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Federated Analysis of Multiple Databases –

Central Analysis of De-centralised Databases Using the DataSHIELD Software

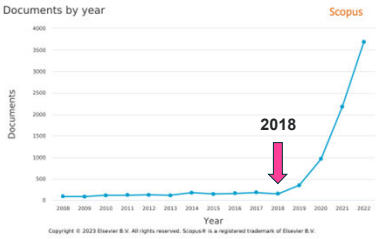
Wilmar Igl[1] & Karen L. Smith[2]
[1] ICON PLC, Sweden; [2] ICON PLC, United Kingdom

What is Federated Analysis?

Federated Analysis (FA) has received rapidly increasing attention over the last five years in the scientific literature (**Figure 1**). It describes the centralized analysis of de-centralized databases while preserving the privacy of personal data [1, 2].

FA was proposed for the identification of rare adverse events in international post-marketing studies to overcome legal barriers [3].

Figure 1. Publications on Federated Analysis over Time



Key Concepts

Federated Databases

- centralized analysis
- decentralized databases
- standardized Advanced Programming Interface (API)
- site-specific data control ("Firewall"), e.g. no access to individual participant data

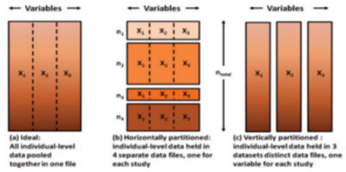
Figure 2. The Concept of Federated Analysis

Key Concepts (cont.)

Data Structures

1. Ideal: All patients and all variables in one database
2. Horizontally partitioned: All variables in all databases, but patients in different databases
3. Vertically partitioned: All patients in all databases, but variables in different databases.

Table 1. Ideal, horizontally partitioned, and vertically partitioned data structures



- Federated Analysis applicable to horizontally and vertically partitioned data, but current developments focus on horizontally partitioned data.

Statistical Concepts

Comparison with Conventional Analysis

Table 1. Comparison of Standard Analysis, Meta-Analysis, and Federated Analysis

	Standard Analysis	Meta-Analysis	Federated Analysis
Architecture	centralized analysis, centralized data	(de)centralized analysis, decentralized data	centralized analysis, decentralized data
Data	id-level	group-level	id|group-level
Statistics	full	limited (fixed vs random)	GLM, Cox PH, … (or in development)
Computation	id ↔ model	id → group ↔ model	id → group ↔ model id ← model
Privacy	low	high	high

Statistical Principle: Decomposition of Statistical Loss

- A global loss function is decomposed into the sum of the weighted combination of multiple local loss functions. [1]
- Statistical loss is a measure of the costs of the statistical errors in the estimation of a parameter used to estimate its optimal value (cf likelihood function).

Equation 1. Statistical Loss

$$\min_{\phi} \mathcal{L}(X;\phi) \quad \text{with} \quad \mathcal{L}(X;\phi) = \sum_{k=1}^{K} w_k \, \mathcal{L}_k(X_k;\phi)$$

- ϕ : parameter
- X : unavailable complete data
- $\sum_{k=1}^{K} w_k \, \mathcal{L}_k(X_k;\phi)$: sum of local loss functions L_k with weight w_k

Statistical Concepts (cont.)

Example: Generalized Linear Models

- Linear Predictor: $\eta_i := g(\mu_i) = \boldsymbol{\beta}^T \boldsymbol{x}_i$
- Iterative Reweighted Least Square Algorithm

$$\boldsymbol{\beta}_{t+1} = \boldsymbol{\beta}_t + \boldsymbol{I}(\boldsymbol{\beta}_t)^{-1} \boldsymbol{s}(\boldsymbol{\beta}_t)$$

- Information Matrix:

$$\boldsymbol{I}(\boldsymbol{\beta}_t) = \boldsymbol{X}^T \boldsymbol{W}_t \boldsymbol{X}$$
$$\boldsymbol{I}(\boldsymbol{\beta}_t) = \sum_{i=1}^{N} w_{ii}(t)\, \boldsymbol{x}_i \boldsymbol{x}_i^T$$

- Score Function

$$\boldsymbol{s}(\boldsymbol{\beta}_t) = \boldsymbol{X}^T \boldsymbol{W}_t \big(\boldsymbol{Y} - \boldsymbol{\mu}(t)\big) g'\big(\boldsymbol{\mu}(t)\big)$$
$$\boldsymbol{s}(\boldsymbol{\beta}_t) = \sum_{i=1}^{N} \big(y_i - \mu_i(t)\big) g'\big(\mu_i(t)\big) w_{ii}(t) \boldsymbol{x}_i$$

- Convergence: $\frac{|D_r - D_{r-1}|}{D_r + 0.1} < 10^{-8}$

Available Statistical Functionality (Present)

- Descriptive statistics and visualizations
- Inference statistics [3, 5, 6]
  - (Meta-analysis)
  - Generalized Linear Models
  - Cox Proportional Hazards Model
  - study-level meta-analysis
  - approximation via log-Poisson model
  - equivalent model available, if individual time-to-events are shared

DataSHIELD software

- DataSHIELD software: Data aggregation through anonymous Summary-statistics from Harmonized Individual levEL Databases (DataSHIELD) [5, 6] (https://datashield.org)
- Multi-component software stack, e.g. OPAL, ROCK/R, Mango/MySQL
- Official R packages (https://cran.datashield.org)
  - Client Packages: dsBaseClient
  - Server Packages: dsBase, opaladmin
  - Testing (serverless implementation): DSLite
- Multiple community packages, e.g.: dsOmics, dsExposome, dsHelper, dsSurvival, dsMediation, dsSwissKnife, dsML, dsGeo, dsDanger, dsMicrobiome, dsQueryLibrary, dsBoltzmannMachines, dsMTL, dsSynthetic, dsClusterAnalysis

DataSHIELD software (cont.)

DataSHIELD Software Stack

- Analyst (Client): R/DataSHIELD packages (DSI, DSOpal, dsBaseClient)
- Data Owner (Server):
  - Data Warehouse: OPAL
  - Database: MANGO/MySQL
  - JAVA
  - R Server: ROCK
  - Statistical Analysis System: R
  - Webserver: NGINX (with TLS certificate)

DOCKER Technology

- OS-level virtualization to deliver software in packages called containers
- A DOCKER configuration file allows the installation of the DataSHIELD software stack on a bare-bone Linux server in about 30 minutes [2]:

```
SHELL> sudo docker-compose -f datashield.yml up -d
```

Example: Post-Vac Syndrome

- "Post-Vac Syndrome": Definition (here) as "Postviral fatigue syndrome/Myalgic encephalomyelitis" (PFS/ME) (ICD-10: G93.3, MedDRA 25.1: 10008874) after vaccination against COVID-19
- Common abbreviations in media: Myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
- Objective: Descriptive analysis of ICD-10 G93.3 disease after vaccination with COVID-19 vaccines
  - Comirnaty (BioNTech and Pfizer)
  - COVID-19 Vaccine (Valneva)
  - Nuvaxovid (Novavax)
  - Spikevax (Moderna)
  - Vaxzevria (AstraZeneca)
  - Jcovden (Janssen)
  - VidPrevtyn Beta (Sanofi Pasteur)
  - Bimervax (HIPRA Human Health S.L.U.)
- Data: VigiBase database (WHO, March 2023 [7]) with data from Europe and America (2021/2022), which was split and stored into separate databases to allow Federated Analysis
- Statistical Analysis: Absolute Frequencies (AF, "counts") and Relative Frequencies (RF, "reporting rate") of Individual Case Safety Report (ICSR) in the Federated Database (FA) based on data from Europe (EU) and America (AM)

Example: Post-Vac (cont.)

- Results:
  - EU: AF(G93.3) = 1074, AF = 2,256,738, RF = 0.48‰
  - AM: AF(G93.3) = 679, AF = 1,676,488, RF = 0.41‰
  - FA: AF(G93.3) = 1753, AF = 3,933,226, RF = 0.45‰
- Conclusion:
  - Federated Analysis can be successfully applied without sharing confidential patient data
  - The data does not allow a causal conclusion of Covid-19 vaccination on PFS/ME as adverse event.

Conclusions

- Federated Analysis offers centralized analysis using the (full) information from de-centralized individual data with high-levels of privacy
- Important statistical models were re-formulated and are available as software
- DataSHIELD software is easily deployed using Docker technology
- Challenges:
  - Administrative and technical burden to implement Federated Analysis
  - "Hard" (e.g. available statistical models) and "soft" (e.g. available software) barriers exist
- Opportunity:
  - Enable scientific collaboration across ethical, institutional, or legal borders
  - Domain knowledge, skills, software & hardware may give new business opportunities

References

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Note: VigiBase is the WHO global database of reported potential side effects of medicinal products, developed and maintained by Uppsala Monitoring Centre. The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The information does not represent the opinion of the UMC or the World Health Organization.

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