The STRATOS initiative, illustrated by issues in Topic group 2: selection of variables and their functional forms

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http://stratos-initiative.org/

STRATOS INITIATIVE

UNIVERSITÄTS KLINIKUM FREIBURG

Overview

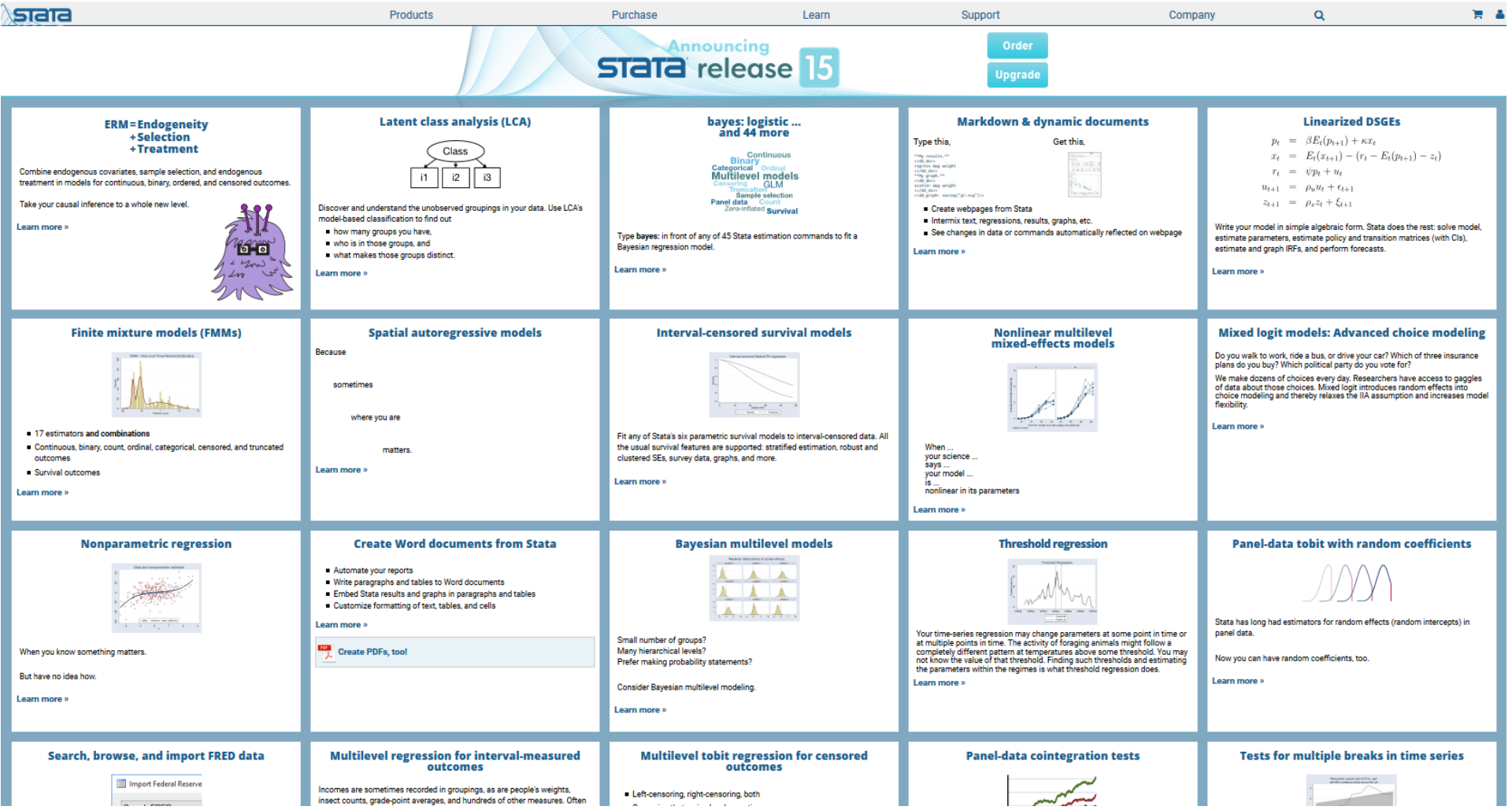
- The STRATOS initiative – Why?
- TG2: Part 1 – Selection of variables
- TG2: Part 2 – Selection of functional forms
- Combine parts 1 and 2: Issues
- Comparison of statistical methods: How?

The STRATOS initiative – Why?
Current situation in statistical methodology

- Statistical methodology has seen substantial development
- Computer facilities 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

Software package STATA

new procedures in 2018



Splines

a brief overview of regression packages in R

Package	Downloads	Vignette	Book	Website	Datasets
quantreg	2001231	X	X		7
mgcv	1438166	X	X		2
survival	1229305	X	X		33
VGAM	297308	X	X	X	50
gbm	271362			X	3
gam	168143		X	X	1
gamlss	78295	X	X	X	29

Perperoglou et al, talk at ISCB 2017, see STRATOS website

Current situation in practical analyses

- Unfortunately, many sensible improvements are ignored

Reasons why improved strategies are ignored

- Overwhelming concern with **theoretical aspects**
- 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 severeness 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 be **grateful for** 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 and the necessary 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 that 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, researches develop new and more complicated approaches. Advantages and usefulness in practice need to be assessed

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**	**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**	**Second general meeting**

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, Werner Vach
4	**Measurement error and misclassification**	Laurence Freedman, Victor Kipnis
5	**Study design**	Mitchell Gail, Suzanne Cadarette
6	**Evaluating diagnostic tests and prediction models**	Gary Collins, Carl Moons, Ewout Steyerberg
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, Stephen Walter
		Co-Chairs:	Mitchell Gail, Petra Macaskill
GP	**Glossary**	Chairs:	Simon Day, Marianne Huebner, Jim Slattery
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, Aris Perperoglou
TP	**Knowledge Translation**	Chair:	Suzanne Cadarette
		Co-Chair:	Catherine Quantin
CP	**Contact Organizations**	Chairs:	Willi Sauerbrei

Topic group 2: Selection of variables and their functional forms in multivariable analysis

Building multivariable regression models – some preliminaries

– Initial data analysis (TG3)

– ‚Reasonable' model class was chosen

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Aim of a model and model complexity

Most important distinction:
„to explain or to predict“ (Shmueli, 2010)

Prediction (TG6)

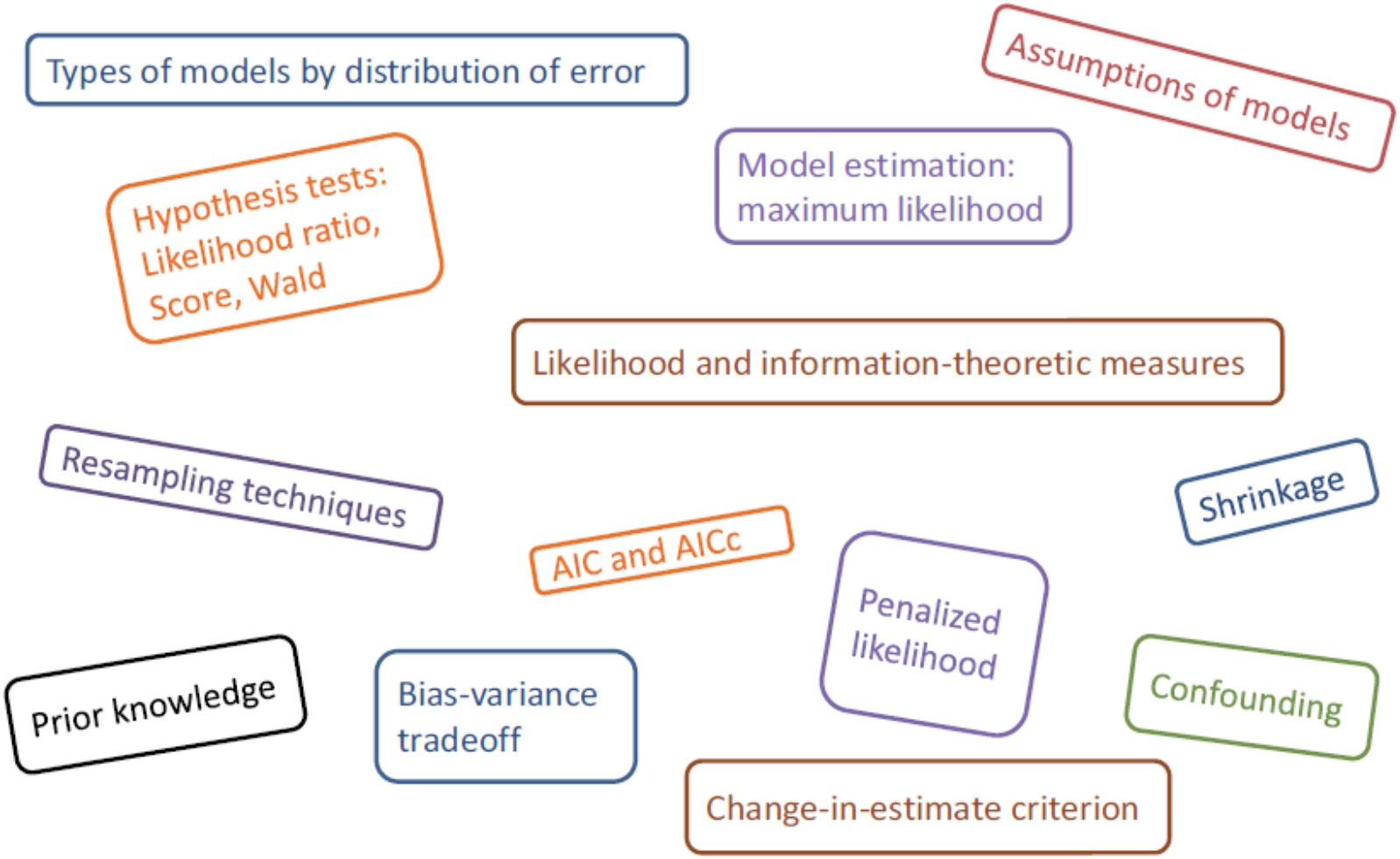
Here: **TG2**
model for explanation (or descriptive modelling)

Causal inference (TG7)

TG2: Part 1 – Selection of variables

- Central issues:
  - To select or not to select (full model)?
  - Which variables to include?
- A large number of methods proposed (for many decades)
- High-dimensional data triggered the development of further proposals
- Many critical issues

Selection of variables: Statistical prerequisites



Heinze et al., BiomJ, 2018

Opinions on variable selection

for models with focus on prediction and explanation

(Harrell, 2001; Steyerberg, 2009; Burnham & Anderson, 2002, Royston & Sauerbrei, 2008)

Heinze et al., BiomJ, 2018

→ **Different philosophies**

→ **Emphasis on different aims**

(Traditional) methods for variable selection

Full model

- variance inflation in the case of multicollinearity
  - Wald-statistic

Stepwise procedures $\Rightarrow$ prespecified (α_{in}, α_{out}) and actual significance level?

- forward selection (FS)
- stepwise selection (StS)
- backward elimination (BE)

All subset selection $\Rightarrow$ which criteria?

- C_p Mallows
- AIC Akaike Information Criterion
- BIC Bayes Information Criterion

Bayes variable selection

Key issue:

More or less complex models?

All approaches are heavily criticised

Other procedures

- Bootstrap selection
- Change-in-estimate
- Variable clustering
- Incomplete principal components
- Penalized approaches (selection and shrinkage; Lasso, Garotte, Boosting, SCAD, …)
  - TG 9: High-dimensional data
- Directed acyclic graph (DAG-) based selections
  - TG 7: Causal inference

. . .

"Recommendations" from the literature

We do not know any recommendation which is supported by good evidence from theory or meaningful simulation studies

Problem of the practicing statistician:
What to do?

TG 2: Part 2 – selection of functional forms

- Assume linearity
  - Often ok but sometimes wrong. Can lead to wrong conclusions
- Cut-points
  - Many problems known for a long time. Nevertheless still very popular
- 'Optimal' cut-points
  - Worse than cutpoints
- Fractional polynomials and Splines
  - Flexible procedures but many open issues
  - More comparisons (simulation studies) needed

Functional forms: Models based on cut-points: problems!

- Cut-points are still popular in clinical and epidemiological research
- Use of cut-points in a model gives a step function
- How many cut-points?
- Where should the cut-points be put?
- Biologically implausible step functions are a poor approximation to the true relationship
- Almost always fits the data less well than a suitable continuous function

- Nevertheless, in many areas still the preferred approach!

TG 2: Part 3 – Combining variable and function selection

Two inter-related questions, common to many multivariable explanatory models

Results of data-dependent selections of independent variables may depend on

- decisions regarding functional forms of both
  1. the variable of interest (X)
  2. other variables, correlated with X

and *vice versa*

For survival data (TG8):

- Effects may vary in time
- Another interrelated issue

Combining variable and function selection

- Multivariable fractional polynomials (MFP)
- Various spline based approaches

Comparison in a large simulation study (Binder et al., 2013)

Nevertheless, much more research is needed!

TG 2 - State of the art?

- Which strategies for variable selection exist?
  What about their properties?
- Data-dependent modeling introduces bias.
  What about the role of shrinkage approaches?
- Comparison of spline procedures in a univariate context.
  Which criteria are relevant? Can we derive guidance for practice?
- What about variables with a ‘spike-at-zero’?
- Multivariable procedures
  MFP well defined strategy
  Which of the spline based procedures?
- Multivariable procedures and correction for selection bias
  How relevant? One step or two step approaches?
  E.g. selection of variables and forms followed by shrinkage
- Big Data
  Does it influence properties of procedures and their comparison?
- Role of model validation

Much research required!

Comparison of statistical methods

How?

LETTER TO THE EDITOR

Biometrical Journal

On the necessity and design of studies comparing statistical methods

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

State-of-the-art - **EVIDENCE** is required
Conduct an informative simulation study - many open issues

"[…]It becomes more and more difficult to get an overview of existing methods, not to mention the overview of their respective performances in different settings.

[…] Moreover, it is well known that studies comparing a suggested new method to existing methods may be (strongly) biased in favor of the new method.

***neutral* comparison studies**

- do not aim to demonstrate the superiority of a particular method
- involve authors who are, as a collective, approximately equally competent on all considered methods.
- may be very time consuming and difficult to both organize and perform"

More (meta)research needed

No consensus on what makes a reliable comparison study

- Which designs are most appropriate?
- What are typical sources of potential biases and how can they be avoided?
- How can the results be interpreted without the tendency for overinterpretation?
- Which mixture of simulated and real data should be used?
- How should real data be selected?
- How should simulated data be generated in a realistic way inspired from real datasets?

… continued

- What parameters and assumptions should be varied across the simulated scenarios?
- What range of sample sizes should be assessed?
- How can we assess the practical relevance of simulation results, which depends on the real-life plausibility of the simulation scenarios?
- How can an acceptable neutrality of the authors team be achieved and how can non-neutrality (the analogon of “conflicts of interest” in clinical research) be disclosed?
- Which “competing methods” should be considered?

We need to recognize that there is **no agreement among experts on the “state-of-the-art” methods for many topics relevant in practice**.”

Guidance needed

- Since there is often not much “evidence” about **relative advantages and disadvantages** of the competing available methods, the specific choice cannot be “evidence based”.

- **Guidance for practice is missing** for many methodological issues and a data analyst facing a practical problem has neither the required time nor the required expertise to conduct meaningful comparison studies

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

TG1 – missing data

TG4 – measurement error and misclassification

TG3 – initial data analysis

have appeared

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

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To work on some of the issues discussed:

Postdoc position for 3 years in Freiburg (Germany)