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

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STRATOS INITIATIVE

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Overview

- Statistical methodology – current situation
- Aims and structure of the STRATOS initiative
- Issues in variable and function selection
  1. Selection of variables
  2. Selection of functional forms
  3. Combining the two parts

Statistical methodology – Current situation

- Statistical methodology has seen some 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 allow a rapid implementation and verification of new statistical ideas

Unfortunately, many sensible improvements are ignored in practical statistical analyses

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 1)

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.

Our belief is that research funders, scientific societies, school and university teachers, professional medical associations, and scientific publishers (and their editors) can use this Series as an opportunity to examine more forensically why they are doing what they do—the purpose of science and science communication—and whether they are getting the most value for the time and money invested in science.

Kleinert and Horton, 2014

Comment (Introduction 2)

- **Biomedical research: increasing value, reducing waste**

- Of 1575 reports about cancer prognostic markers published in 2005, 1509 (96%) detailed at least one significant prognostic variable. However, few identified biomarkers have been confirmed by subsequent research and few have entered routine clinical practice.
  ….
- Global biomedical and public health research involves billions of dollars and millions of people. In 2010, expenditure on life sciences (mostly biomedical) research was US$240 billion. The USA is the largest funder, with about $70 billion in commercial and $40 billion in governmental and non-profit funding annually, representing slightly more than 5% of US health-care expenditure. 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

Improvement

At least two tasks are essential

- **Experts** in specific methodological areas have to work towards **developing guidance**
- 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
- Point out weaknesses of approaches often used despite of problems (e.g. categorizing continuous variables in the analysis; complete case analysis if a case has missing values in one or more variables)
- Propose methods which may not be optimal or state of the art, but which are easy to use and which are still acceptable from a methodological point of view
- Software should be generally available

Different levels of statistical knowledge

Level 2: Experienced statistician

- Methodology perhaps slightly below state of the art, but doable by every experienced analyst
- Advantages and disadvantages of competing approaches, point to the importance and implications of underlying assumptions
- Sufficient guidance about software plays a key role that the approaches are also used in practice

Different levels of statistical knowledge

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 are unclear • Often, advantages are presented in a small number of examples and in specific situations but a more systematic comparison to the state of the art is needed
- Software requires specific knowledge and may not be generally available
- Overview of recent research with statements about possible advantages and disadvantages is needed
- Could help to identify important weaknesses of level 2 proposals
- Help to identify areas needing more methodological research
- Trigger the development of software for more general use

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	Banff	Workshop
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

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

Topic groups

Topic Group		Chairs and further members	
1	**Missing data**	Chairs: Members:	**James Carpenter, Kate Lee** Melanie Bell, Els Goetghebeur, Joe Hogan, Rod Little, Andrea Rotnitzky, Kate Tilling, Ian White
2	**Selection of variables and functional forms in multivariable analysis**	Chairs: Members:	**Michal Abrahamowicz, Willi Sauerbrei, Aris Perperoglou** Heiko Becher, Harald Binder, Frank Harrell, Georg Heinze, Patrick Royston, Matthias Schmid
3	**Initial data analysis**	Chairs: Members:	**Marianne Huebner, Saskia le Cessie, Werner Vach** Maria Blettner, Dianne Cook, Heike Hofmann, Hermann-Josef Huss, Lara Lusa, Carsten Oliver Schmidt
4	**Measurement error and misclassification**	Chairs: Members:	**Laurence Freedman, Victor Kipnis** Raymond Carroll, Veronika Deffner, Kevin Dodd, Paul Gustafson, Ruth Keogh, Helmut Küchenhoff, Pamela Shaw, Janet Tooze
5	**Study design**	Chairs: Members:	**Mitchell Gail, Suzanne Cadarette** Doug Altman, Gary Collins, Luc Duchateau, Neil Pearce, Peggy Sekula, Elizabeth Williamson, Mark Woodward
6	**Evaluating diagnostic tests and prediction models**	Chairs: Members:	**Gary Collins, Carl Moons, Ewout Steyerberg** Patrick Bossuyt, Petra Macaskill, David McLernon, Ben van Calster, Andrew Vickers
7	**Causal inference**	Chairs: Members:	**Els Goetghebeur, Ingeborg Waernbaum** Bianca De Stavola, Saskia le Cessie, Niels Keiding, Erica Moodie, Michael Wallace
8	**Survival analysis**	Chairs: Members:	**Michal Abrahamowicz, Per Kragh Andersen, Terry Therneau** Richard Cook, Pierre Joly, Torben Martinussen, Maja Pohar-Perme, Jeremy Taylor
9	**High-dimensional data**	Chairs: Members:	**Lisa McShane, Joerg Rahnenfuehrer** Axel Benner, Harald Binder, Anne-Laure Boulesteix, Tomasz Burzykowski, Riccardo De Bin, W. Evan Johnson, Lara Lusa, Stefan Michiels, Sherri Rose, Willi Sauerbrei

Cross-cutting panels

Panels		Chairs and Co-Chairs
1	Glossary (GP)	Simon Day, Marianne Huebner, Jim Slattery
2	Data Sets (DP)	Saskia Le Cessie, Aris Perperoglou, Hermann Huss
3	Publications (PP)	Stephen Walter, Bianca De Stavola, Mitchell Gail, Petra Macaskill
4	New Membership (MP)	James Carpenter, Willi Sauerbrei
5	Website (WP)	Joerg Rahnenfuehrer, Willi Sauerbrei
6	Literature Review (RP)	Gary Collins, Carl Moons
7	Simulation Studies (SP)	Michal Abrahamowicz, Harald Binder
8	Contact with other societies and organizations (OP)	Willi Sauerbrei, Douglas Altman
9	Knowledge Transfer (TP)	Suzanne Cadarette, Catherine Quantin

On requirements for evidence supported guidance

Issues in variable and function selection

(consider low dimensional data and not ‘too small‘ sample sizes)

Building multivariable regression models – some preliminaries

- ‚Reasonable' model class was chosen
- Comparison of strategies
  - Theory

    only for limited questions, unrealistic assumptions
  - Examples or simulation
    - Examples based on published data
      - oversimplifies the problem
      - data clean
      - ‚relevant' predictors given

    → rigorous pre-selection → what is a full model?

… preliminaries continued

More problems are available,

see discussion on initial data analysis in Chatfield (2002) section ‚*Tackling real life statistical problems*‘

see also Mallows (1998), The zeroth problem, Am. Stat.

TG3 – Initial Data Analysis

TG2: Selection of variables and functional forms in multivariable analysis

In multivariable analysis, it is common to have a mix of binary, categorical (ordinal or unordered) and continuous variables that may influence an outcome. While TG6 considers the situation where the main task is predicting the outcome as accurately as possible, the main focus of TG2 is to identify influential variables and gain insight into their individual and joint relationship with the outcome. Two of the (interrelated) main challenges are selection of variables for inclusion in a multivariable explanatory model and choice of the functional forms for continuous variables.

[…] The effects of continuous predictors are typically modeled by either categorizing them (which raises such issues as the number of categories, cutpoint values, implausibility of the resulting step-function relationships, local biases, power loss, or invalidity of inference in case of data-dependent cutpoints) or assuming linear relationships with the outcome, possibly after a simple transformation (e.g. logarithmic or quadratic). Often, however, the reasons for choosing such conventional representation of continuous variables are not discussed and the validity of the underlying assumptions is not assessed.

To address these limitations, statisticians have developed flexible modeling techniques based on various types of smoothers, including fractional polynomials and several 'flavors' of splines.

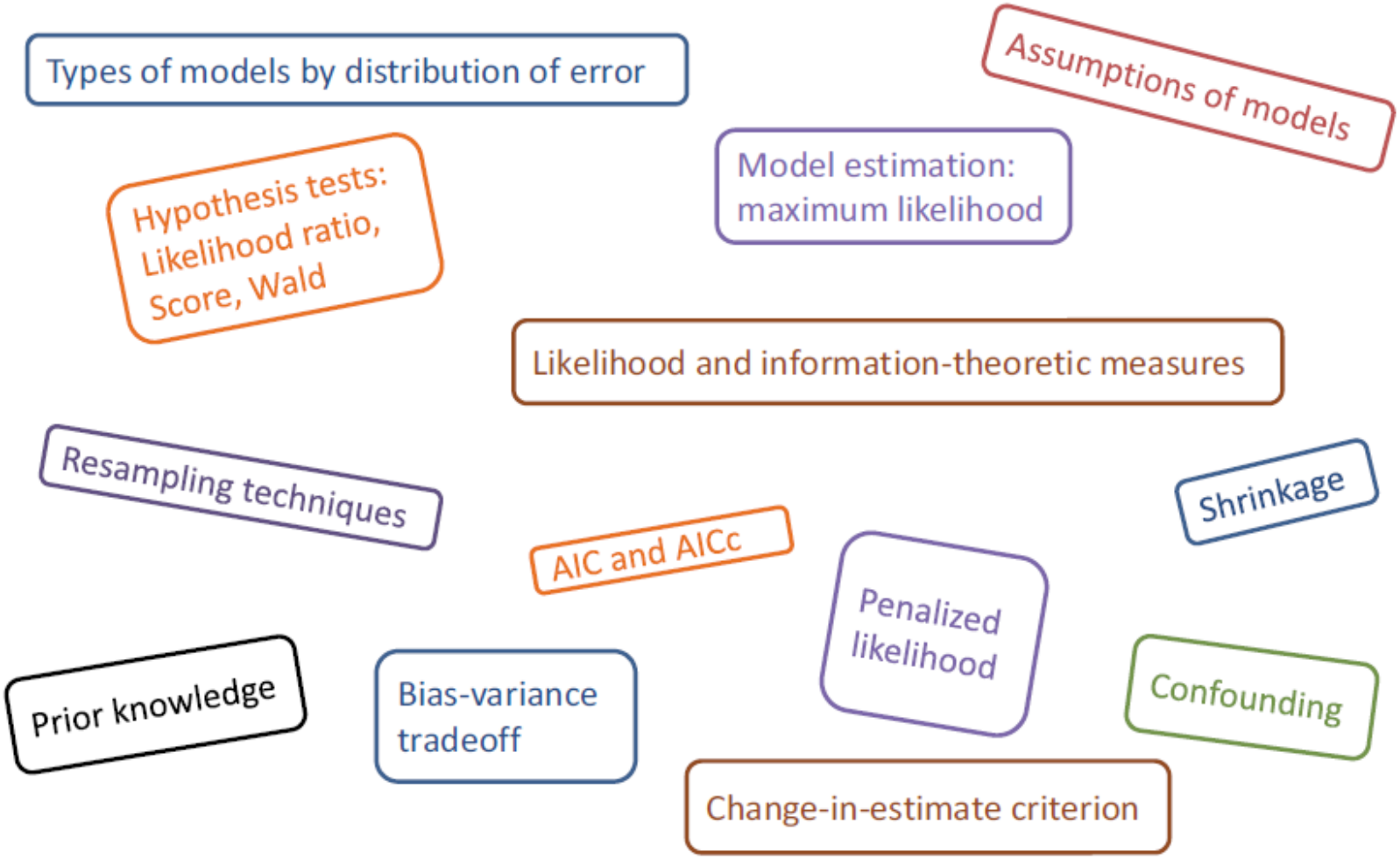
[…] collaborations with other TGs to account for such complexities as missing data, measurement errors, time-varying confounding or issues specific to modeling continuous predictors in survival analyses.

TG2: Part 1 – Selection of variables

- Central issues:
  - Model with focus on prediction or explanation?
  - 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

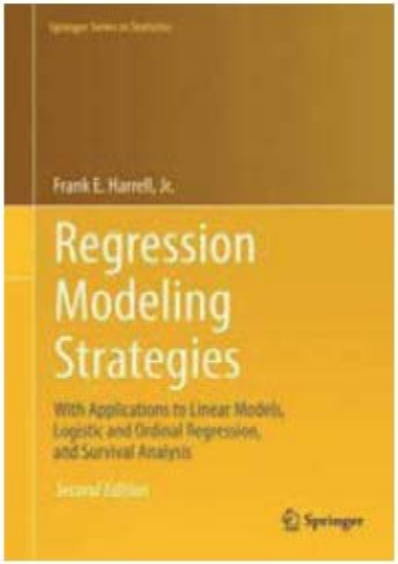
Selection of variables: Statistical prerequisites

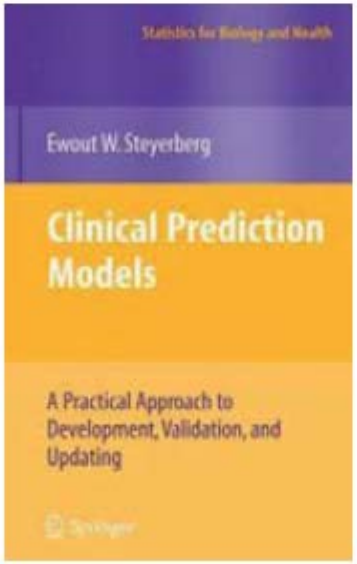


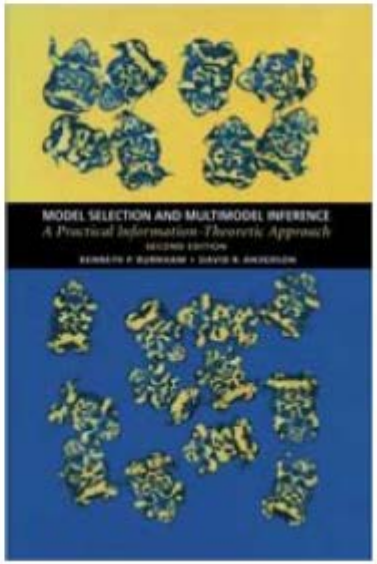
Opinions on variable selection

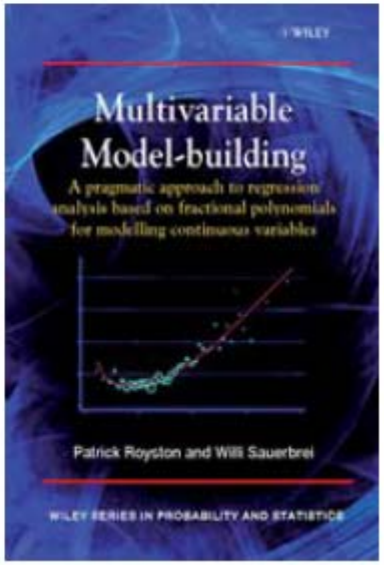
for models with focus on prediction and explanation.

Variable selection









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

(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

MORE OR LESS COMPLEX MODELS?

Stepwise procedures

Central Issue:

- significance level
  choice depends on aim of the study

Criticism

- FS and StS start with ‚bad' univariate models (underfitting)
- BE starts with the full model (overfitting),
  less critical
- Multiple testing, P-values incorrect

Nevertheless very popular in practice

Other procedures

- Bootstrap selection
- Change-in-estimate
- Variable clustering
- Incomplete principal components
- Penalized approaches (selection and shrinkage; Lasso, Garotte, 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

TG 2: Part 2 - selection of functional forms

- Assume linearity
- Cut-points
- ‘Optimal’ cut-points
- Fractional polynomials
- Splines

Functional forms: the problem (1)

"Quantifying epidemiologic risk factors using non-parametric regression: model selection remains the greatest challenge"

Rosenberg PS et al, Statistics in Medicine 2003; 22:3369-3381

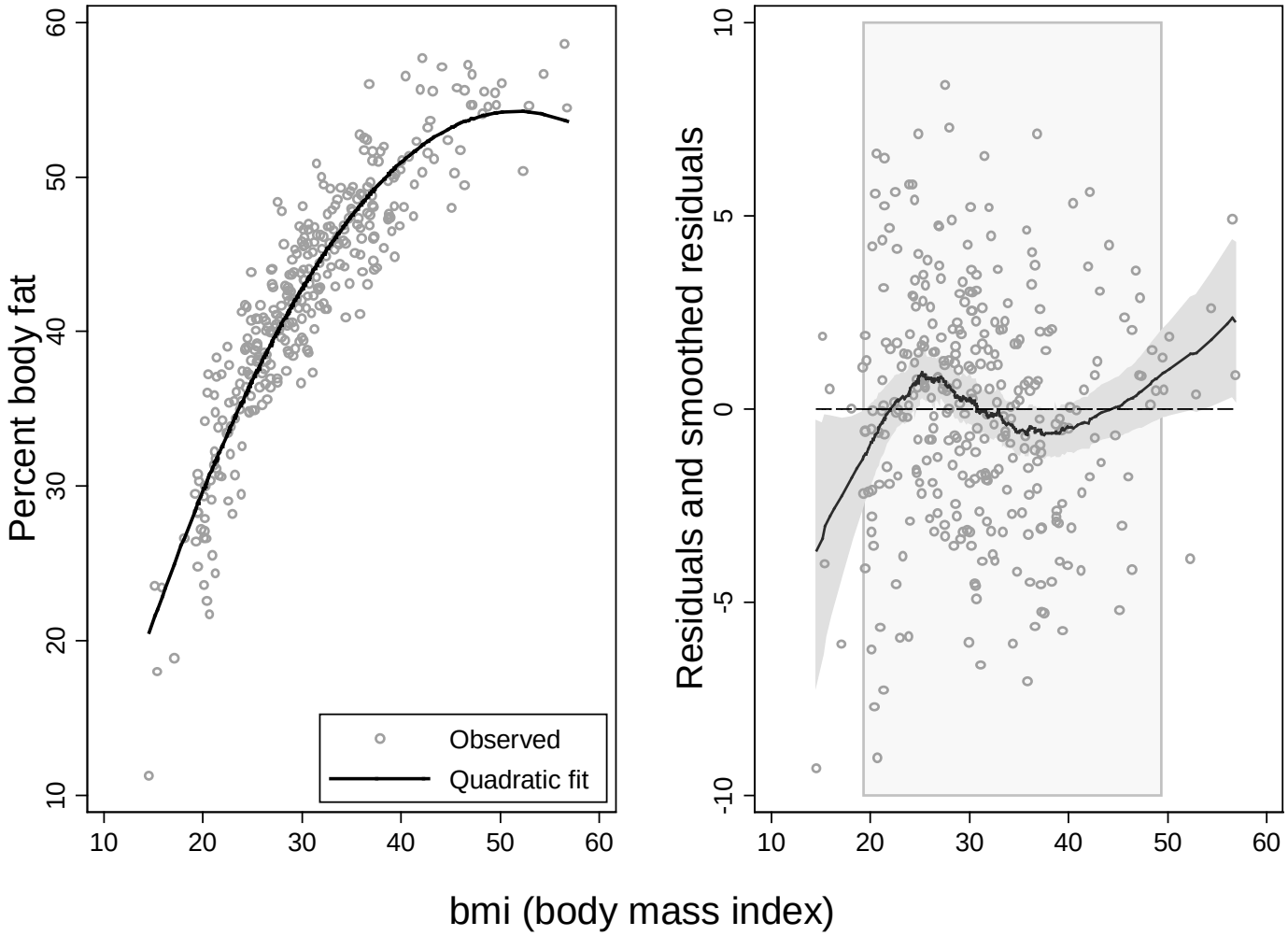
Discussion of issues in (univariate) modelling with splines

Trivial nowadays to *fit* almost any model

To *choose* a good model is much harder

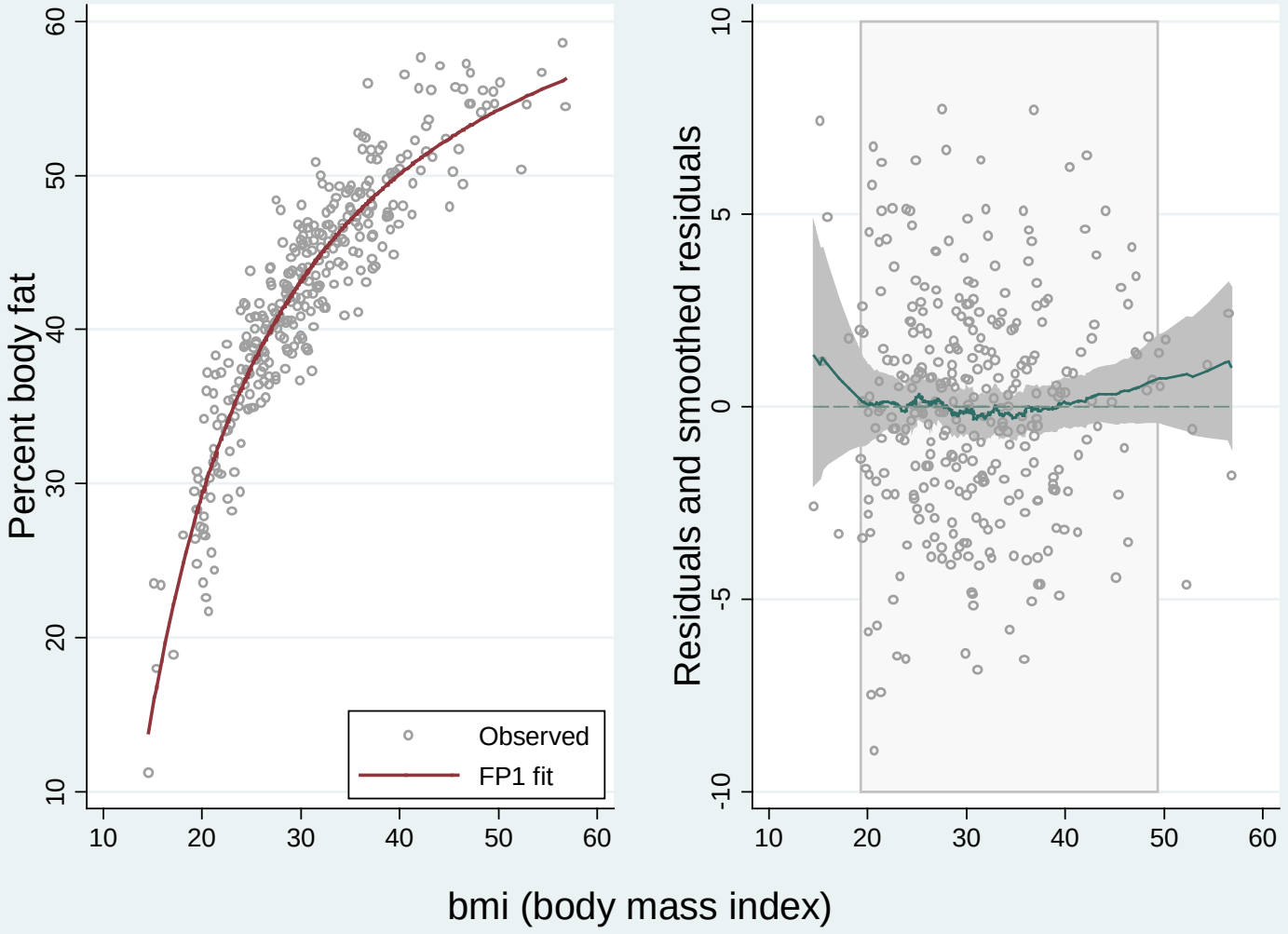
Functional forms: the problem (2)

Body fat data: quadratic model fits the data badly



Functional forms: a possible solution

Fractional polynomial does better

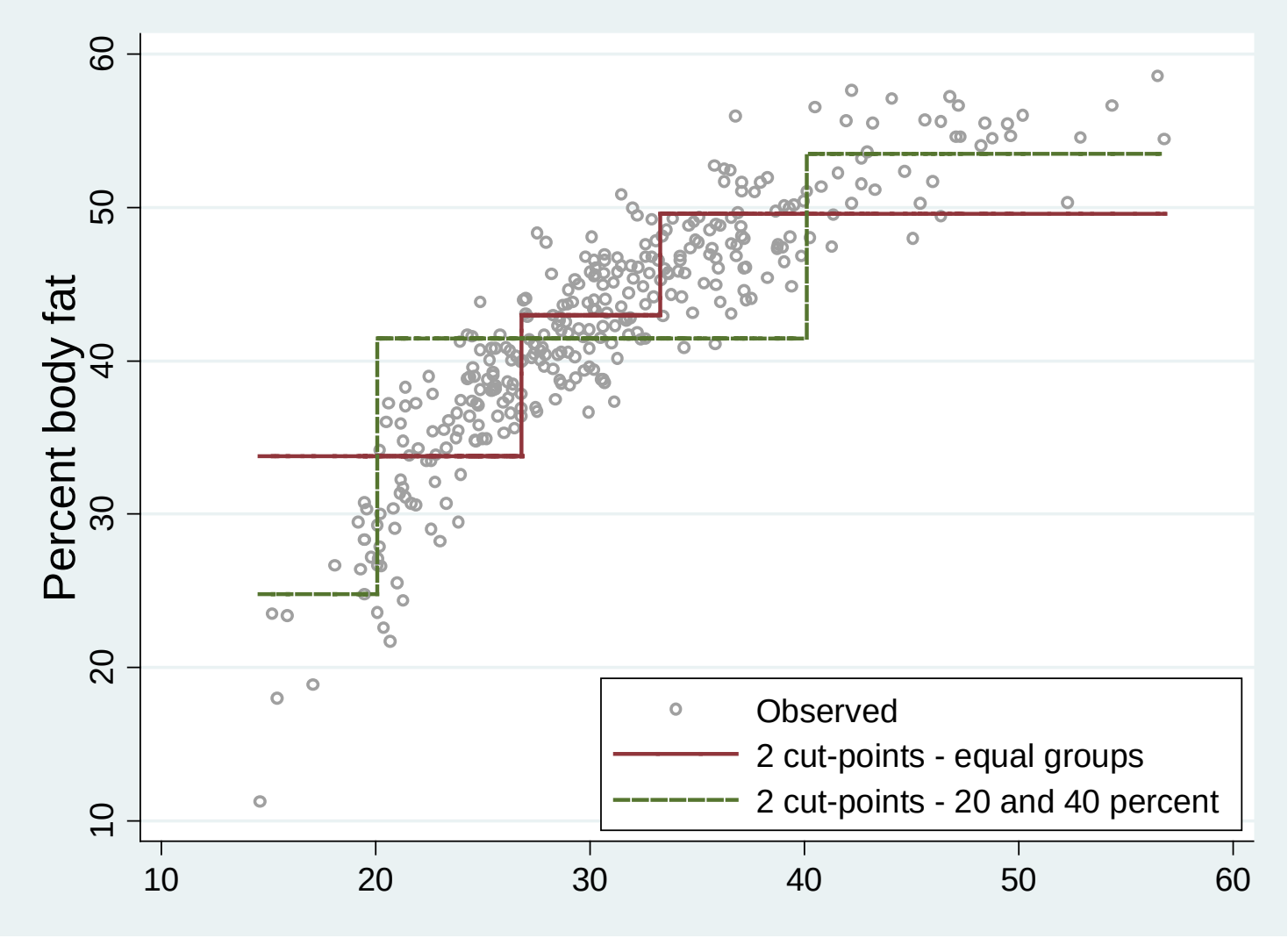


Functional forms: Models based on cut-points: problems!

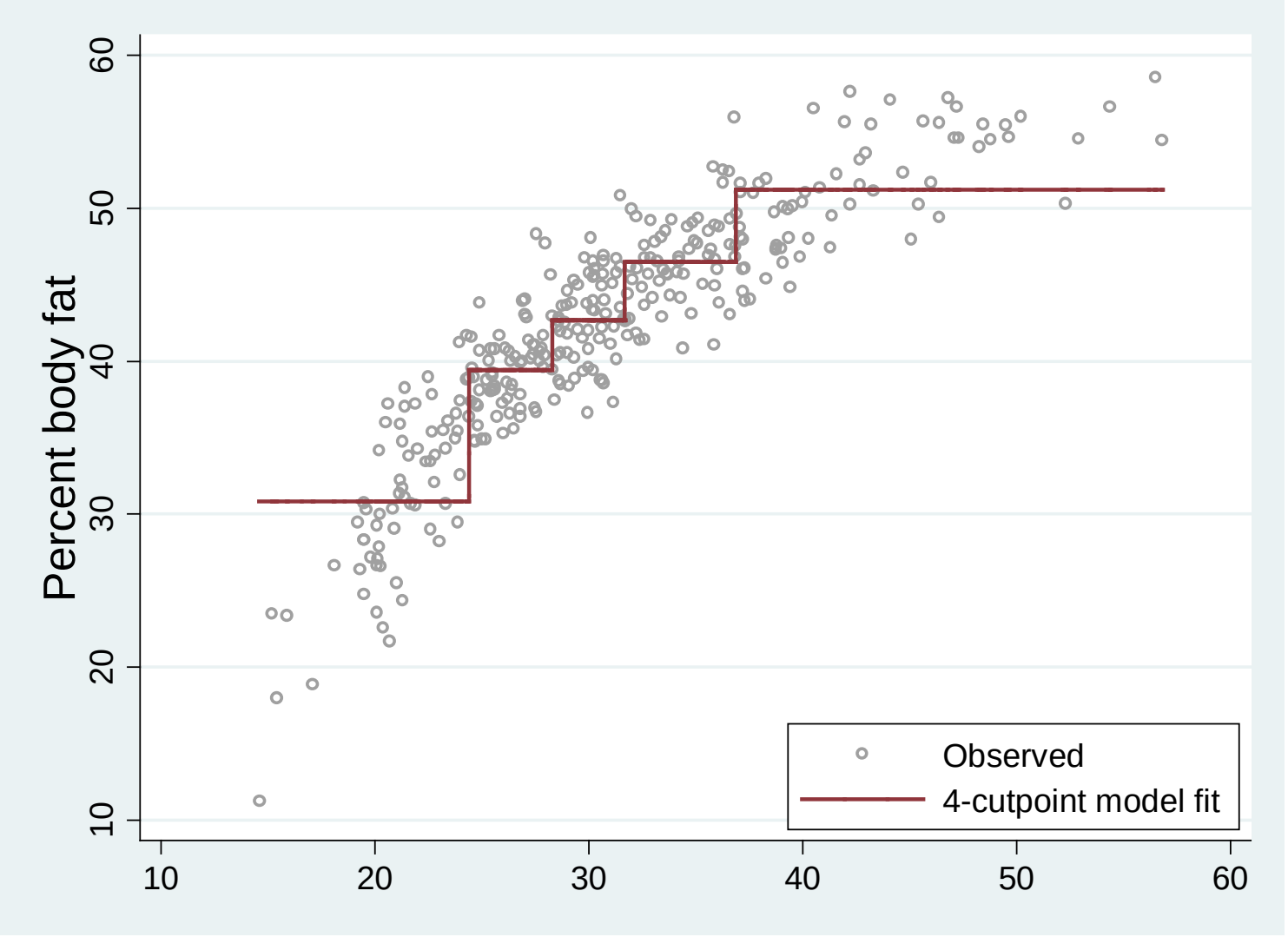
- Cut-points are still popular in clinical and epidemiological research
- Use of cut-points in a model gives a step function
- How many cut-points?
- Where should the cut-points be put?
- Biologically implausible step functions are a poor approximation to the true relationship
- Almost always fits the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

- Nevertheless, in many areas still the preferred approach!

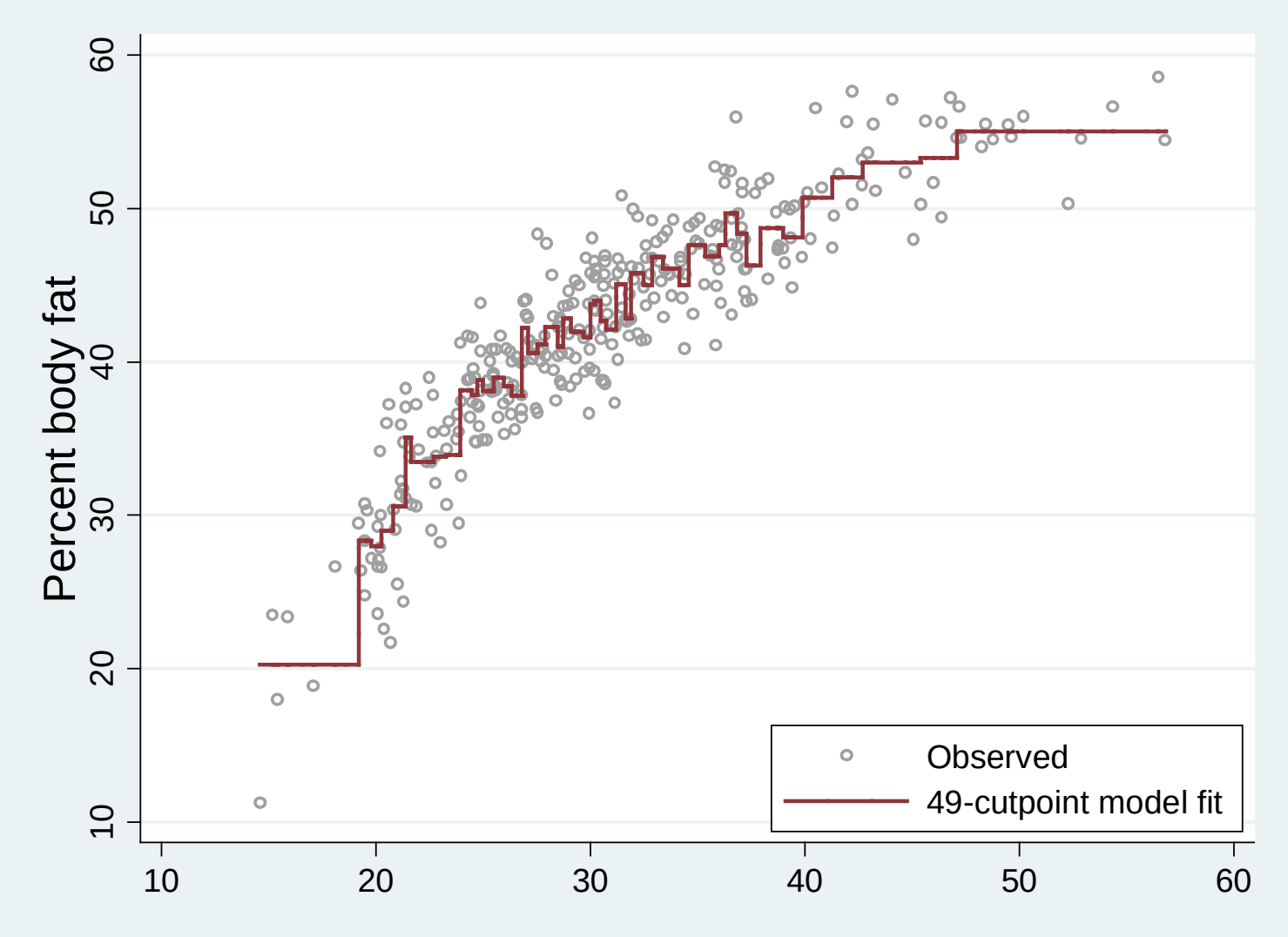
Body fat data (1) – two cutpoints



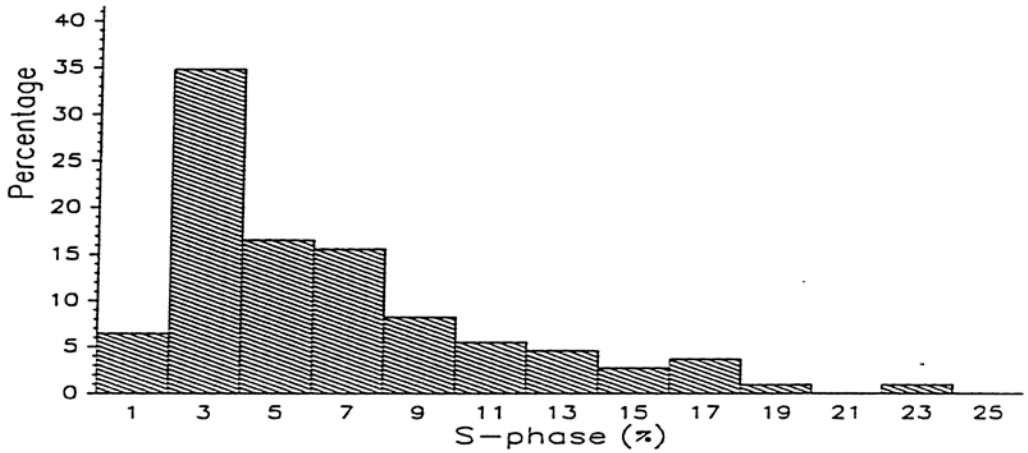
Body fat data (2) – four cutpoints

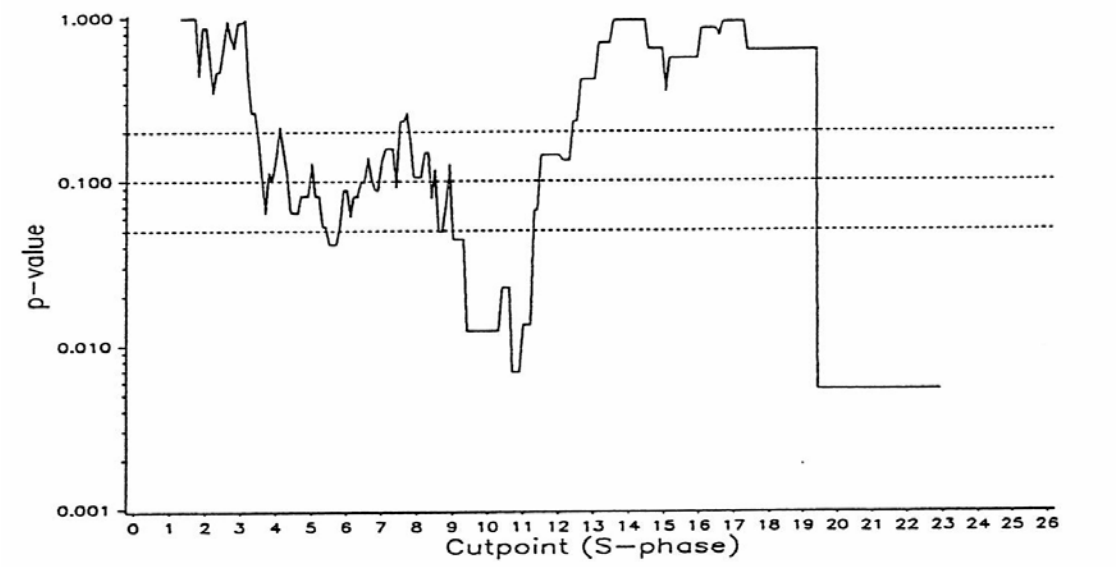


Body fat data (3) – 49 cutpoints



‘Optimal’ cutpoint (better: minimal P-value approach)





Optimal cutpoints: problems!

- Multiple testing $\Rightarrow$ inflation of significance level
  - 40% instead of nominal 5%
- Inflated significance level does not disappear with increased sample size
- Large bias in estimate of difference between groups
- Results depend on chance
- Never reproducible – impossible to summarize across studies

Spline packages

bs: B-Spline Basis for Polynomial Splines

ns: Generate a Basis Matrix for Natural Cubic Splines

For some comparisons see ISCB 2017 talk by Aris Perperoglou

Other spline packages

Package	Description	Authors
gss	General Smoothing Splines	C Gu
polspline	Polynomial spline routines	C Kooperberg
pspline	Penalized Smoothing Splines	B Ripley
cobs	Constrained B-Splines	PT Ng and M Maechler
crs	Categorical Regression Splines	JS Racine, Z Nie, BD R
bigsplines	Smoothing Splines for Large Samples	NE Helwig
bezier	Bezier Curve and Spline Toolkit	A Olsen
freeknotsplines	Free-Knot Splines	S Spiriti, P Smith, P Le
Orthogonal splinebasis	Orthogonal B-Spline Functions	A Redd
pbs	Periodic B Splines	S Wang
logspline	Logspline density estimation routines	C Kooperberg
episplineDensity	Density Estimation Exponential	S Buttrey, J Royset, R
Hmisc, rms	restricted cubic splines, plots	F Harrell

A brief overview of regression packages

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

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!

What about state-of-the-art?

State-of-the-art *refers to the* ***highest level of general development****, as of a device, technique, or scientific field achieved at a particular time.*

Wikipedia, 12 June 2017

General issue in all studies

- missing data (TG1)
- measurement error (TG4)
- was the study well designed ? (TG5)

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?
  Comparison in large simulation studies needed
- 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!

Conclusion

We are far away from 'state-of-the-art' on selection of variables and functional forms

Many more comparisons are urgently needed!

'Exact distributional results are virtually impossible to obtain, even for simplest of common subset selection algorithms'

Picard & Cook, JASA, 1984

=> Informative simulation studies are needed!

The STRATOS Initiative

STRengthening Analytical Thinking for Observational Studies

STRATOS INITIATIVE

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Stratos Initiative

The validity and practical utility of observational medical research depends critically on good study design, excellent data quality, appropriate statistical methods and accurate interpretation of results. Statistical methodology has seen substantial development in recent times. Unfortunately, many of these methodological developments are ignored in practice. Consequently, design and analysis of observational studies often exhibit serious weaknesses. The lack of guidance on vital practical issues discourages many applied researchers from using more sophisticated and possibly more appropriate methods when analyzing observational studies. Furthermore, many analyses are conducted by researchers with a relatively weak statistical background and limited experience in using statistical methodology and software. Consequently, even 'standard' analyses reported in the medical literature are often flawed, casting doubt on their results and conclusions. *An efficient way to help researchers to keep up with recent methodological developments is to develop guidance documents that are spread to the research community at large.*

These observations led to the initiation of the STRATOS (STRengthening Analytical Thinking for Observational Studies) initiative, a large collaboration of experts in many different areas of biostatistical research. *The objective of STRATOS is to provide accessible and accurate guidance in the design and analysis of observational studies. The guidance is intended for applied statisticians and other data analysts with varying levels of statistical education, experience and interests* (click to enlarge).

The Steering Group has decided to start with seven topics of general interest. Two topic groups were added later. Guidance documents will be developed by separate topic groups (TGs), each comprising experts in different area of statistical methodology, alongside applied researchers who may represent future end-users of the STRATOS documents. Each TG will start by developing guidance aimed primarily at level 2 statistical knowledge, which is perhaps slightly below state of the art. STRATOS structure and the initial road map (click to enlarge). The STRATOS initiative is closely connected to the International Society of Clinical Biostatistics (ISCB) and was launched at a half-day Mini-Symposium on the last day of the ISCB meeting in Munich, in August 2013.

Panels

To co-ordinate the initiative, to share best research practices and to disseminate research tools and results from the work of the topic groups (TG), several cross-cutting panels have been started recently. They aim to develop recommendations (sometimes rather loose as for simulation studies, sometimes more strict as for STRATOS publications) and to provide the infrastructure for those aspects of the initiative that apply to all or most of the TGs, and to coordination of the efforts of the individual TGs. Recommendations aim to support, simplify and harmonize work within and across the TGs. They will also help increase transparency in deriving guidance documents in STRATOS.

The following Panels have been created to date:

MP	Membership	GP	Glossary	RP	Literature Review	BP	Bibliography
PP	Publications	SP	Simulation Studies	DP	Data Sets	TP	Knowledge Translation
WP	Website	CP	Contact Organizations				

News

GMDS 2017
Two session:
September 17 - 21, 2017
Oldenburg, Germany

DGEpi, DGMS, GDSMP
Invited talk:
September 5-8, 2017
Lübeck, Germany

CEN ISBS joint conference
Two sessions:
August 28 - September 1, 2017
Vienna, Austria

ISCB 2017
Two talks:
July 9 - 13, 2017
Vigo, Spain

More news...

Topic groups

1 Missing data
2 Selection of variables and functional forms in multivariable analysis
3 Initial data analysis
4 Measurement error and misclassification
5 Study design
6 Evaluating diagnostic tests and prediction models
7 Causal inference
8 Survival analysis
9 High-dimensional data

All groups

Introductory Paper for Series in the IBS Biometric Bulletin

STRATOS initiative – Guidance for designing and analysing observational studies

http://www.stratos-initiative.org

Thanks to all members of TG2 !

- Michal Abrahamowicz (Canada)
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- Harald Binder (Germany)
- Frank Harrell (U.S.A)
- Georg Heinze (Austria)
- Patrick Royston (U.K.)
- Matthias Schmid (Germany)