulcer Data

- 41 randomized trials of a treatment for stomach ulcers (Efron 1996)

```
> library(gmeta)
> data(ulcer); ulcer.o <- as.matrix(ulcer) # original data
> ulcer.o
```

	TrtEvent	TrtNonevent	CtrlEvent	CtrlNonevent
[1,]	7	8	11	2
[2,]	8	11	8	8
[3,]	5	29	4	35
[4,]	7	29	4	27
[5,]	3	9	0	12
[6,]	4	3	4	0
[7,]	4	13	13	11
...				
...				
[36,]	10	30	12	8
[37,]	3	13	2	14
[38,]	4	30	5	14
[39,]	7	31	15	22
[40,]	0	34	34	0
[41,]	0	9	0	16

Example 1: p -value combination

- make continuity correction
- calculate log odds ratios and their standard deviations
- calculate p -value for all studies

```
> # impute 0.5 to zero events
> ulcer <- ifelse(ulcer.o==0, 0.5, ulcer.o)

> # summary statistics
> ulcer.theta <- log( (ulcer[,1]*ulcer[,4]) / (ulcer[,2]*ulcer[,3]) )
> ulcer.sigma <- sqrt(1/ulcer[,1] + 1/ulcer[,2] + 1/ulcer[,3] + 1/ulcer[,4])

> # p-values from individual studies for H0: LOR >=0 vs. Ha: LOR < 0
> ulcer.pvalues <- 1 - pnorm(0, mean=ulcer.theta, sd=ulcer.sigma)

> ulcer.pvalues
[1] 2.364514e-02 3.204119e-01 7.170408e-01 7.631117e-01 9.045478e-01
[6] 1.435593e-01 2.786246e-02 2.963888e-04 2.499260e-01 1.713687e-03
.....
.....
[36] 5.038550e-03 6.858163e-01 9.294398e-02 1.960676e-02 1.402044e-05
[41] 6.108883e-01
```


Example 1: p -value combination - Stouffer & Tippett

```
> ## apply Stouffer (Normal) method ##
> gmo.pvalue1 <- gmeta(ulcer.pvalues, gmi.type='pvalue', method='normal')
> print(gmo.pvalue1)
```

P-value combination through CD-Framework

```
Combine Method:    normal
Combined p-value:  1.10779e-16
```

```
> ## apply Tippett method ##
> gmo.pvalue2 <- gmeta(ulcer.pvalues, gmi.type='pvalue', method='tippett')
> print(gmo.pvalue2)
```

P-value combination through CD-Framework

```
Combine Method:    tippett
Combined p-value:  0.0005746768
```

Example 1: p -value Combination - all 5 methods

```

> ## Table of the results from all p-value combination methods
> pvalue.combine.methods = c('fisher', 'stouffer', 'tippet', 'max', 'sum')
> combined.pvalue.vector = rep(NA, 5)
> for ( i in 1:5 ) {
>   combined.pvalue.vector[i] <- gmeta(ulcer.pvalues, gmi.type='pvalue',
>   method=pvalue.combine.methods[i])$cmbd.pvalue
> }
> mthds <- 'method'
> pvlus <- 'p-value'
> for ( i in 1:5) {
>   mthds = paste(mthds, pvalue.combine.methods[i], sep='\t\t& ')
>   pvlus = paste(pvlus, combined.pvalue.vector[i], sep='\t& ')
> }

```

p value combination results:

Method	Fisher	Stouffer	Tippet	Max	Sum
p-value	2.1684e-19	1.1078e-16	5.7468e-04	1.6357e-02	4.8591e-09

Model-based Meta-analysis

- *method* argument:
 - fixed-effects: `method='fixed-mle'`
 - random-effects:
 - `method='random-mm'` (DL estimator)
 - `method='random-reml'` (REML estimator)

- *linkfunc* argument - specifying $a_0(\cdot)$ function
 - default value - 'inverse-normal-cdf': $a_0(\cdot) = \Phi^{-1}(\cdot)$
 - other choice - 'inverse-laplace-cdf':

- *weight* argument - specifying study-specific weights
 - default NULL - assigning weights depending on linkfunc
 - inverse standard deviation weights when `linkfunc='inverse-normal-cdf'`
 - all ones when `linkfunc='inverse-laplace-cdf'`

Example 2: Fixed-effects Meta-analysis

```
> ## use summary statistics ##
> ulcer.theta <- log( (ulcer[,1]*ulcer[,4]) / (ulcer[,2]*ulcer[,3]) )
> ulcer.sigma <- sqrt(1/ulcer[,1] + 1/ulcer[,2] + 1/ulcer[,3] + 1/ulcer[,4])
> ulcer.pivots <- data.frame(mns=ulcer.theta, sds=ulcer.sigma)
> ulcer.pivots
```

```
-----
           mns      sds
1  -1.8382795  0.9266964
2  -0.3184537  0.6825753
3   0.4111958  0.7162780
....
....
40 -8.4390154  2.0146522
41  0.5753641  2.0429418
-----
```

```
> ## fixed-effect model - use default linkfunc='inverse-normal-cdf' ##
> ##   for Fisher efficiency                                     ##
> gmo.fx1 <- gmeta(ulcer.pivots, method='fixed-mle',
>                 gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.fx1)
```

Example 2: Fixed-effects Meta-analysis - cont'd

Model-Based Meta-Analysis through CD-Framework

Call:

```
gmeta.default(gmi = ulcer.pivots, method = "fixed-mle",
  gmo.xgrid=seq(-20, 20, by=0.001))
```

Summary of Combined CD:

	mean	median	stddev	ci.lower	ci.upper
Combined CD	-0.8875844	-0.8875844	0.1255535	-1.133665	-0.6415031

```
> ## using DE link for combining with default weight - Bahadur efficiency ##
> gmo.fx2 <- gmeta(ulcer.pivots, method='fixed-mle',
>   + linkfunc='inverse-laplace-cdf', gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.fx2)
```

Summary of Combined CD:

	mean	median	stddev	ci.lower	ci.upper
Combined CD	-1.063764	-1.064124	0.1061674	-1.271884	-0.8534409

Example 3: Random-effects Meta-analysis

```
> ## random-effects meta-analysis, DL estimator for tau2 ##
> gmo.rd1 <- gmeta(ulcer.pivots, method='random-mm',
>   gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.rd1)
```

Summary of Combined CD:

	mean	median	stddev	ci.lower	ci.upper
Combined CD	-1.097574	-1.097574	0.2103224	-1.509798	-0.6853496

```
> ## random-effects meta-analysis, REML estimator for tau2
> gmo.rd2 <- gmeta(ulcer.pivots, method='random-reml',
>   gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.rd2)
```

Summary of Combined CD:

	mean	median	stddev	ci.lower	ci.upper
Combined CD	-1.091384	-1.091384	0.2069317	-1.496963	-0.6858053

Example 4: Robust Meta-analysis

– *method* = 'fixed-robust1': the large number of studies case

```
> gmo.robust1 <- gmeta(ulcer.pivots, method='fixed-robust1',
>   gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.robust1)
```

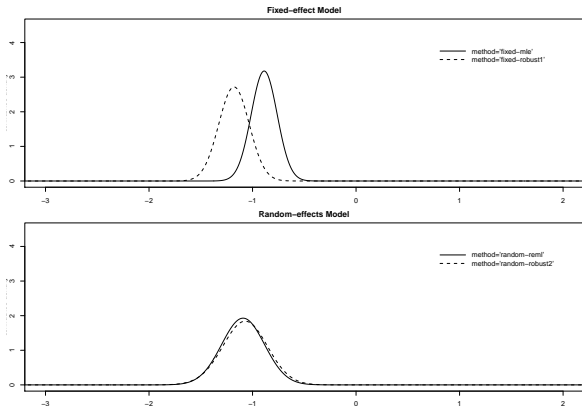
```
-----
                        Summary of Combined CD:
              mean          median      stddev      ci.lower      ci.upper
Combined CD -1.179134    -1.179134    0.1467666    -1.466792    -0.8914757
-----
```

– *method* = 'random-robust2': the large sample size case

```
> gmo.robust2 <- gmeta(ulcer.pivots, method='random-robust2',
>   gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.robust2)
```

```
-----
                        Summary of Combined CD:
              mean          median      stddev      ci.lower      ci.upper
Combined CD -1.073812    -1.072808    0.2170723    -1.505937    -0.647466
-----
```

Example 4: Robust Meta-analysis - no outlying studies



- slight wider combined CDs from robust methods
- trade efficiency for robustness

Example 4: Robust Meta-analysis - robustness in play

- construct a contaminated data set with outlying studies
 - multiplying $\hat{\theta}$ in studies-05,13,14,22,35,41 by 10
- use random-effects meta-analysis and robust meta-analysis on
 - original data
 - contaminated data
- estimated θ and its 95% confidence interval

	original data	contaminated data
random-effects meta-analysis	-1.090(-1.497, -0.686)	-0.099(-0.504, 0.307)
robust meta-analysis	-1.074(-1.506, -0.648)	-1.010(-1.499, -0.509)

Example 5: Meta-analysis of 2×2 Tables

```
> ## data format (x, n, y, m) for 2 by 2 tables ##
> ulcer.2x2 <- cbind(ulcer.o[,1], ulcer.o[,1]+ulcer.o[,2],
>   ulcer.o[,3], ulcer.o[,3]+ulcer.o[,4])
```

– *method = 'MH'* - Mantel-Haenszel method; Result: OR

```
> gmo.MH <- gmeta(ulcer.2x2dt, gmi.type='2x2', method='MH',
  gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.MH)
```

Summary of Combined CD:

	mean	median	stddev	ci.lower	ci.upper
Combined CD	0.3370037	0.3370037	0.03746689	0.26357	0.4104375

– *method = 'Peto'* - Peto method; Result: LOR

```
> gmo.Pt <- gmeta(ulcer.2x2d, gmi.type='2x2', method='Peto',
>   gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.Pt)
```

Summary of Combined CD:

	mean	median	stddev	ci.lower	ci.upper
Combined CD	-1.132064	-1.132064	0.1093015	-1.346291	-0.9178366

Example 5: Meta-analysis of 2×2 Tables

- *method* = 'exact1' - Liu et al. 2015; Result: LOR
 - use significant functions based on mid-p adaption of Fisher's exact test for individual CD
 - adjustment for improvement in efficiency

```
> gm0.exact1 <- gmeta(ulcer.2x2d, gmi.type='2x2', method='exact1',
>   gmo.xgrid=seq(-20,20,by=0.001))
> summary(gmo.exact1)
```

Summary of Combined CD:

	mean	median	stddev	ci.lower	ci.upper
Combined CD	-1.239827	-1.240056	0.1270008	-1.485981	-0.9882136

Concluding Remarks

- Meta-analysis (or fusion learning more generally) using CDs
 - provides an effective way to combine information from diverse sources
 - explores heterogeneous data
- This talk provided an illustration of some examples with gmeta demonstrations
 - p -value combining
 - model-based fixed-effects meta-analysis
 - model-based random-effects meta-analysis
 - robust meta-analysis
 - exact meta-analysis

Related Research: current and forthcoming

- Expand gmeta package
 - meta-analysis with fixed, unknown, and study-specific parameters (Clagett et al 2014)
 - no need to assume either fixed-effects or random-effects model
 - uses a novel resampling method via CDs the study-level parameters for inference
 - non-parametric approach
 - expected data of release: end of 2016
 - meta-analysis of heterogeneous studies (Liu et al 2015)
 - estimable parameters different from one study to another
 - use some mapping functions to link estimable parameters in different studies with the common parameter of interest
 - expected date of release: spring of 2017

Related Research: current and forthcoming - cont'd

- Analysis of recurrent event data (i.e. hospital readmission, relapse of a disease, etc)
 - data sources:
 - universal billing data from NJ hospitals from 1986 to 2015
 - NJ death records
 - (partial) NJ cancer register
 -
 - computing difficulties \Rightarrow split-conquer-combine approach
 - use CD combining framework to aggregate results
- Individualized medicine studies of cardiovascular disease (i.e. heart failure)
 - build survival models for each patient
 - borrow strength from models of similar patients then use CD for combination

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