Network meta-analysis: Applying graph theory

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Outline

Networks are omnipresent

A graph-theoretical approach to network meta-analysis

Graphs and networks consist of nodes and edges connecting them

Adjustment for multi-armed studies

This is a special requirement in network meta-analysis

Example

Conclusion

Networks

Networks are omnipresent

- Social networks (Facebook, LinkedIn, etc.)
- Publication/citation/information networks
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-
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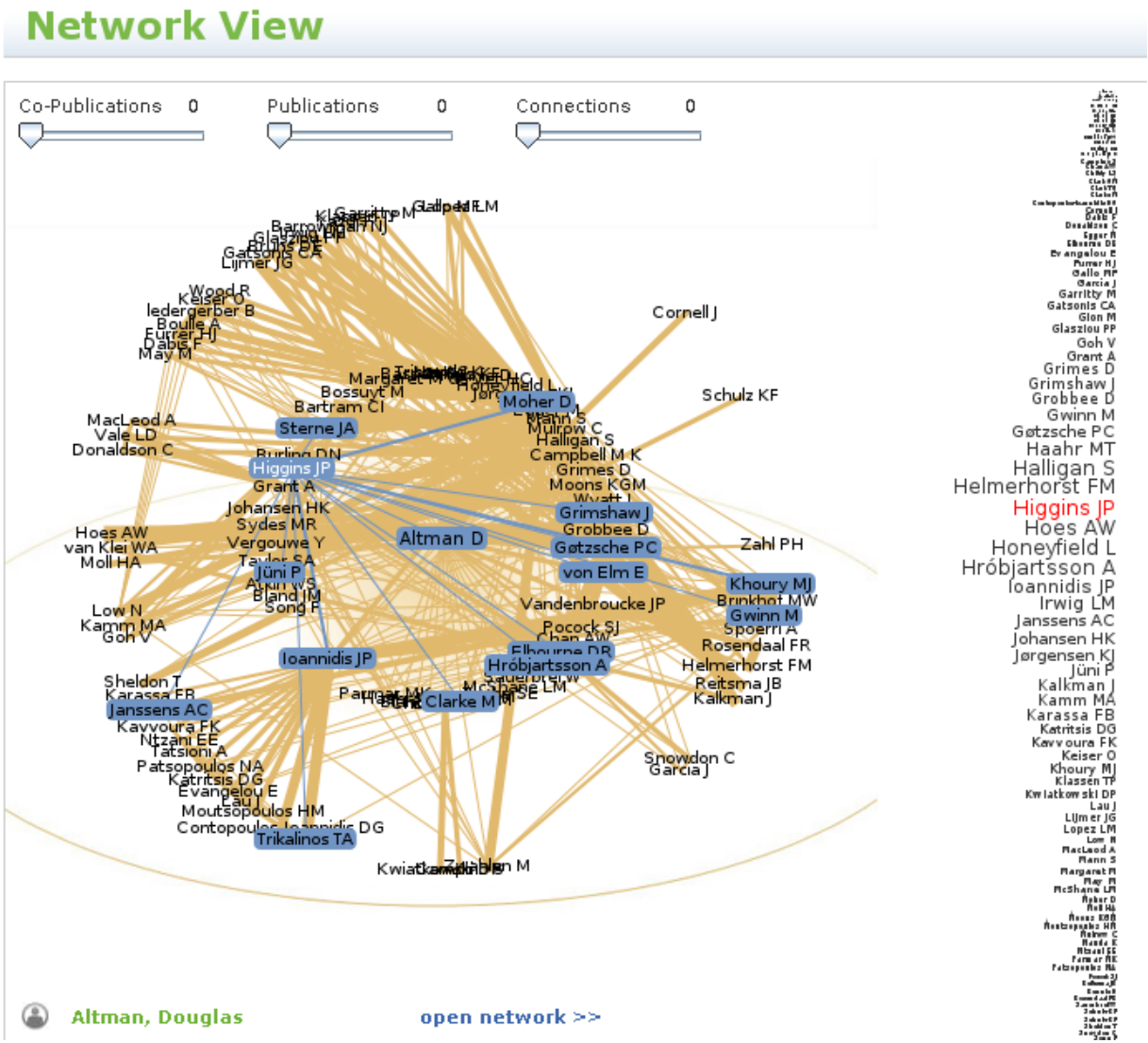
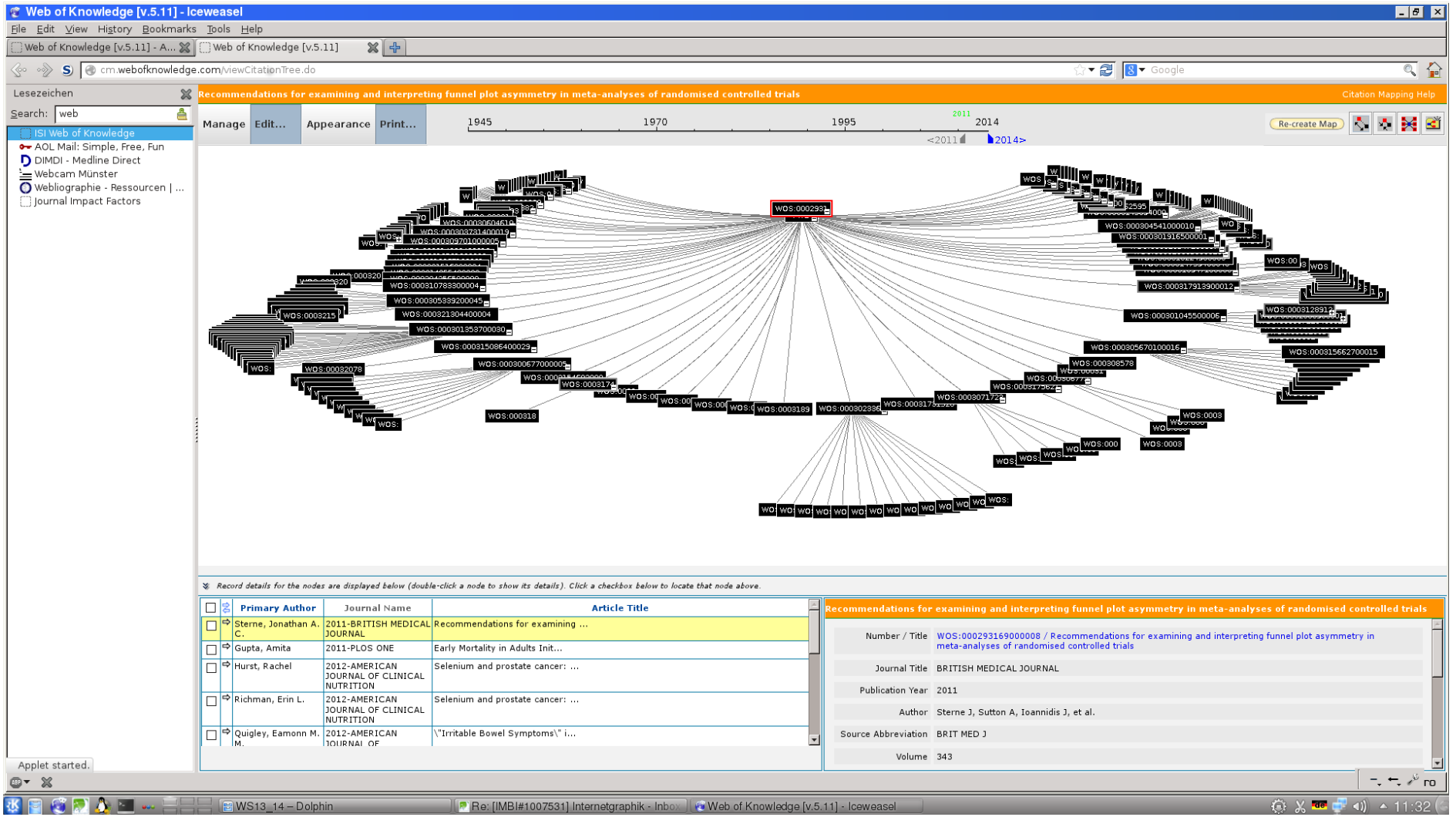
An authors' network (http://www.biomedexperts.com/)



A citation network (Sterne et al., 2011, http://cm.webofknowledge.com/)



Networks

Networks are omnipresent

- Social networks
- Publication/citation/information networks
- Traffic/transportation networks
- Experimental design (Yates, 1940; Tjur, 1991; Bailey, 2007)
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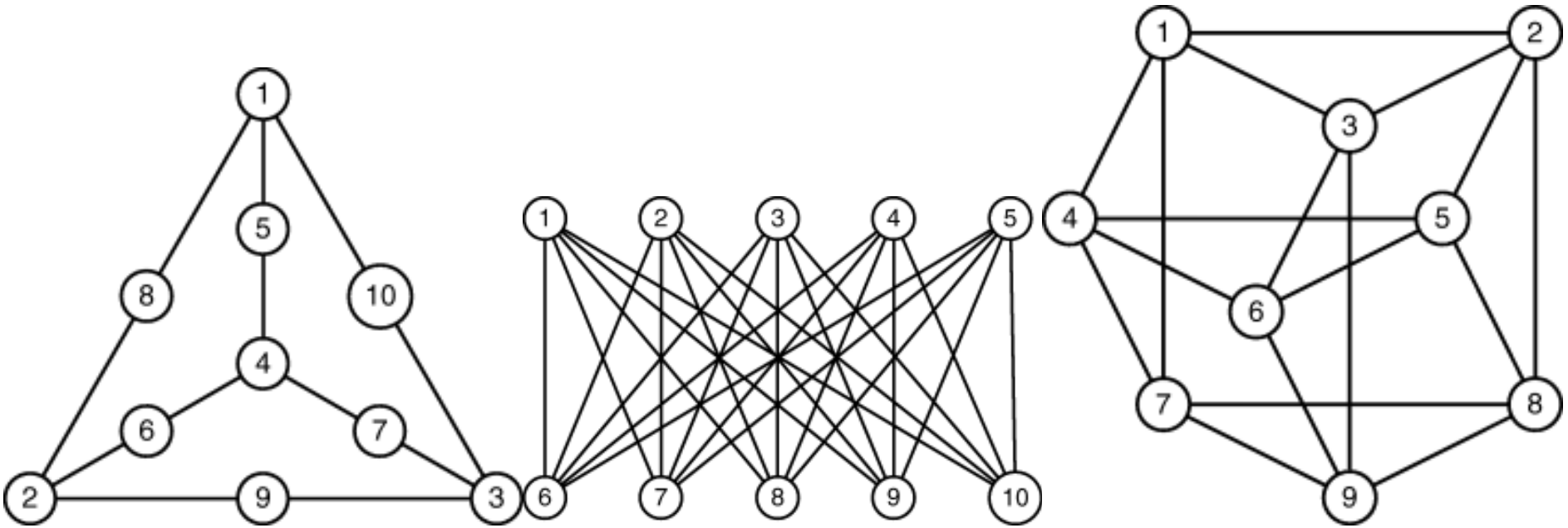
Incomplete balanced block designs (Bailey, 2007)



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Electrical networks (Klein and Randić, 1993)

D.J. Klein, M. Randić, Resistance distance

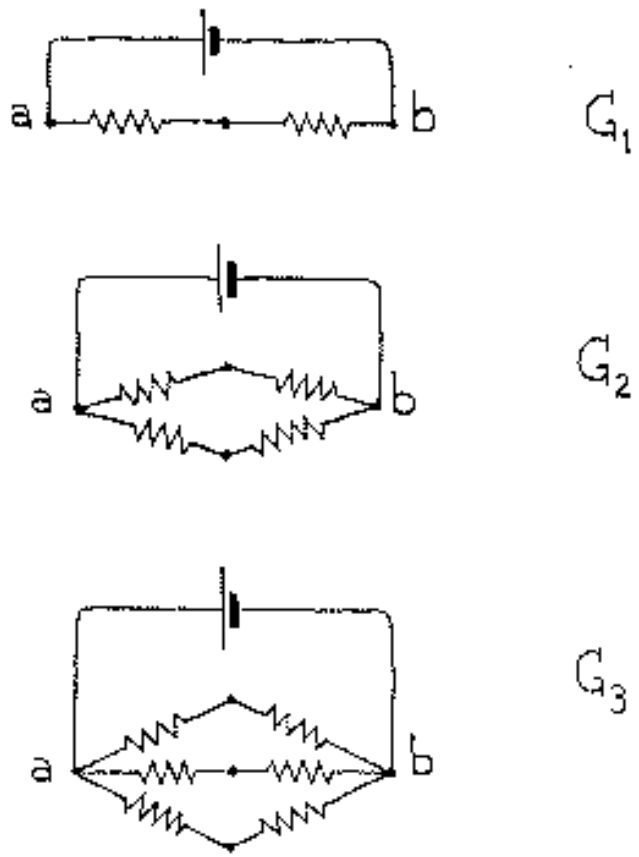

Fig. 2. The three graphs of fig. 1 with resistors (denoted by —WW—) introduced on each edge, while a battery (denoted by —|ı—) is linked between the a, b-pair of vertices.

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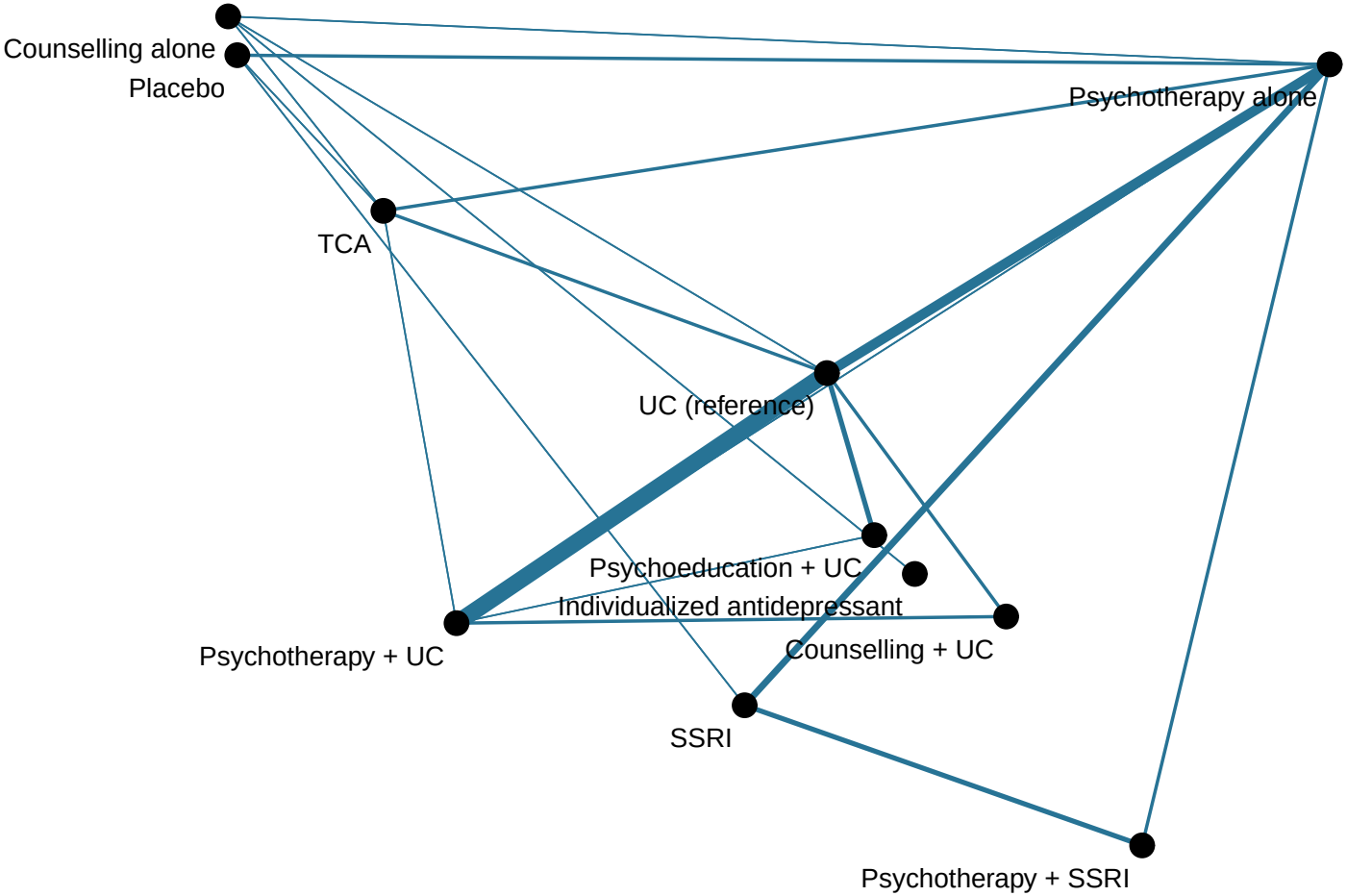
- Network meta-analysis

Network meta-analysis of psychological treatments for patients with depression (Linde et al., 2013)



11 treatments, 26 trials (17 two-armed, 8 three-armed, one four-armed trial)

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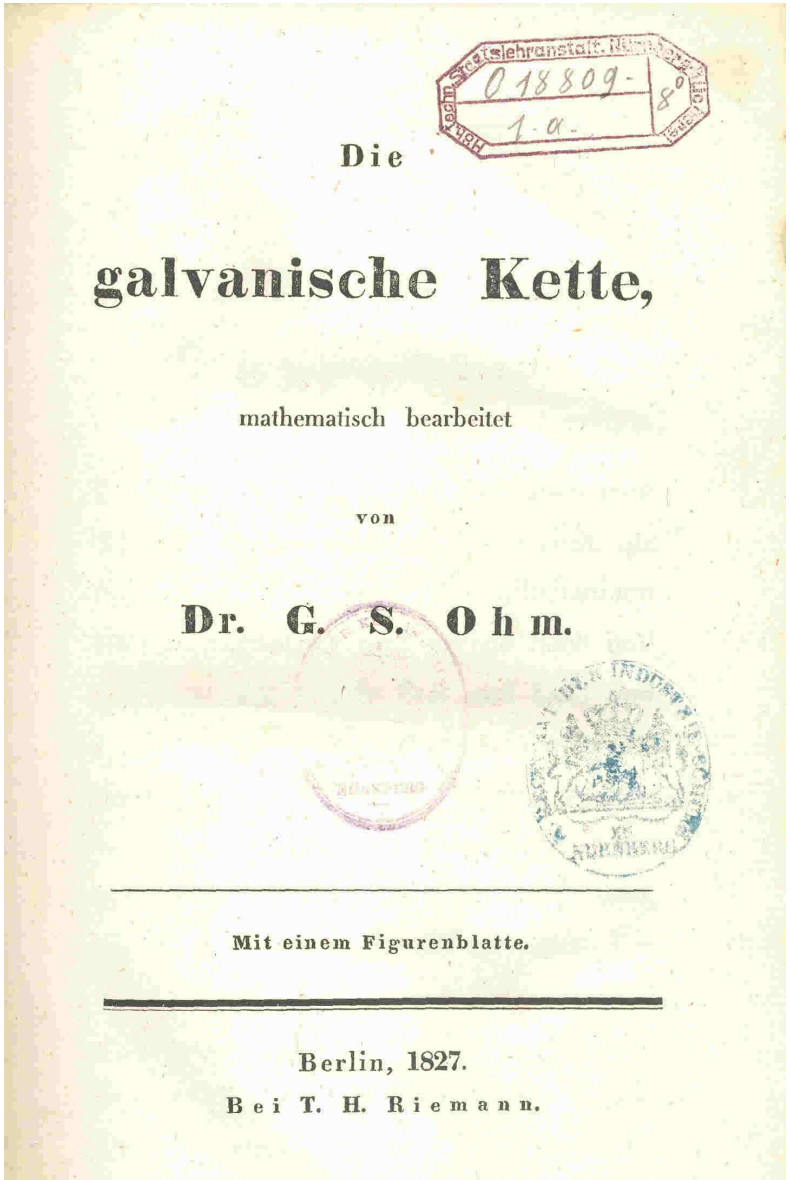
. . . and graph theory deals with them.

So, why reinvent the wheel?

Georg Simon Ohm (1826/27), Gustav Kirchhoff (1847)



Die

galvanische Kette,

mathematisch bearbeitet

von

Dr. G. S. Ohm.

Mit einem Figurenblatte.

Berlin, 1827.

Bei T. H. Riemann.

1847. ANNALEN No. 12

DER PHYSIK UND CHEMIE.

BAND LXXII.

I. *Ueber die Auflösung der Gleichungen, auf welche man bei der Untersuchung der linearen Vertheilung galvanischer Ströme geführt wird;*
von G. Kirchhoff.

Ist ein System von n Drähten: 1, 2 ... n gegeben, welche auf eine beliebige Weise unter einander verbunden sind, und hat in einem jeden derselben eine beliebige elektromotorische Kraft ihren Sitz, so findet man zur Bestimmung der Intensitäten der Ströme, von welchen die Drähte durchflossen werden, I_1, $I_2 \ldots I_n$, die nöthige Anzahl linearer Gleichungen durch Benutzung der beiden folgenden Sätze [1]):

I. Wenn die Drähte k_1, k_2, ... eine geschlossene Figur bilden, und w_k bezeichnet den Widerstand des Drahtes k, E_k die elektromotorische Kraft, die in demselben ihren Sitz hat, nach derselben Richtung positiv gerechnet als I_k, so ist, falls I_{k1}, I_{k2}, ... alle nach *einer* Richtung als positiv gerechnet werden:

$$w_{k1} I_{k1} + w_{k2} I_{k2} + \ldots = E_{k1} + E_{k2} + \ldots$$

II. Wenn die Drähte λ_1, λ_2, ... in einem Punkte zusammenstofsen, und $I_{\lambda 1}$, $I_{\lambda 2}$, ... alle nach diesem Punkte zu als positiv gerechnet werden, so ist:

$$I_{\lambda 1} + I_{\lambda 2} + \ldots = 0.$$

Ich will jetzt beweisen, dafs die Auflösungen der Gleichungen, welche man durch Anwendung dieser Sätze für I_1, $I_2 \ldots I_n$ erhält, vorausgesetzt, dafs das gegebene System von Drähten nicht in mehrere völlig von einander getrennte zerfällt, sich folgendermafsen allgemein angeben lassen:

Es sey m die Anzahl der vorhandenen Kreuzungspunkte, d. h. der Punkte, in denen zwei oder mehrere Drähte zusammenstofsen, und es sey $\mu = n - m + 1$, dann ist

1) Bd. 64, S. 513 dieser Annalen.

Terminology in meta-analytic networks and electrical networks

Meta-analytic network		Electrical network
Treatments $i = 1, \ldots, n$	$\Longleftrightarrow$	Nodes $i = 1, \ldots, n$
Existing comparisons $e = 1, \ldots, m$	$\Longleftrightarrow$	Edges $e = 1, \ldots, m$
Variance V_e	$\Longleftrightarrow$	Resistance R_e
Inverse variance weight $w_e = 1/V_e$	$\Longleftrightarrow$	Conductance $1/R_e$
Outcome of treatment i	$\Longleftrightarrow$	Potential at node i
Treatment effect $i - j$	$\Longleftrightarrow$	Voltage at edge $i - j$
Weighted treatment effect $i - j$	$\Longleftrightarrow$	Current flow at edge $i - j$

Meta-analytic networks and electrical networks

There is a complete correspondence!

- 'Variances combine like electrical resistances' (Bailey, 2007)
- This can be used to apply methods from electrical network theory to network meta-analysis (Rücker, 2012)
- Ohm's law relates treatment effects and weights
- Kirchhoff's current law says how to combine the observed effects
- Kirchhoff's potential law guarantees consistency of the estimated treatment effects over closed circuits
  - Consistency means that the difference between two treatments is always the same, whatever (direct or indirect) path is chosen

Meta-analytic networks and electrical networks

A bit of technique

- W diagonal matrix of inverse variance weights of all edges
- B edge-vertex incidence matrix, corresponds to design matrix
- $L = B^\top WB$ Laplacian matrix (also called Kirchhoff matrix or admittance matrix), corresponds to information matrix
- L^+ Moore-Penrose pseudoinverse of L
- $H = BL^+B^\top W$ hat matrix
- Geometrical interpretation:
  H projects the (inconsistent) observed effects to the subspace of consistent effects

Meta-analytic networks: Adjustment for multi-armed studies

Standard approach: Reduce the dimension

(Lu et al., 2011; Senn et al., 2012; Krahn et al., 2013)

- Based on standard regression methodology
- Choose a baseline treatment
- Cut off all edges not connected to the baseline treatment

New approach: Adjust the weights

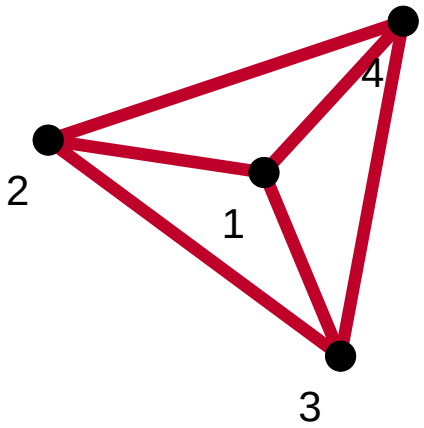
(Rücker, 2012; Rücker and Schwarzer, 2013a)

- Based on electrical network methodology
- For a k-armed study, reduce all conductances by specific factors (average shrinkage factor $2/k$)

Meta-analytic networks: Adjustment for multi-armed studies

Consider, e.g., a four-armed study. Before 'flowing the whole network',

given a four-armed study with six comparisons:



Meta-analytic networks: Adjustment for multi-armed studies

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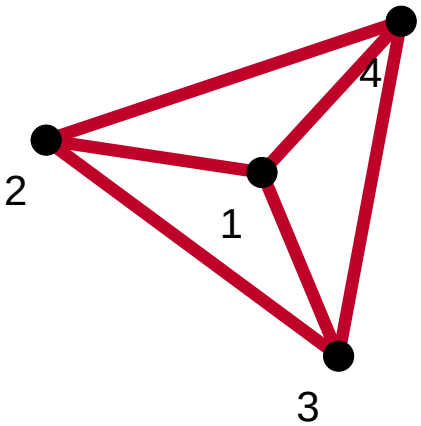
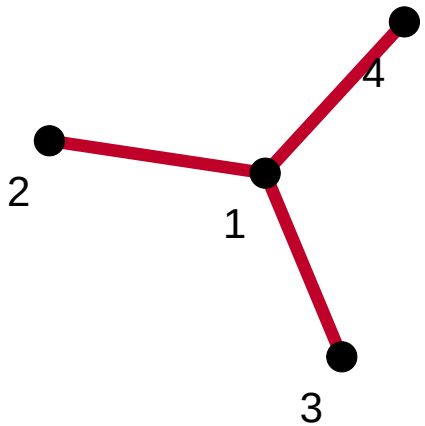
The statistician cuts off three of six edges:





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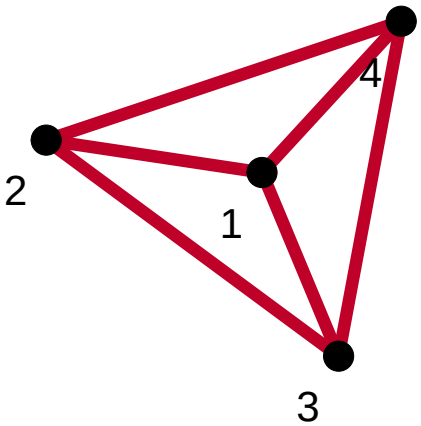

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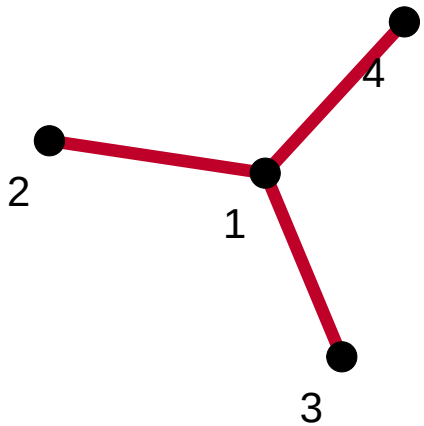
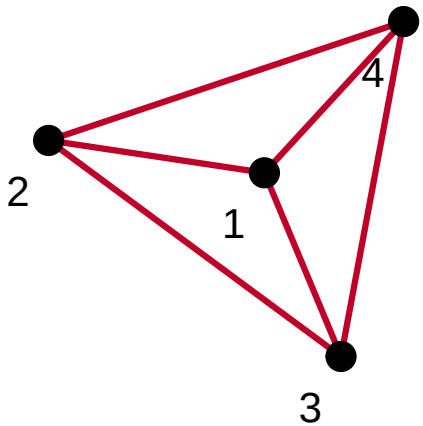


The electrician reduces all conductances by about 1/2:



Theorem: The approaches are equivalent!

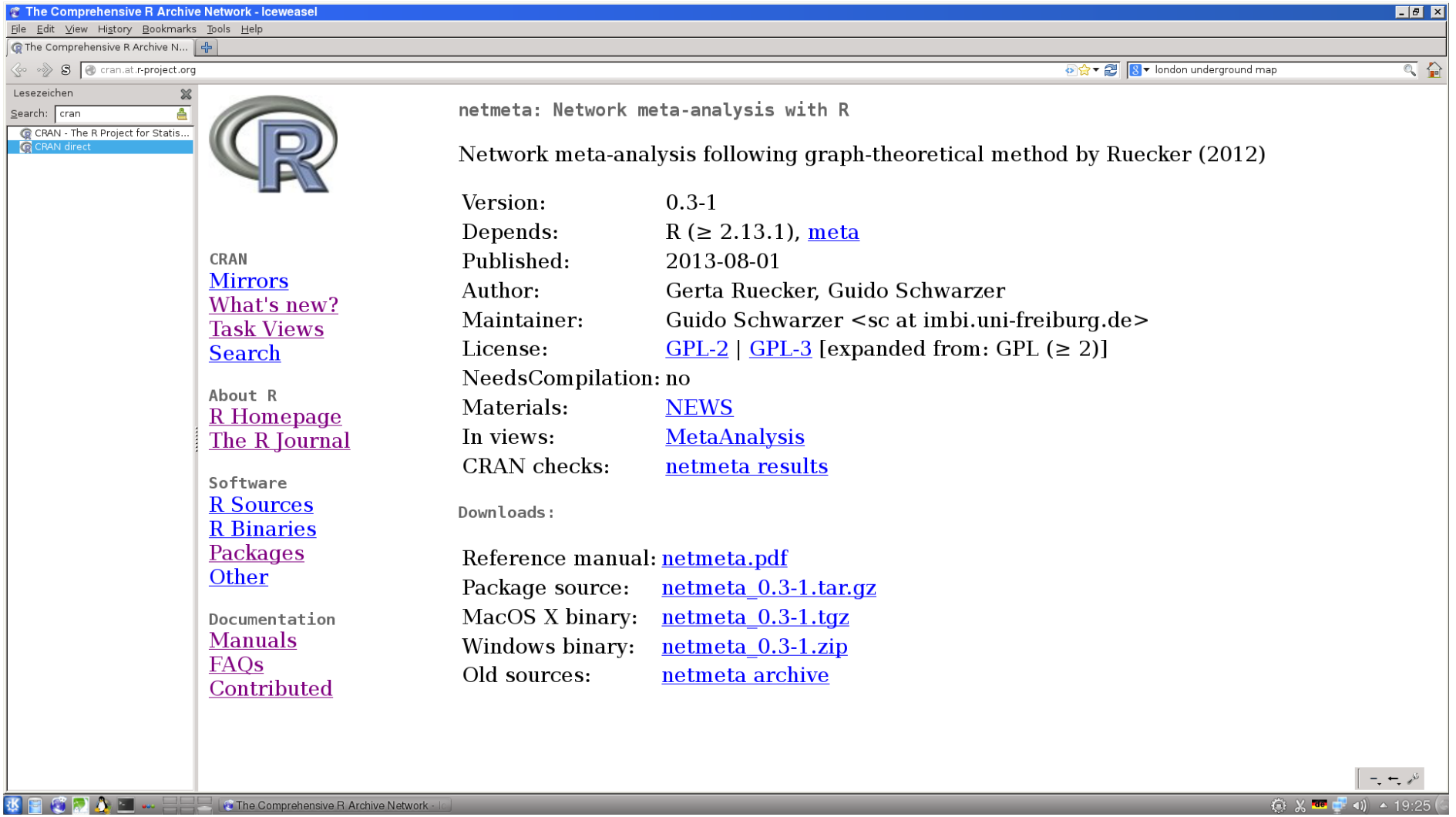
Standard frequentist approach

- natural for statisticians with a background in regression analysis

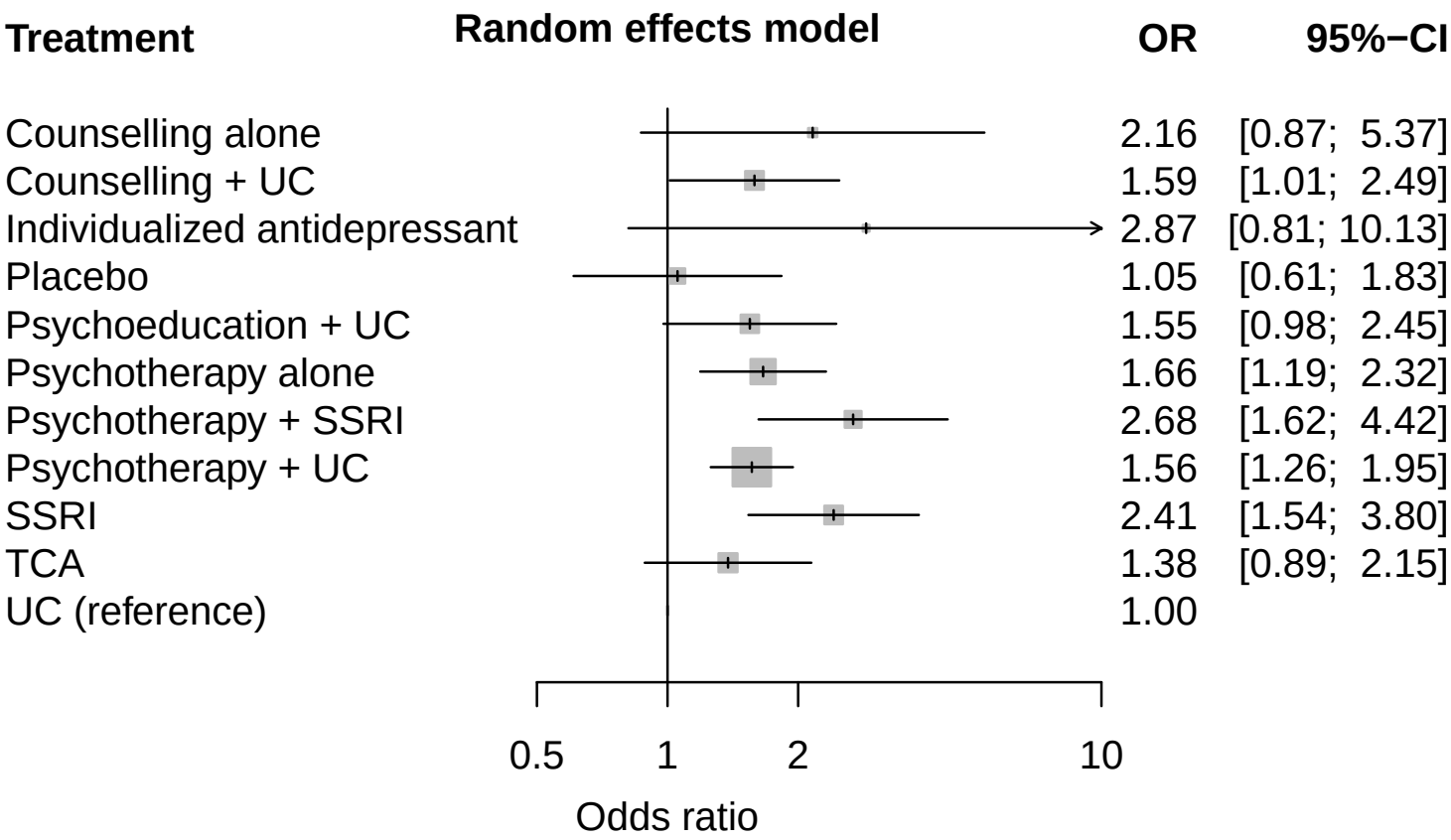
Graph-theoretical approach

- natural for scientists coming from graph theory and its applications
- means constructing a network of two-armed trials that is equivalent to the given one
- Straightforward generalisation to random effects model via multivariate methods of moments estimate for τ^2 (Jackson et al., 2012)

R package netmeta (Rücker and Schwarzer, 2013b)



Network meta-analysis of psychological treatments for patients with depression (Linde et al., 2013): Outcome response, all treatments compared to UC = Usual care



Conclusion

The graph-theoretical approach

- is equivalent to the standard frequentist approach
- handles multi-arm studies adequately
- offers both fixed and random effects model
- allows some simple inconsistency diagnostics

The R package `netmeta`

- is readily available from CRAN
- is much faster than the Bayesian approach, with very similar results
  - run time using `netmeta`: 0.21 sec (fixed and random effects model)
  - run time using WinBUGS: ca. 75 sec (random effects model)

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