On the Use of Hierarchical Models in Method Comparison Studies

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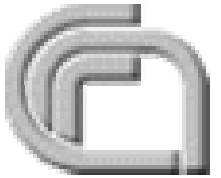
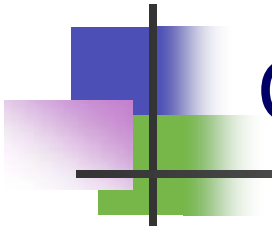


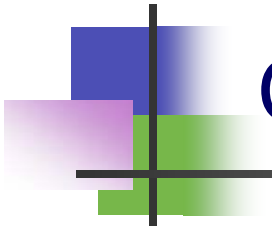


Credits

- Alberto Salvan (LADSEB-CNR, LIA-ISS)
- Stefano Roletti (ARPA-Piemonte)

- SETIL study

- Funding: AIRC, MIUR



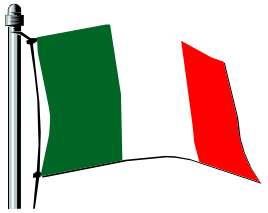
Outline

1) Background
    a) The SETIL project
    b) The EMDEX™ calibration data
2) Hierarchical modeling approach

    → Applied to the EMDEX™ calibration data

3) Conclusion, discussion & ongoing research

The SETIL project



- epidemiological multi-centric case-control study
- investigates risk factors for childhood leukemia, non-Hodgkin's lymphoma and neuroblastoma

→ residential exposure to ELF-MF

Study protocol

Material: EMDEX™ dosimeters

(Enertech Consultants Ltd., USA)

1) *spot* measurements: EMDEX II™

2) *long-term* exposure: EMDEX Lite™

Technical specifications

RMS dosimeters

- EMDEX II™:

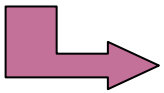
  range : 0.01-300 μT
  accuracy : 1% (± 0.01 μT)

- EMDEX Lite™:

  range : 0.01-70 μT
  accuracy : 2% (± 0.01 μT)

Questions of interest

- Are the instruments used reliable?
- Do the two instrument types agree?

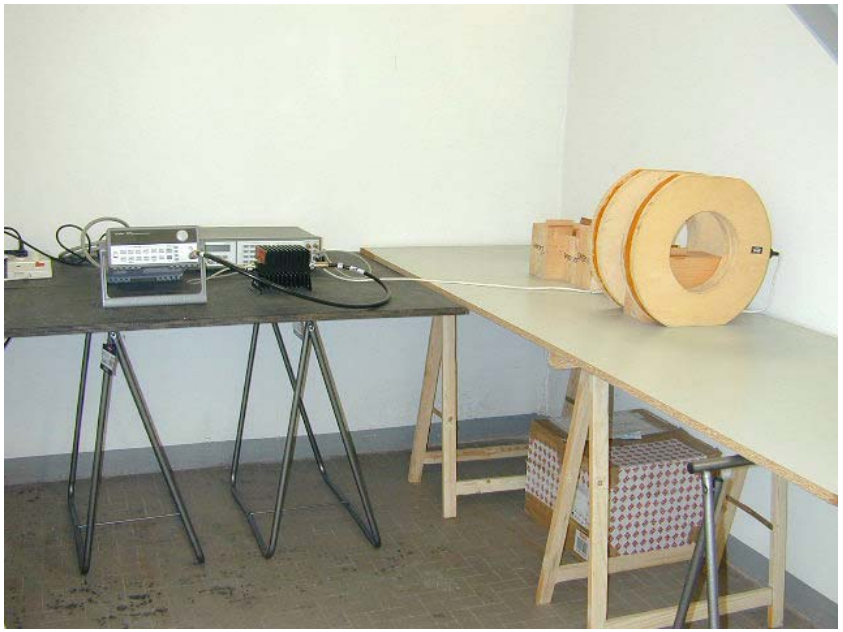


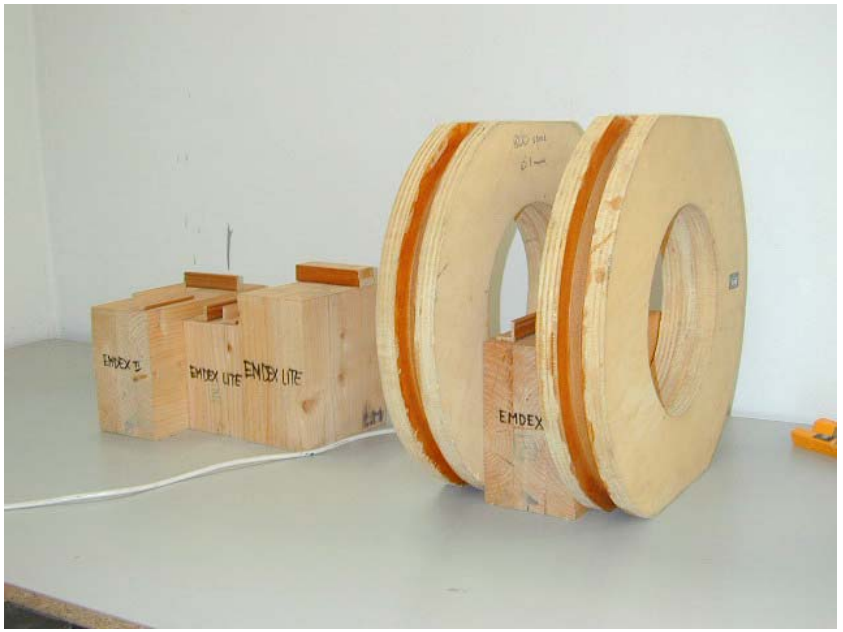
method comparison studies

(approximate & gold standard)

[Lewis et al., 1991]

Calibration study





Helmholtz coil facility

[Borsero et al., 2001]

Study design

- 23 EMDEX II™, 20 EMDEX Lite™ meters
- nominal values: 0.1, 0.2, 0.4, 0.8, 1.0 μT (50 Hz)
- true MF density derived from current measurements
- in turn one of the three sensing coils pointed in the direction of the MF vector
- two sessions

→ resultant + orthogonal projections

Study design (cont.)

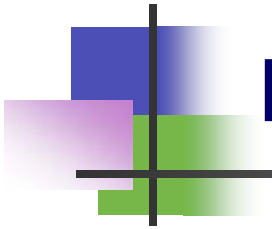
data record

name	matr	coil	hz	B.g	x	y	z	B.m	date	time
"EMDEX LITE"	104430	1	50	0.11	0.11	0.03	0.01	0.11	"17/08/01"	12.45

Method comparison studies

Two main approaches → do not apply to our case!

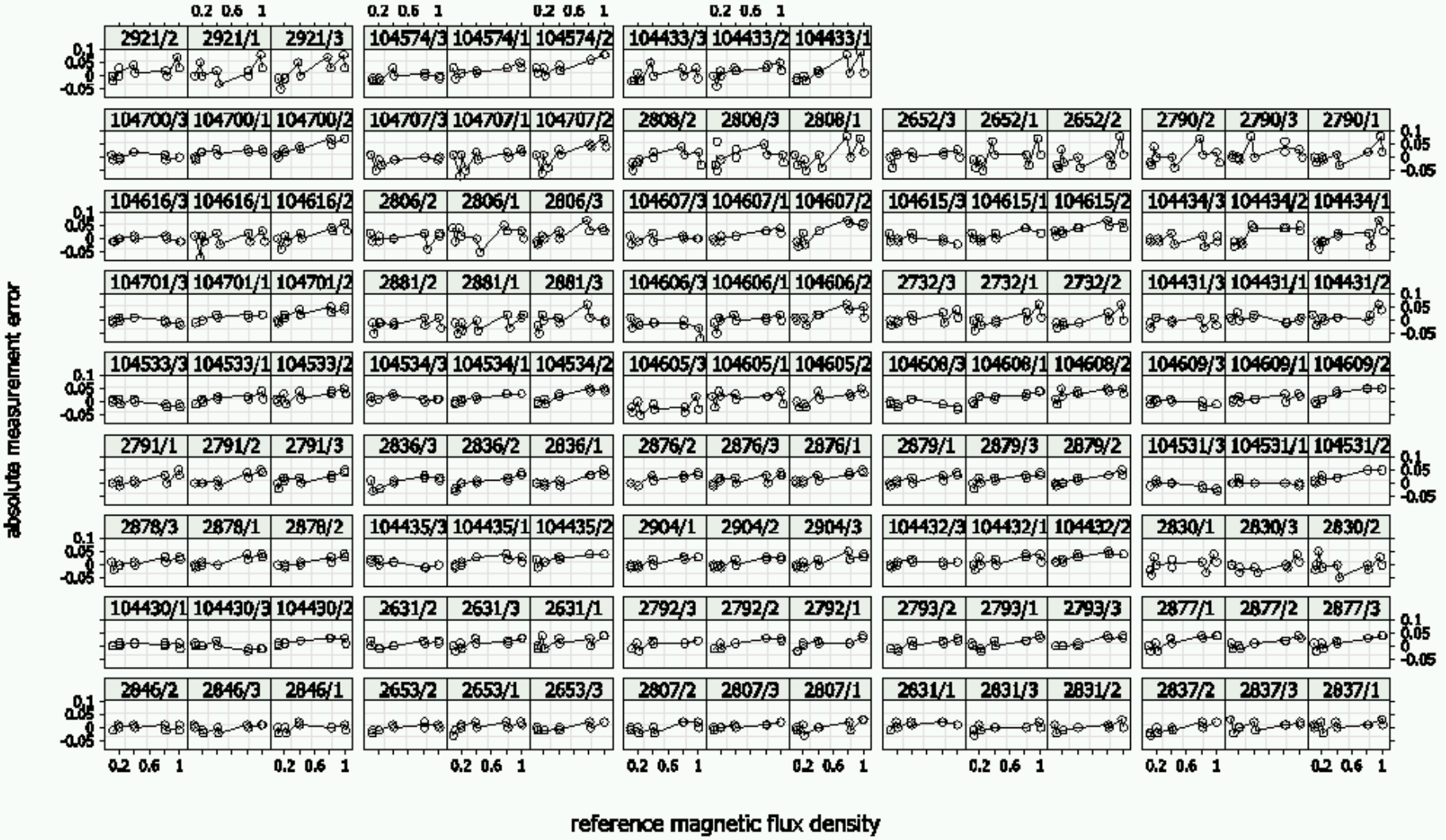
1. Bland & Altman (1986)
   - graphical representations
   - measures of agreement
2. Lewis et al. (1991)
   - one-way random-effects model
   - intra-class correlation coefficient



Hierarchical modeling approach

- linear mixed-effects models with nested random coefficients [Goldstein, 1995]
- widely used to describe relationships between variables that are grouped according to one or more classification factors
- also used to model interactions between covariates associated with random effects

The EMDEX™ calibration data



The EMDEX™ calibration model

Baseline formulation

$$d_{ijkm} = \alpha + \beta x_{ijkm} + \sigma_{ij}\varepsilon_{ijkm}$$

$$\rightarrow \; d_{ijkm} = B.m_{ijkm} - B.g_{ijkm}$$
$$\rightarrow \; x_{ijkm} = B.g_{ijkm}$$
$$\rightarrow \; \varepsilon_{ijkm} \sim N(0,1)$$

i=1,2 (type), j=1,2,3 (coil orientation)
k=1,…,43 (serial number), m=1,2 (session)

The EMDEX calibration model (cont.)

Extension

- $d_{ijkm} = (\alpha + a_i + a_{ij} + a_{ijk}) + (\beta + b_i + b_{ij} + b_{ijk})\, x_{ijkm} + \sigma_{ij}\varepsilon_{ijkm}$

  1. $(a_i, b_i) \sim N(\underline{0}, \Sigma_1)$
  2. $(a_{ij}, b_{ij}) \sim N(\underline{0}, \Sigma_2)$,
  3. $(a_{ijk}, b_{ijk}) \sim N(\underline{0}, \Sigma_3)$

  } indip.

- $\sigma_{ij} = \sigma |x_{ijkm}|^{\delta_{ij}}$

The EMDEX™ calibration model (cont.)

Interpretation

$$\frac{E[B.m_{ijkm}] - B.g_{ijkm} - \alpha}{B.g_{ijkm}} = \beta$$

- α: systematic error component
- β: relative measurement error

⇒ conditional expectations

The EMDEX calibration model (cont.)

Model fit

- maximum likelihood (REML), BLUP
- conditional t-tests and F-tests

  variance function $\rightarrow$ random effects $\rightarrow$ fixed effects

- R library *nlme* [Pinheiro & Bates, 2000]
  SAS PROC MIXED [SAS Institute Inc., 2001]

Results

Final model

- $d_{ijkm} = (a_i + a_{ijk}) + (\beta + b_{ij} + b_{ijk})x_{ijkm} + \sigma_i \varepsilon_{ijkm}$

$$a_i \sim N(0,\sigma_a^2), \quad b_{ij} \sim N(0,\sigma_b^2)$$

$$(a_{ijk},b_{ijk}) \sim N(\underline{0}, \mathrm{diag}[\sigma_{aa}^2, \sigma_{bb}^2])$$

i=1,2 (type), j=1,2,3 (coil orientation)

k=1,…,43 (serial number), m=1,2 (session)

- $\sigma_2 = \delta\sigma_1$

Results (cont.)

Parameter	β	σ_a	σ_b	σ_{aa}	σ_{bb}	σ_1	δ	
lower	0.0157	0.0027	0.0095	0.0026	0.0058	0.0168	0.816	
MLE	0.0296	0.0074	0.0170	0.0041	0.0081	0.0177	0.886	
upper	0.0436	0.0204	0.0304	0.0066	0.0115	0.0188	0.961	
Random effect	a_1*	a_2*	b_{11}*	b_{12}*	b_{13}*	b_{21}*	b_{22}*	b_{23}*
lower	-0.0126	-0.0045	-0.0068	-0.0137	-0.0082	-0.0186	0.0072	-0.0474
BLUP	-0.0101	-0.0021	0.0078	0.0009	0.0064	-0.0040	0.0218	-0.0328
upper	-0.0076	0.0003	0.0224	0.0155	0.0209	0.0106	0.0364	-0.0182

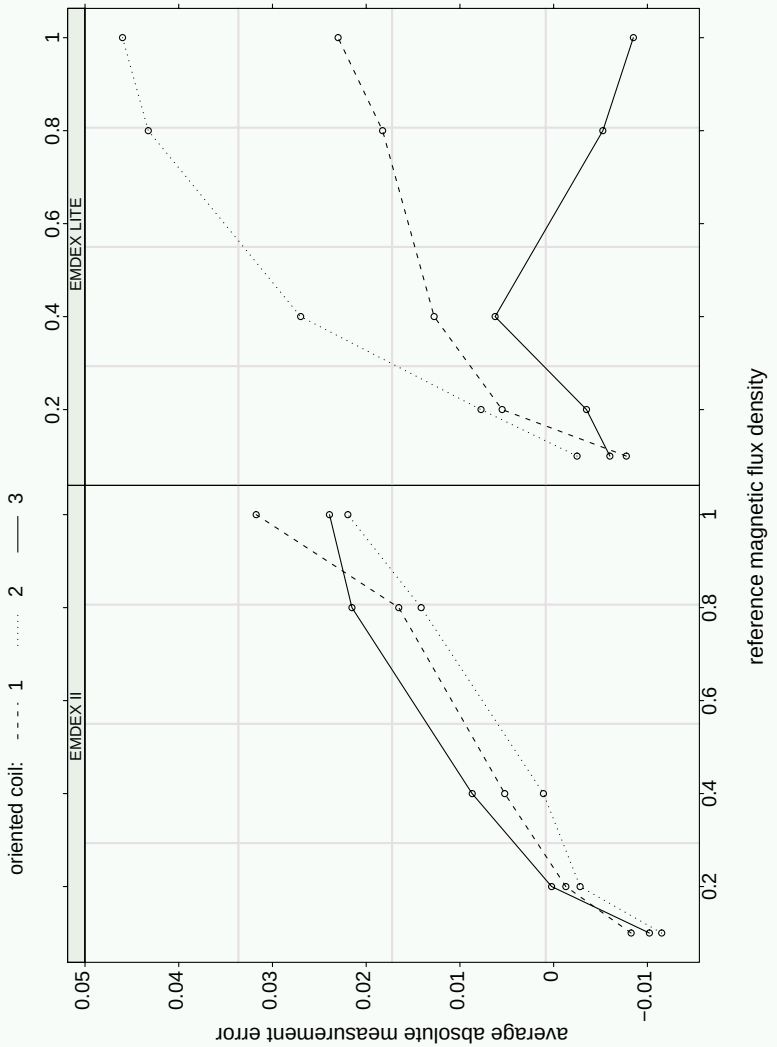
Results (cont.)

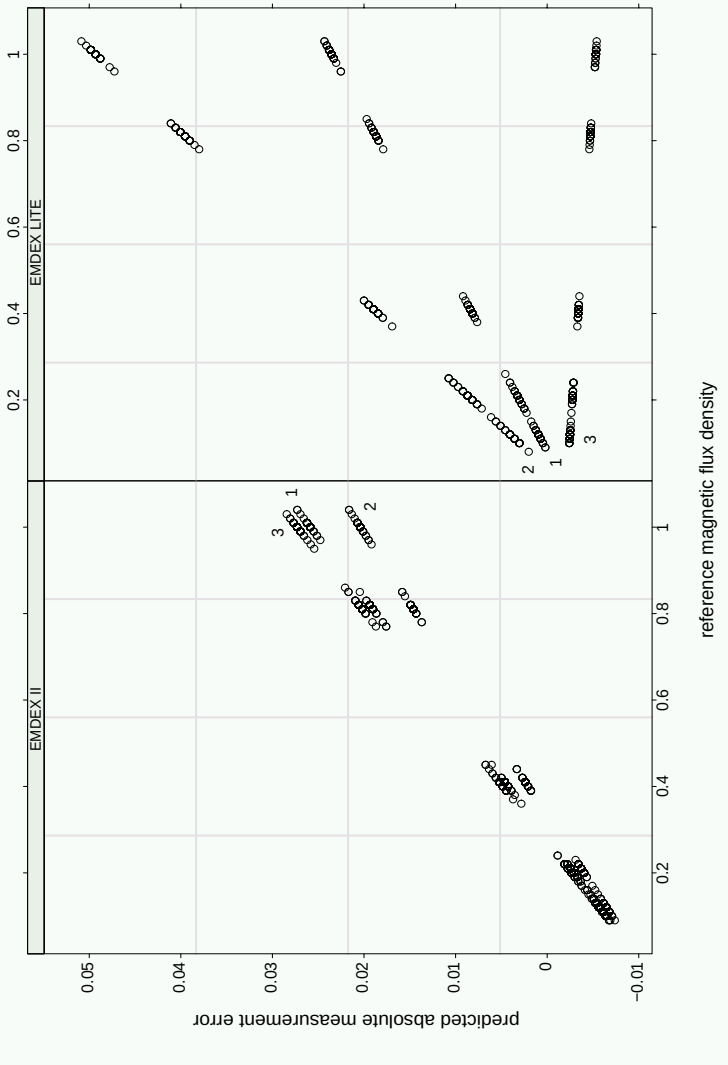
Bias and accuracy

- systematic error of -0.01 µT for EMDEX II™ meters
  [-0.013 µT, -0.007 µT]
- relative error of 3% for both instrument types
  [1.6%, 4.4%]

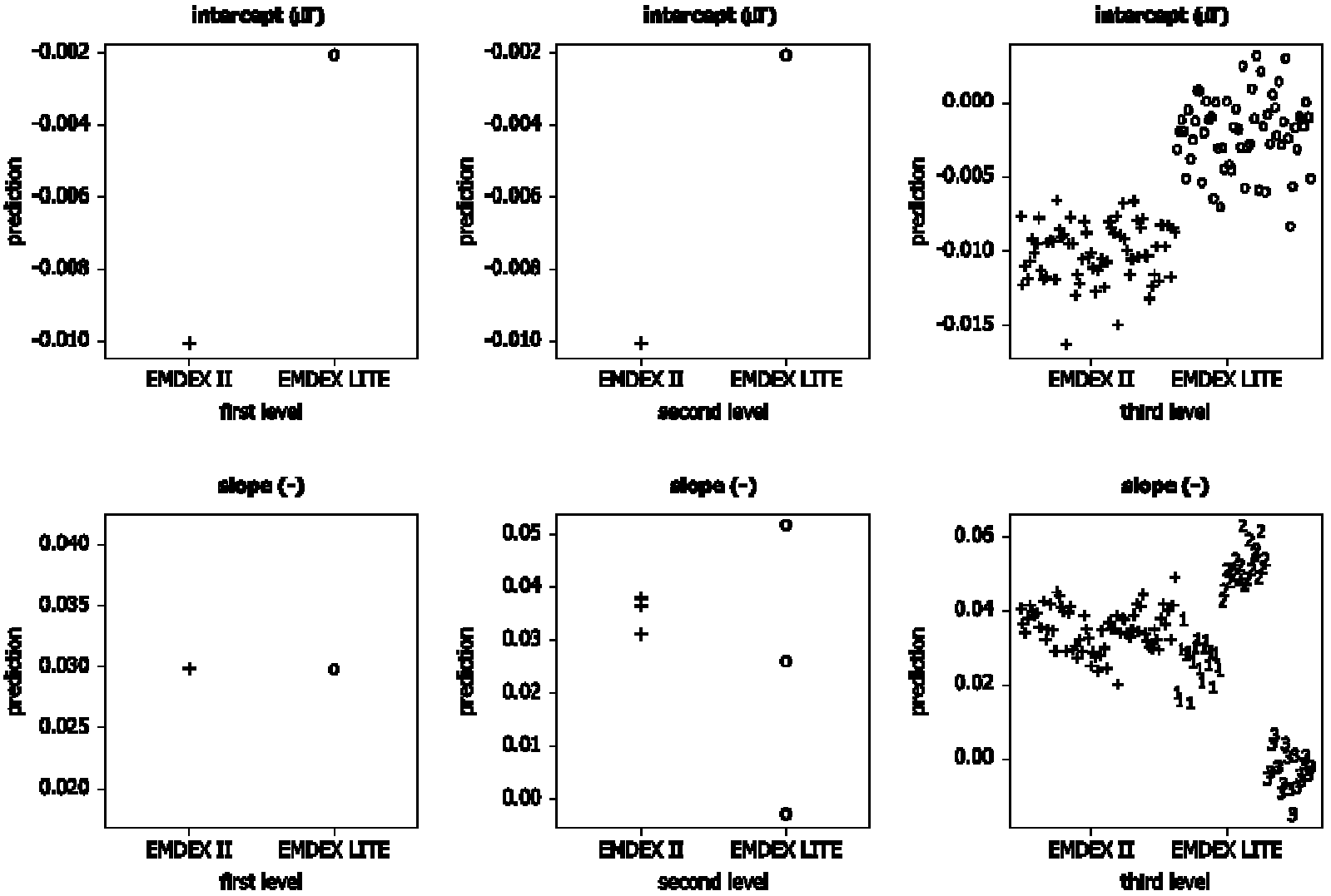
	coil 1	coil 2	coil 3
EMDEX II™	**3.7%** [2.9,4.5]	**3.1%** [2.3,3.8]	**3.6%** [2.8,4.4]
EMDEX Lite™	**2.6%** [1.8,3.6]	**5.1%** [4.3,5.9]	**-0.3%** [-1.1,0.5]

Results (cont.)





Results (cont.)



Conclusions

- reliability
  - similar findings in literature for overall bias and relative error [UKCCS (2000)]
  - good agreement with technical specifications by manufacturer [0.01 μT, 1%-2%]
- agreement
  - EMDEX II™ possibly biased
  - relative error depends on the level considered

  → needs further investigation!

Discussion

"Perplexities"

- random effects for instrument type and coil orientation factors
- model does not obey to weak heredity principle
- generated magnetic flux density measured without error

Final remarks

- extension of one-way random-effects model
  - complex experimental assets
  - parsimony and ease of interpretation
- *epidemiologically* relevant influence on the final outcome
  - work in progress …

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