The STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative – on recent progress of the topic groups and panels

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http://stratos-initiative.org/

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Overview

- The STRATOS initiative – Why and for whom?

- History and collaborations

- Recent progress and ideas for the future

The STRATOS initiative – Why?
Current situation in statistical methodology

- Statistical methodology has seen substantial development
- Computing capabilities can be viewed as the cornerstone
- Possible to assess properties and compare complex model building strategies using simulation studies
- Resampling and Bayesian methods allow investigations that were impossible two decades ago
- Wealth of new statistical software packages allows a rapid implementation and verification of new statistical ideas

Statistical research…

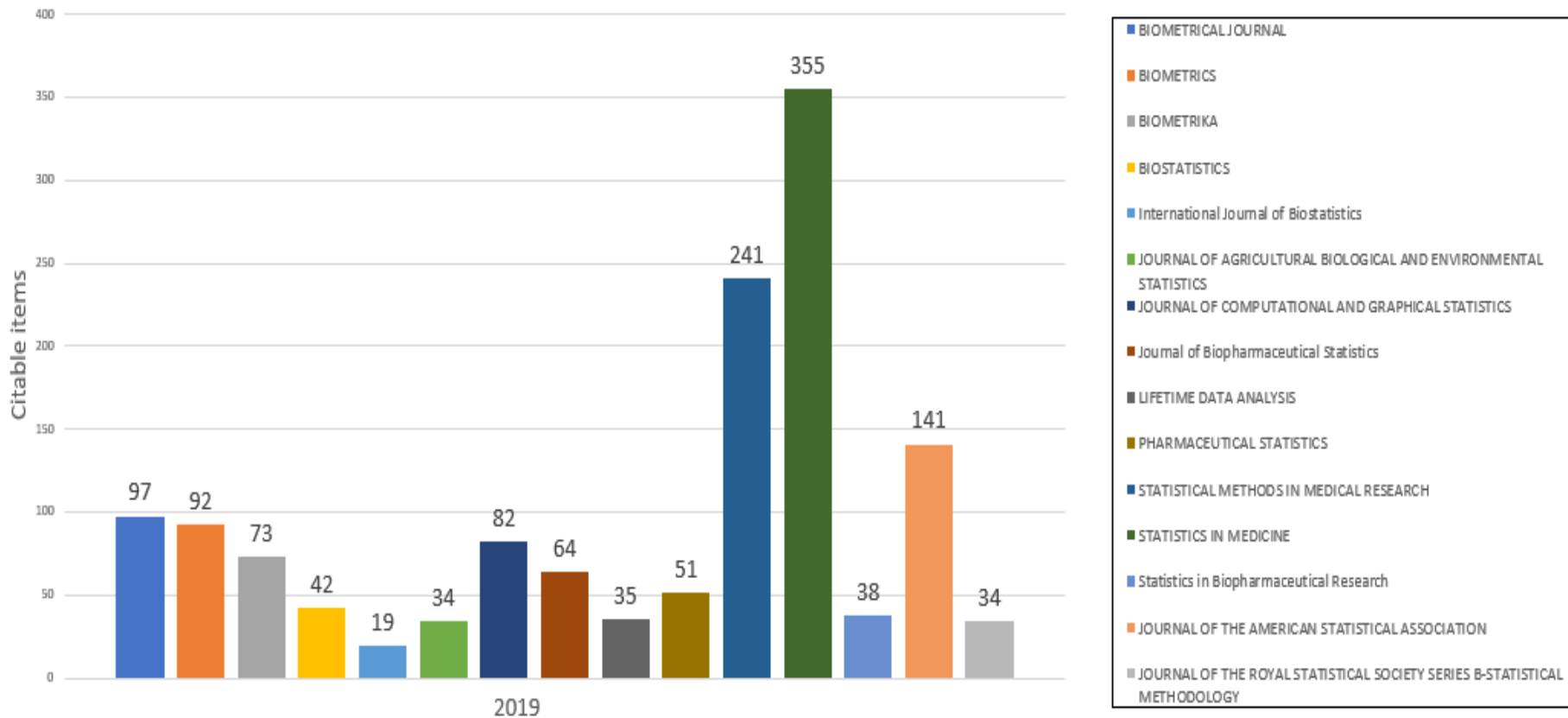- Number of articles per year in 124 ‚Statistics & Probability' journals

https://jcr.clarivate.com/
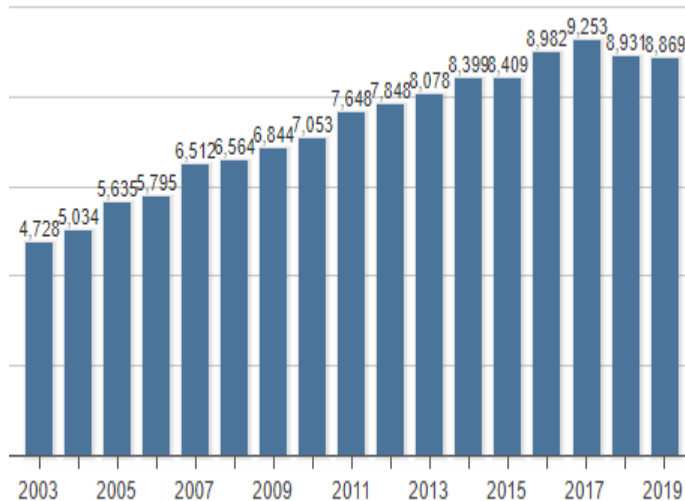
- Now, every year more than 8,000 new articles full of novel methodology are published…

… **bio**statistical research …

Restricting to ‚bio*', ‚medic*', ‚pharma*', ‚life*' journals:
1,241 articles in 2019, in addition: JASA, JRSS B

https://jcr.clarivate.com/

Current situation in practical analyses

- Unfortunately, many sensible improvements are ignored

Reasons why improved strategies are ignored

- Overwhelming concern with **theoretical aspects.** Theoretical results are only available under strong assumptions which do not hold in practice
- Very **limited guidance** on key issues that are **vital in practice**, discourages analysts from utilizing more sophisticated and possibly more appropriate methods in their analyses.

Statistical methodology – problems are well known

The severity of problems is even discussed in the public press:

The Economist 'Unreliable research: Trouble at the lab.' (October 2013):

"Scientists' grasp of statistics has not kept pace with the development of complex mathematical techniques for crunching data. Some scientists use inappropriate techniques because those are the ones they feel comfortable with; others latch on to new ones without understanding their subtleties. Some just rely on the methods built into their software, even if they don't understand them."

The Lancet Research:
Increasing Value, Reducing Waste Series

Comment (Introduction)

How should medical science change?

In 2009, we published a Viewpoint by Iain Chalmers and Paul Glasziou called "Avoidable waste in the production and reporting of research evidence", which made the extraordinary claim that as much as 85% of research investment was wasted.

Kleinert and Horton, 2014

"Although this vast enterprise has led to substantial health improvements, many more gains are possible if the waste and inefficiency in the ways that biomedical research is chosen, designed, done, analysed, regulated, managed, disseminated, and reported can be addressed."

Macleod et al., 2014

Better use of statistical methods

- At least two tasks are essential:

  1. **Experts** in specific methodological areas have to work towards **developing guidance**

  2. An ever-increasing need for **continuing education** at all stages of the career

- For busy applied researchers it is often difficult to follow methodological progress even in their principal application area

  – Reasons are diverse

  – Consequence is that analyses are often deficient

- **Knowledge** gained through research on statistical methodology needs to be **transferred** to the broader community

- Many **analysts** would **appreciate** an overview on the current **state of the art** and for **practical guidance**

Aims of the initiative

- **Provide evidence supported guidance** for highly relevant issues in the design and analysis of observational studies

- As the **statistical knowledge** of the analyst **varies** substantially, guidance has to keep this background in mind. **Guidance** has to be provided **at several levels**

- For the **start** we will concentrate on **state-of-the-art** guidance based on substantial evidence

- Help to identify questions requiring much more primary research

The overarching long-term aim is to improve key parts of design and statistical analyses of observational studies in practice

Different levels of statistical knowledge

Level 1: Low statistical knowledge

• Most analyses are done by analysts at this level

Level 2: Experienced statistician

• Methodology perhaps slightly below state of the art, but doable by every experienced analyst

Level 3: Expert in a specific area

• To improve statistical models and to adapt them to complex real problems, researchers develop new and more complex approaches. Advantages and usefulness in practice need to be assessed

Guidance for analysis is needed for many stakeholders (analysts with different levels of knowledge, teachers, reviewers, journalists, ...)
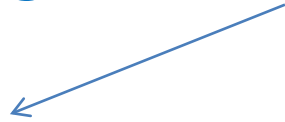
Researchers

First in a Series of Papers for the Biometric Bulletin

STRATOS initiative – Guidance for designing and analyzing observational studies

STRATOS
INITIATIVE

Willi Sauerbrei[1], Marianne Huebner[2], Gary S. Collins[3], Katherine Lee[4], Laurence Freedman[5], Mitchell Gail[6], Els Goetghebeur[7], Joerg Rahnenfuehrer[8] and Michal Abrahamowicz[9] on behalf of the STRATOS initiative.

➡ Short papers from all TGs and some panels

Consumers

Guidance for designing and analysing observational studies:

The STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative

Willi Sauerbrei[1], Gary S. Collins[2],
Marianne Huebner[3], Stephen D. Walter[4],
Suzanne M. Cadarette[5], and
Michal Abrahamowicz[6] on behalf of the
STRATOS initiative

Volume 26 Number 3 | Medical Writing September 2017 | 17

Journal of the European Medical Writers Association (EMWA)

STRengthening Analytical Thinking for Observational Studies: the STRATOS initiative

Willi Sauerbrei,[a*†] Michal Abrahamowicz,[b]
Douglas G. Altman,[c] Saskia le Cessie,[d] and[‡] James Carpenter[e]
on behalf of the STRATOS initiative

Statistics in Medicine 2014

2011	ISCB Ottawa, Epidemiology Sub-Comm.	Preliminary ideas
2012	ISCB Bergen	Discussions, SG
2013	ISCB Munich	Initiative launched
2014-16	ISCB	Invited Sessions
2016	**BIRS, Banff, Canada**	**First general meeting**
2016	IBC Victoria	Invited Session
2016	HEC Munich	Invited Session
2017	IBS-EMR Thessaloniki	Invited Session
2017	ISCB Vigo	Scientific topic
2017	CEN-ISBS Vienna	Invited Session
2017	GMDS Oldenburg	Invited Session
2018	ISCB, RSS, …	Invited Sessions
2019	**BIRS, Banff, Canada,** ISCB, ..	**Second general meeting**
2020	ISCB, IBC, …	

http://www.stratos-initiative.org/

Topic groups

	Topic Group	Chairs
1	**Missing data**	James Carpenter, Kate Lee
2	**Selection of variables and functional forms in multivariable analysis**	Georg Heinze, Aris Perperoglou, Willi Sauerbrei
3	**Initial data analysis**	Marianne Huebner, Saskia le Cessie, Carsten Oliver Schmidt
4	**Measurement error and misclassification**	Laurence Freedman, Victor Kipnis
5	**Study design**	Mitchell Gail, Suzanne Cadarette
6	**Evaluating diagnostic tests and prediction models**	Ewout Steyerberg, Ben van Calster
7	**Causal inference**	Els Goetghebeur, Ingeborg Waernbaum
8	**Survival analysis**	Michal Abrahamowicz, Per Kragh Andersen, Terry Therneau
9	**High-dimensional data**	Lisa McShane, Joerg Rahnenfuehrer

Cross-cutting panels

Panel		Chairs and Co-Chairs	
MP	Membership	Chairs:	James Carpenter, Willi Sauerbrei
PP	Publications	Chairs:	Bianca De Stavola, Pam Shaw
		Co-Chairs:	Mitchell Gail, Petra Macaskill
GP	Glossary	Chairs:	Martin Boeker, Marianne Huebner,
WP	Website	Chairs:	Joerg Rahnenfuehrer, Willi Sauerbrei
RP	Literature Review	Chairs:	Gary Collins, Carl Moons
BP	Bibliography	Chairs:	to be determined
SP	Simulation Studies	Chairs:	Michal Abrahamowicz, Anne-Laure Boulesteix
DP	Data Sets	Chairs:	Saskia Le Cessie, Maarten van Smeden
TP	Knowledge Translation	Chair:	Rolf Groenwold, Maarten van Smeden
CP	Contact Organisations	Chairs:	Willi Sauerbrei
VP	Visualisation	Chairs:	Mark Baillie

TG 2: Selection of variables and functional forms in multivariable analysis

State of the art in selection of variables and functional forms in multivariable analysis—outstanding issues

Willi Sauerbrei[1*], Aris Perperoglou[2], Matthias Schmid[3], Michal Abrahamowicz[4], Heiko Becher[5], Harald Binder[1], Daniela Dunkler[6], Frank E. Harrell Jr[7], Patrick Royston[8], Georg Heinze[6] and for TG2 of the STRATOS initiative

Table 1 Relevant issues in deriving evidence-supported state of the art guidance for multivariable modelling

No.	Item
1	Investigation and comparison of the properties of variable selection strategies
2	Comparison of spline procedures in both univariable and multivariable contexts
3	How to model one or more variables with a 'spike-at-zero'?
4	Comparison of multivariable procedures for model and function selection
5	Role of shrinkage to correct for bias introduced by data-dependent modelling
6	Evaluation of new approaches for post-selection inference
7	Adaption of procedures for very large sample sizes needed?

A review of spline function procedures in R

Aris Perperoglou[1*] (iD), Willi Sauerbrei[2], Michal Abrahamowicz[3], Matthias Schmid[4] on behalf of TG2 of the STRATOS initiative

See also „Educational work"

TG 4: Measurement error and misclassification

Epidemiologic analyses with error-prone exposures: review of current practice and recommendations

Pamela A. Shaw, PhD [a,*], Veronika Deffner, PhD [b], Ruth H. Keogh, DPhil [c], Janet A. Tooze, PhD [d], Kevin W. Dodd, PhD [e], Helmut Küchenhoff, PhD [b], Victor Kipnis, PhD [e], Laurence S. Freedman, PhD [f,g], on behalf of Measurement Error and Misclassification Topic Group (TG4) of the STRATOS Initiative

TUTORIAL IN BIOSTATISTICS

STRATOS guidance document on measurement error and misclassification of variables in observational epidemiology: Part 1—Basic theory and simple methods of adjustment

Ruth H. Keogh[1] | Pamela A. Shaw[2] | Paul Gustafson[3] | Raymond J. Carroll[4,5] | Veronika Deffner[6] | Kevin W. Dodd[7] | Helmut Küchenhoff[8] | Janet A. Tooze[9] | Michael P. Wallace[10] | Victor Kipnis[11] | Laurence S. Freedman[12,13]

Statistics in Medicine (2020).

TUTORIAL IN BIOSTATISTICS

STRATOS guidance document on measurement error and misclassification of variables in observational epidemiology: Part 2—More complex methods of adjustment and advanced topics

Pamela A. Shaw[1] | Paul Gustafson[2] | Raymond J. Carroll[3,4] | Veronika Deffner[5] | Kevin W. Dodd[6] | Ruth H. Keogh[7] | Victor Kipnis[6] | Janet A. Tooze[8] | Michael P. Wallace[9] | Helmut Küchenhoff[5] | Laurence S. Freedman[10,11]

Statistics in Medicine (2020).

See also „Educational work"

TG 1: Missing data

Framework for the Treatment And Reporting of Missing data in Observational Studies: The TARMOS framework

Lee KJ [1,2] ✉, Tilling K [3], Cornish RP [3], Little RJA [4], Bell ML [5], Goetghebeur E [6], Hogan JW [7], Carpenter JR [8], the STRATOS initiative

TG 3: Initial data analysis

Hidden analyses: a review of reporting practice and recommendations for more transparent reporting of initial data analyses

Marianne Huebner[1,2*], Werner Vach[3], Saskia le Cessie[4], Carsten Oliver Schmidt[5], Lara Lusa[6,7] and on behalf of the Topic Group "Initial Data Analysis" of the STRATOS Initiative (STRengthening Analytical Thinking for Observational Studies, http://www.stratos-initiative.org)

A Contemporary Conceptual Framework for Initial Data Analysis

Marianne Huebner   huebner@stt.msu.edu
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Carsten O. Schmidt   Carsten.schmidt@uni-greifswald.de
Institute for Community Medicine, SHIP-KEF
University Medicine of Greifswald
Greifswald, Germany

Werner Vach   Werner.vach@usb.ch
Department of Orthopaedics and Traumatology
University Hospital Basel
Basel, Switzerland

TG 5: Study design

Design choices for observational studies of the effect of exposure on disease incidence

Mitchell H Gail [1], Douglas G Altman,[2] Suzanne M Cadarette,[3] Gary Collins,[4] Stephen JW Evans,[5] Peggy Sekula [6], Elizabeth Williamson,[7] Mark Woodward[8]

TG 6: Evaluating diagnostic tests and prediction models

Three myths about risk thresholds for prediction models

Laure Wynants[1,2*], Maarten van Smeden[3,4], David J. McLernon[5], Dirk Timmerman[1,6], Ewout W. Steyerberg[4], Ben Van Calster[1,4] and on behalf of the Topic Group 'Evaluating diagnostic tests and prediction models' of the STRATOS initiative

Calibration: the Achilles heel of predictive analytics

Ben Van Calster[1,2,6*], David J. McLernon[3,6], Maarten van Smeden[2,4,6], Laure Wynants[1,5], Ewout W. Steyerberg[2,6]
On behalf of Topic Group 'Evaluating diagnostic tests and prediction models' of the STRATOS initiative[6]

Correspondence

Flawed external validation study of the ADNEX model to diagnose ovarian canceron behalf of TG6 of the STRATOS initiative

TG 7: Causal inference

Formulating causal questions and principled statistical answers

Els Goetghebeur[1,2] | Saskia le Cessie[3] | Bianca De Stavola[4] | Erica EM Moodie[5] | Ingeborg Waernbaum[6] | "on behalf of" the topic group Causal Inference (TG7) of the STRATOS initiative

Statistics in Medicine (2020).

TG 8: Survival analysis

Analysis of time-to-event for observational studies: Guidance to the use of intensity models

Per Kragh Andersen[1] | Maja Pohar Perme*[2] | Hans C. van Houwelingen[3] | Richard J. Cook[4] | Pierre Joly[5] | Torben Martinussen[1] | Jeremy M.G. Taylor[6] | Michal Abrahamowicz[7] | Terry M. Therneau[8] | for the STRATOS TG8 topic group

Statistics in Medicine (2020).

TG 9: High-dimensional data

Talk from Lisa McShane

Biometrical Bulletin
since 3/2017 articles from all TGs and from some panels

STRengthening Analytical Thinking for Observational Studies (STRATOS)

Introducing the Visualisation Panel (SP)

Marc Baillie (1) and Marc Vandemeulebroecke (1); on behalf of the Visualisation Panel (1) Biostatistical Sciences and Pharmacometrics, Novartis Pharma AG, Basel, Switzerland

Glossary Panel (GP) - Defining common meaning for statistical terms

Martin Boeker (1) Patrick Tippmann (1), Simon Day (2), Marianne Huebner (3), Willi Sauerbrei (1)

(1) Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center - University of Freiburg, Germany

(2) Clinical Trials Consulting & Training Limited, North Marston, UK

(3) Department of Statistics and Probability, Michigan State University, EastLansing, MI, USA

Simulation panel
Comparison of statistical methods: How?
Simulation studies play a key role

On the necessity and design of studies comparing statistical methods

Anne-Laure Boulesteix[1] iD
Harald Binder[2]
Michal Abrahamowicz[3]
Willi Sauerbrei[2]
for the Simulation Panel of the STRATOS Initiative

See also „Educational work"

Talk from Tim Morris

Collaboration partner in SISAQOL

'SISAQOL-IMI: Generating recommendations for the design, analysis and interpretation of Patient Reported Outcomes (PROs) for cancer clinical trials

- International multidisciplinary consortium, co-led by the European Organisation for Research and Treatment of Cancer (EORTC) and Boehringer Ingelheim (BI),

- A public-private collaborative research project. Forty one stakeholder groups are involved, including pharmaceutical industry, academia, cancer institutes, regulators, and patient advocacy organisations.'

On behalf of STRATOS Saskia le Cessie and Els Goetghebeur lead WP3-Feasibility of developing recommendations for non-RCTs, with single-arm studies as a case study.

Issues from (nearly) all TGs will play a role.

Educational work

TG 2

PLOS ONE | https://doi.org/10.1371/journal.pone.0241427   December 21, 2020

REGISTERED REPORT PROTOCOL

Systematic review of education and practical guidance on regression modeling for medical researchers who lack a strong statistical background: Study protocol

Paul Bach[1,2,3], Christine Wallisch[1,2,4], Nadja Klein[3], Lorena Hafermann[1,2], Willi Sauerbrei[5], Ewout W. Steyerberg[6], Georg Heinze[4], Geraldine Rauch[1,2]*, for topic group 2 of the STRATOS initiative[¶]

Introduction to statistical simulations in health research

Anne-Laure Boulesteix [iD],[1] Rolf HH Groenwold,[2,3] Michal Abrahamowicz,[4] Harald Binder,[5] Matthias Briel,[6,7] Roman Hornung,[1] Tim P Morris [iD],[8] Jörg Rahnenführer,[9] Willi Sauerbrei,[5] for the STRATOS Simulation Panel

SIGNIFICANCE | February 2020

Analysis in an imperfect world

TG 4

When we observe the world, we sometimes make mistakes. **Michael Wallace**, on behalf of the measurement error topic group of the STRATOS Initiative, explains the potentially severe consequences of this often overlooked issue, and how statistics can help bring us back – or at least a little closer – to the truth

Videos, Shiny apps

Knowledge translation

- Tutorials from several TGs
    - Measurement error (TG4)
    - Causal inference (TG7)
    - Variable selection (TG2)
- Become active on *Twitter*

- Websites from all TGs

They will provide much more information

Summary

- Data and data science becomes more and more important
- Answering questions empirically through data analyses often requires the use of complex methodology. It is important to develop suitable approaches; needs to be done by experts (Level 3)
- Experienced statisticians (Level 2) need to be supported by suitable guidance. There are (too) many approaches (some are useless) available and suitable comparisons are missing
- Better simulation studies are required to assess properties, compare approaches and derive evidence based guidance for practice.
- Suitable educational material is the key to improve analyses at a broad level
- For practically relevant topics we need greater emphasis on development of Level 1 and 2 guidance