The many hats of a Health Technology Assessment statistician

Anders Gorst-Rasmussen
Statistical Director
Novo Nordisk A/S

Disclaimer

Views and opinions expressed are those of the speaker and not necessarily Novo Nordisk

Health Technology ... *what*?!


Drug development
REGULATORY ASSESSMENT
Marketing authorization
HEALTH TECHNOLOGY ASSESSMENT (HTA)
Availability to patients

Can I drive it?

TYPE APPROVAL

- Safety
- Emissions

Should I buy it?

PROSPECTIVE BUYER

- Household budget
- Features
- Needs
- Etc

Can we use it?

REGULATORY ASSESSMENT

- Benefit-risk
- Quality

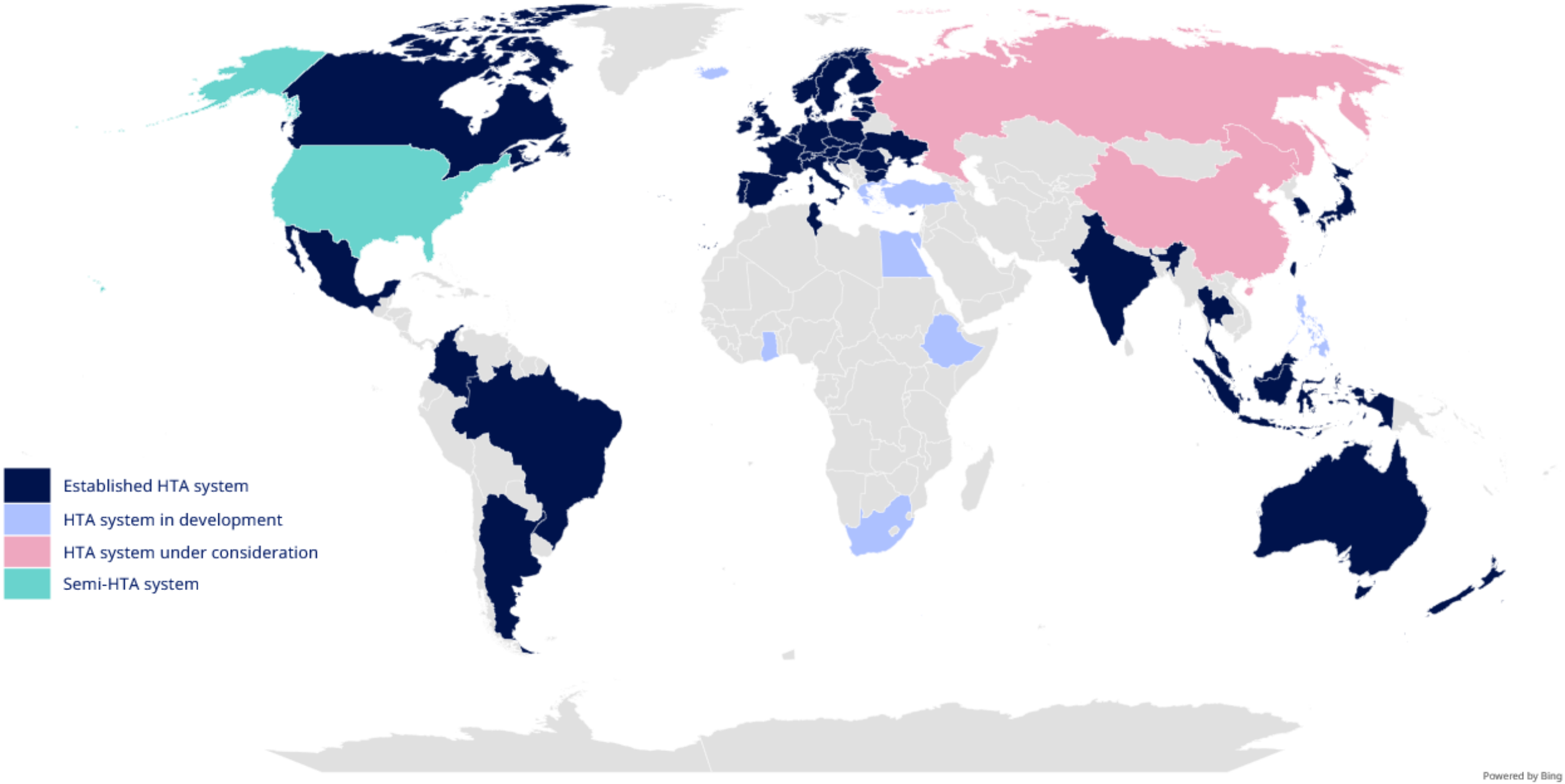
Should we use it?

HEALTH TECHNOLOGY ASSESSMENT

- Local comparators
- Local value perspective
- Health care budget
- Etc

Many different HTA agencies around the world

Novo Nordisk®



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SUMMARY OF PRODUCT CHARACTERISTICS

Therapeutic indications
Used in adults satisfying:

- Criteria 1
- Criteria 2

Clinical efficacy and safety

The 26-week double-blind randomized trial showed an effect of versus placebo of […]

HTA AGENCY

SCOPE

Effect **versus local standard of care** in adults satisfying:

- Criteria 1
- Criteria 2
- **Criteria 3**

NOVO NORDISK

BIOSTATISTICS HTA


Milana


Christian


Simon


Anders


Martin


Pepa

...a part of

Data Science

- at a glance

Unlocking and driving value for patients, society and Novo Nordisk through data science

Creating the right data foundation and applying world-class analytics to transform data into business opportunities

DATA I ANALYTICS I PEOPLE

50/50 %

male/female

Novo Nordisk is a global healthcare leader powered by data, analytics and digital technologies

~800 colleagues

Boston, MA
Søborg/Aalborg, DK
Madrid, Spain
Bangalore, IN

31 nationalities

COMMUNITY OF PROFESSIONALS

- Automation Engineers
- Biostatisticians
- Computational Biologists
- Data Engineers
- Epidemiologists
- Machine Learning Scientists
- Pharmacologists
- ... and many others!

CURRENT FOCUS

Faster and smarter product development by more *automation* and, *real time* data analytics

Increased insights and value of assets by modelling & simulation infirmed R&D + analytics across multiple data sources

Enable Precision Health through omics, imaging, digital biomarker data analyses

Ensure the right capabilities and culture and get access to best-in-class talents

Automation | Data infrastructure | AI / Machine learning | Outstanding workplace

Hat #1

‘the Bayesian hat’

“Your randomized trial shows how A works versus B. But in our health care system, we need to know how A works versus C.

Indirect treatment comparisons

JOURNAL OF SCIENTFIC ENDEAVOURS

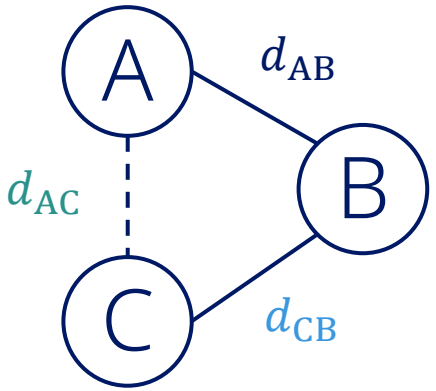
A randomized controlled trial to compare the effect of A vs B

The treatment effect on change from baseline was $\hat{d}_{AB}$ with 95% confidence interval …

PROCEEDINGS OF VERY IMPORTANT THINGS

How does C work versus B? A randomized controlled study

Treatment effect was $\hat{d}_{CB}$ with 95% confidence interval …

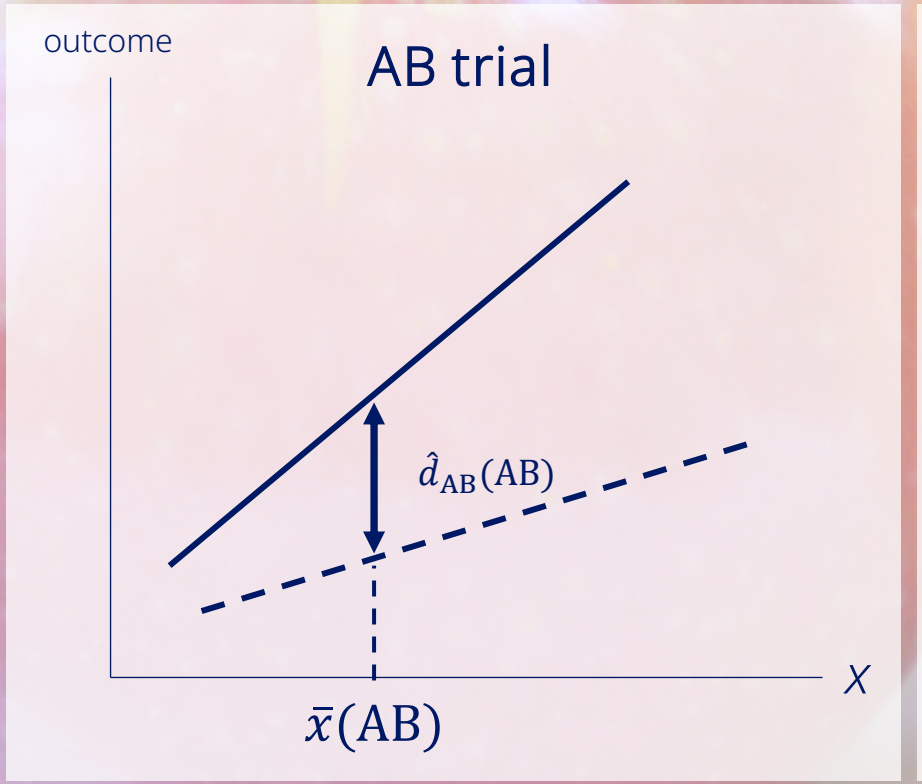


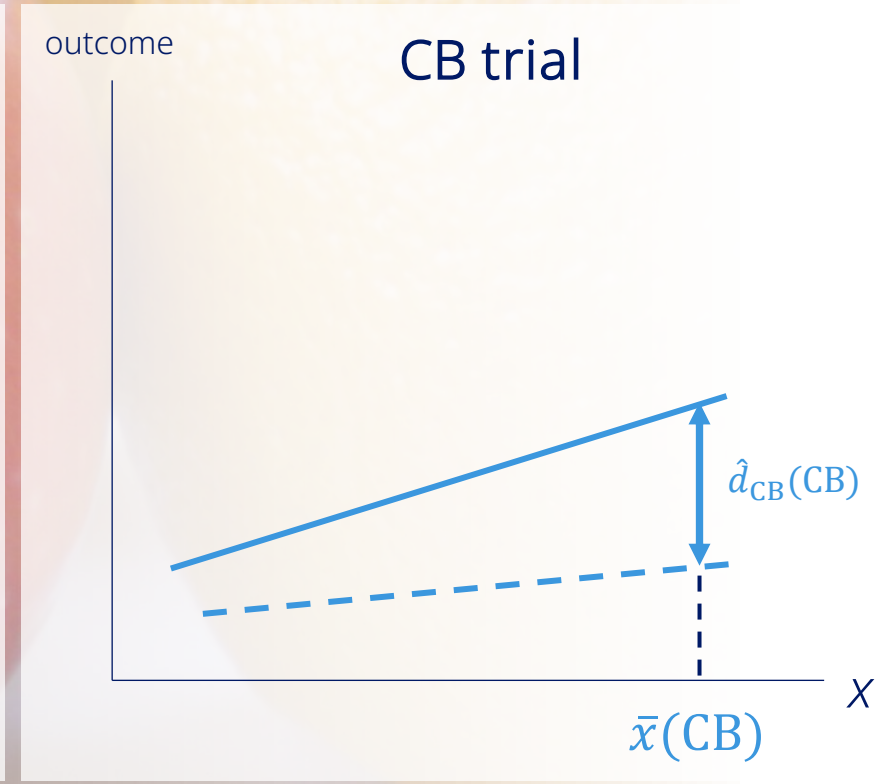
$$d_{AC} = d_{AB} - d_{CB}$$

$$\hat{d}_{AC} = \hat{d}_{AB} - \hat{d}_{CB}$$

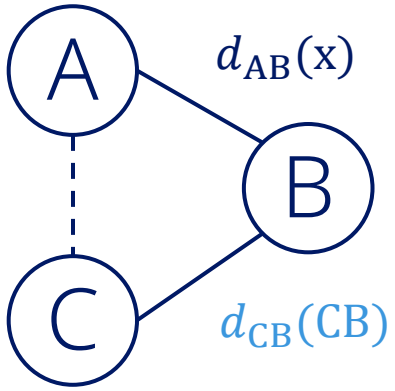
$$\widehat{SE}(\hat{d}_{AC})^2 = \widehat{SE}(\hat{d}_{AB})^2 + \widehat{SE}(\hat{d}_{CB})^2$$

Doesn’t work if there are differences in the distribution of effect modifiers between trials





Leveraging individual participant data



Treatment	Body weight	x	Outcome
A	109	43	3.1
A	73	28	2.4
B	88	72	1.9
A	102	51	2.3
.	.	.	.
.	.	.	.
.	.	.	.

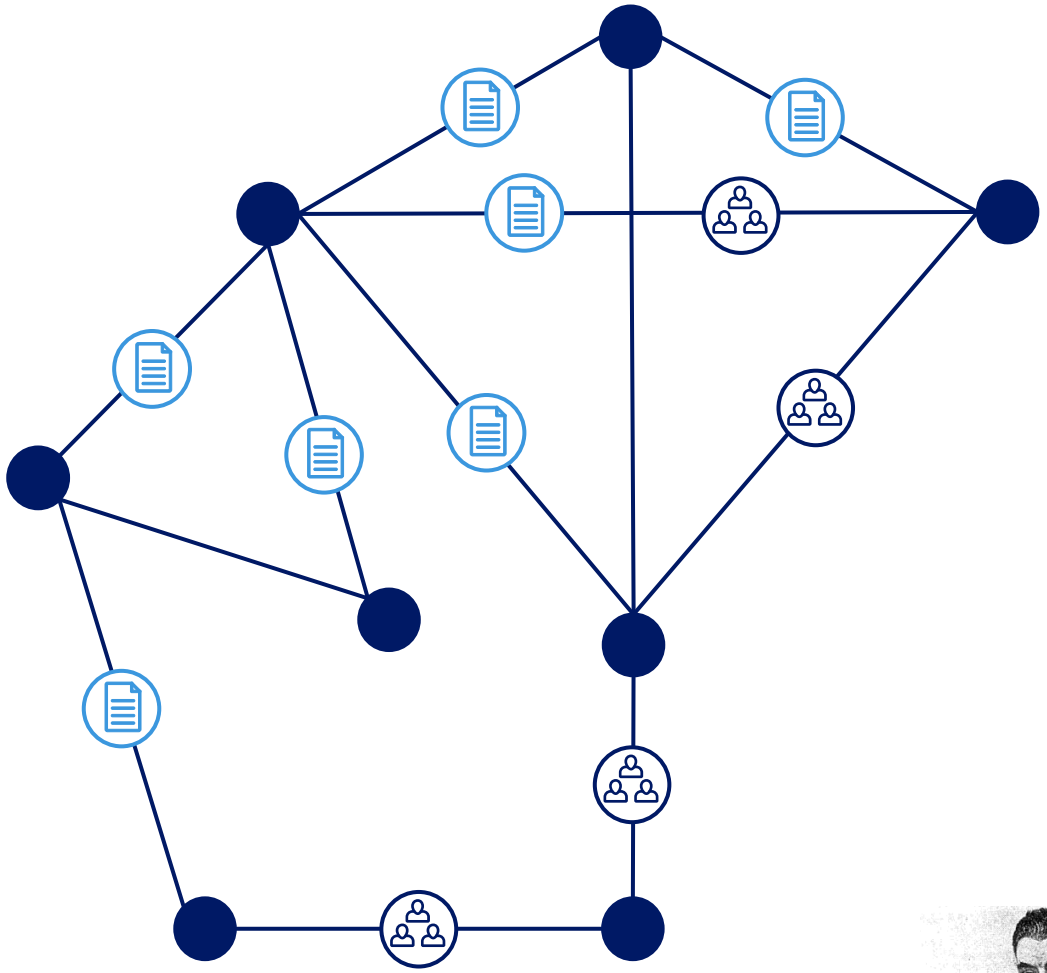
PROCEEDINGS OF VERY IMPORTANT THINGS

How does C work versus B? A randomized controlled study

Treatment effect of C vs B on mean change from baseline was $\hat{d}_{CB}$ with associated 95% confidence interval …

$$d_{AC}(CB) = d_{AB}[\bar{x}(CB)] - d_{CB}(CB)$$

MULTI-LEVEL NETWORK META REGRESSION (ML-NMR)



Philippo et al. (2020) Multilevel network meta-regression for population-adjusted treatment comparisons. *J R Stat Soc Ser A Stat Soc*. 183(3): 1189–1210. doi: 10.1111/rssa.12579
https://dmphillippo.github.io/multinma/

GLM version of ML-NMR

Participants *i*, comparisons *j*, trials *k*

INDIVIDUAL PARTICIPANT DATA (IPD)

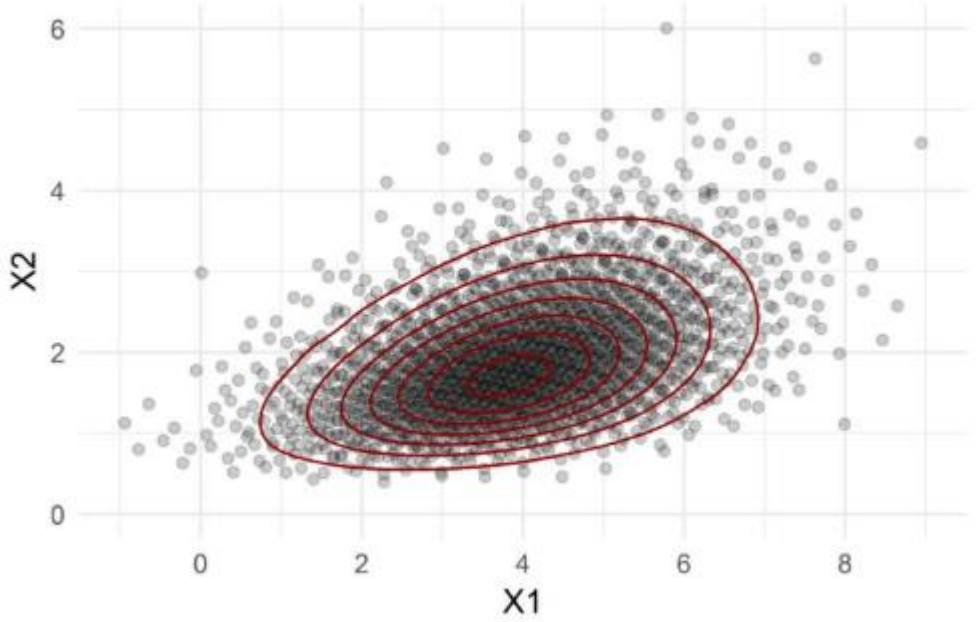
$$y_{ijk} \sim \pi_{\text{IPD}}(\theta_{ijk})$$

$$\theta_{ijk} \sim g^{-1}(\beta' x_{ijk})$$

AGGREGATE DATA (AgD)

$$y_{\bullet jk} \sim \pi_{\text{AgD}}(\theta_{\bullet jk})$$

$$\theta_{\bullet jk} \sim \text{E}_{\text{AgD x dist.}}[g^{-1}(\beta' x)]$$



- Model joint *x* distribution w/copulas (using structural information from IPD *x*)
- Quasi-Monte Carlo integration

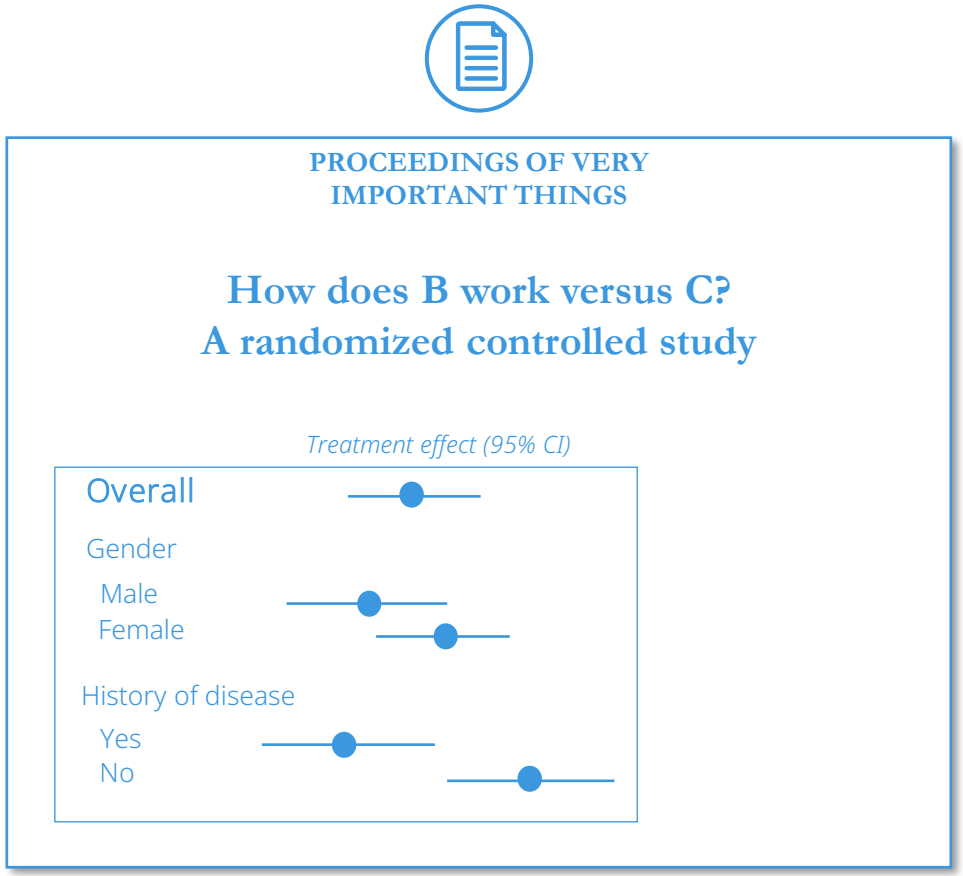
Integration point graphics from by D.M. Philippo (https://dmphillippo.github.io/ESMARConf2021_multinma/#6)

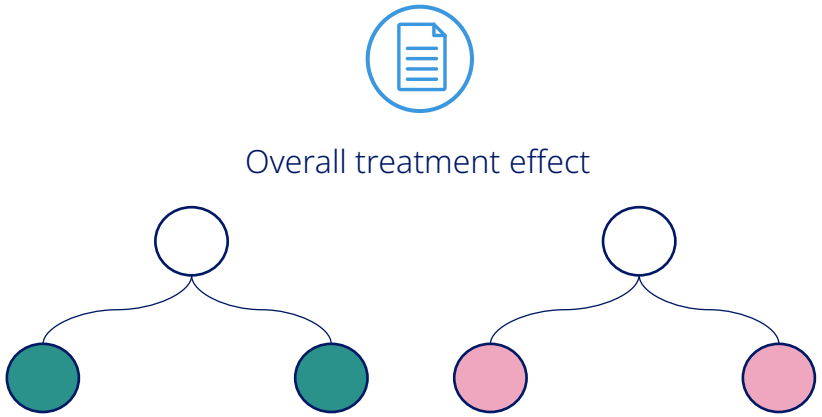
An interesting problem
(that I don’t know the solution of)

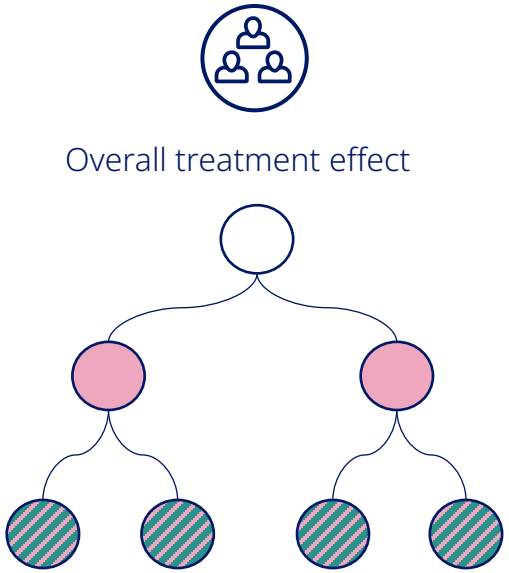
A fairly common situation

(knowing *"something"* about AgD potential effect modifiers)

Treatment	Gender	History of disease	Outcome
A	Male	Yes	3.1
A	Female	No	2.4
B	Female	No	1.9
A	Male	Yes	2.3
.	.	.	.
.	.	.	.
.	.	.	.



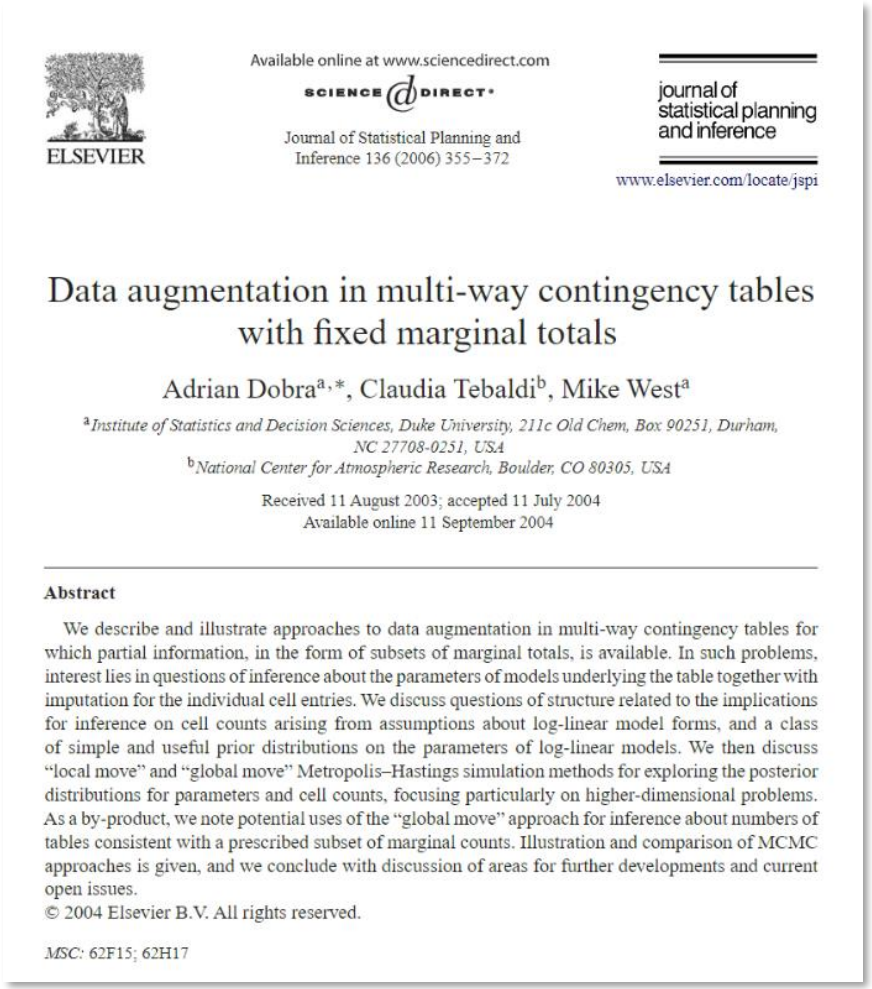




How to account for 1st order AgD subgroup evidence

(when the underlying model includes effect modification by subgroups)?

Log-linear model version of the problem
(relevant for count/survival data ML-NMR)



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Journal of Statistical Planning and Inference 136 (2006) 355–372

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Data augmentation in multi-way contingency tables with fixed marginal totals

Adrian Dobra[a,*], Claudia Tebaldi[b], Mike West[a]

[a] Institute of Statistics and Decision Sciences, Duke University, 211c Old Chem, Box 90251, Durham, NC 27708-0251, USA
[b] National Center for Atmospheric Research, Boulder, CO 80305, USA

Received 11 August 2003; accepted 11 July 2004
Available online 11 September 2004

Abstract

We describe and illustrate approaches to data augmentation in multi-way contingency tables for which partial information, in the form of subsets of marginal totals, is available. In such problems, interest lies in questions of inference about the parameters of models underlying the table together with imputation for the individual cell entries. We discuss questions of structure related to the implications for inference on cell counts arising from assumptions about log-linear model forms, and a class of simple and useful prior distributions on the parameters of log-linear models. We then discuss "local move" and "global move" Metropolis–Hastings simulation methods for exploring the posterior distributions for parameters and cell counts, focusing particularly on higher-dimensional problems. As a by-product, we note potential uses of the "global move" approach for inference about numbers of tables consistent with a prescribed subset of marginal counts. Illustration and comparison of MCMC approaches is given, and we conclude with discussion of areas for further developments and current open issues.

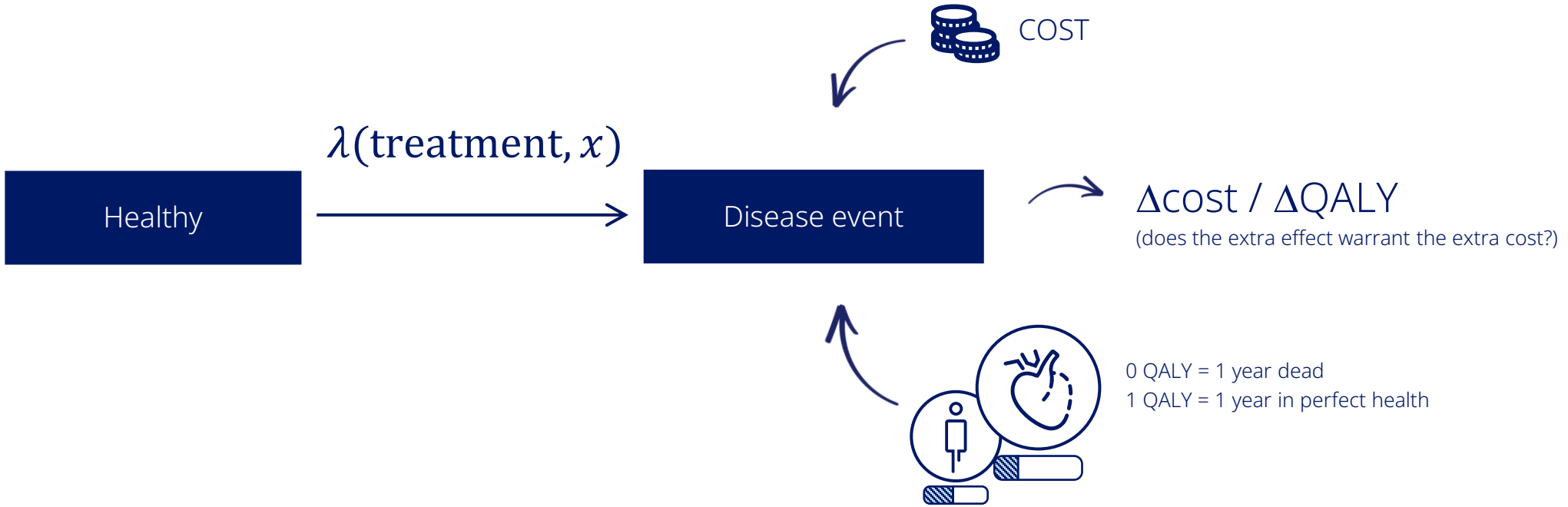
MSC: 62F15; 62H17

> "Bayesian inference in this context is in principle straightforward: we aim to compute posterior distributions for the unobserved cell counts and parameters underlying models for cell probabilities, jointly.

Hat #2

‘the economist hat’

State-based health economic models

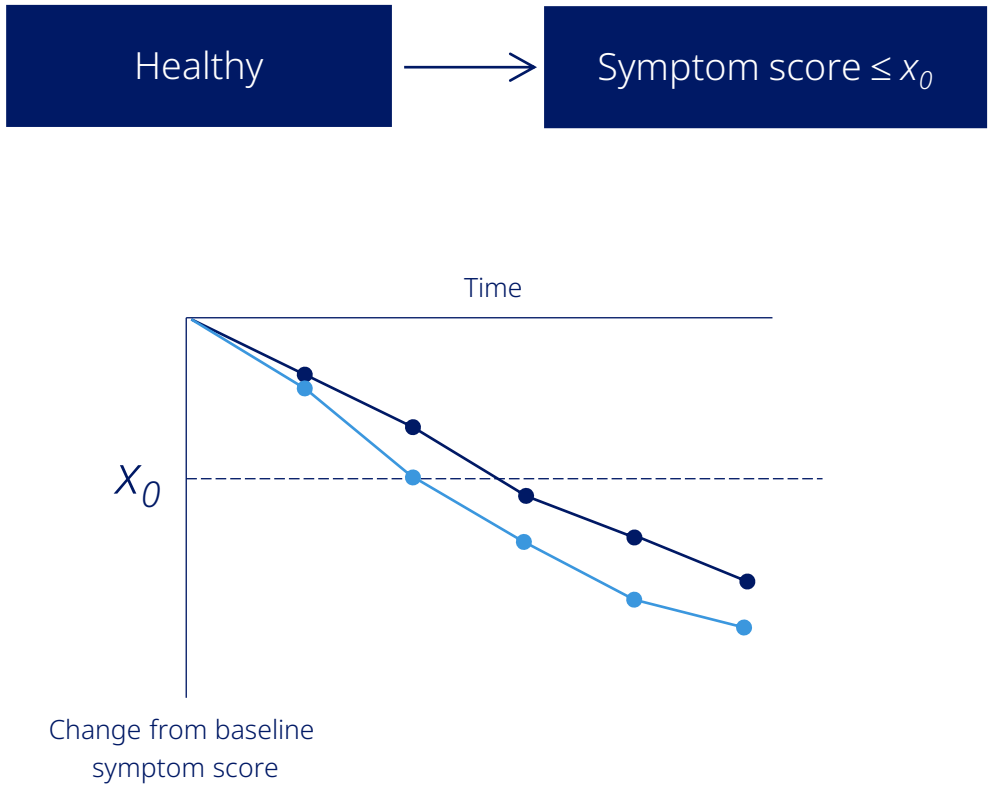


HEALTH ECONOMIC MODELLING IS *HARD*

because you lack relevant information about λ because you

- …don't observe disease events in your trial (only proxies) and/or
- …don't observe disease events in the right time horizon and/or
- …don't observe disease events in the right population

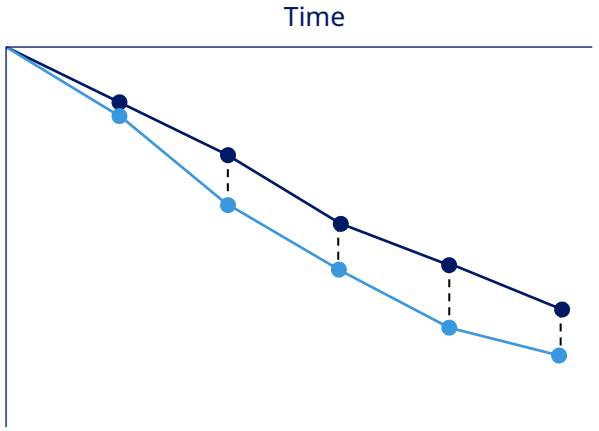
State-based models and progressive disease



This may not be a very efficient way of modelling for slowly progressing diseases

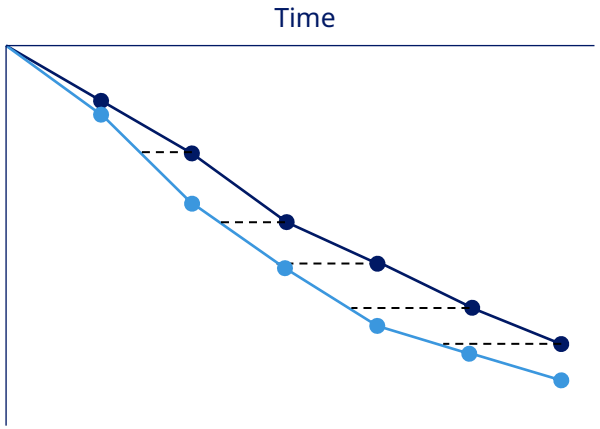
It may also not be the most relevant to patients (who decides, x_0 anyway??)

Conventional modelling



Reductions in outcome

Progression modelling



Delay in progression

Received: 9 September 2021 | Revised: 21 August 2022 | Accepted: 5 September 2022
DOI: 10.1002/sim.9581

RESEARCH ARTICLE

Statistics in Medicine WILEY

Progression models for repeated measures: Estimating novel treatment effects in progressive diseases

Lars Lau Raket[1,2]

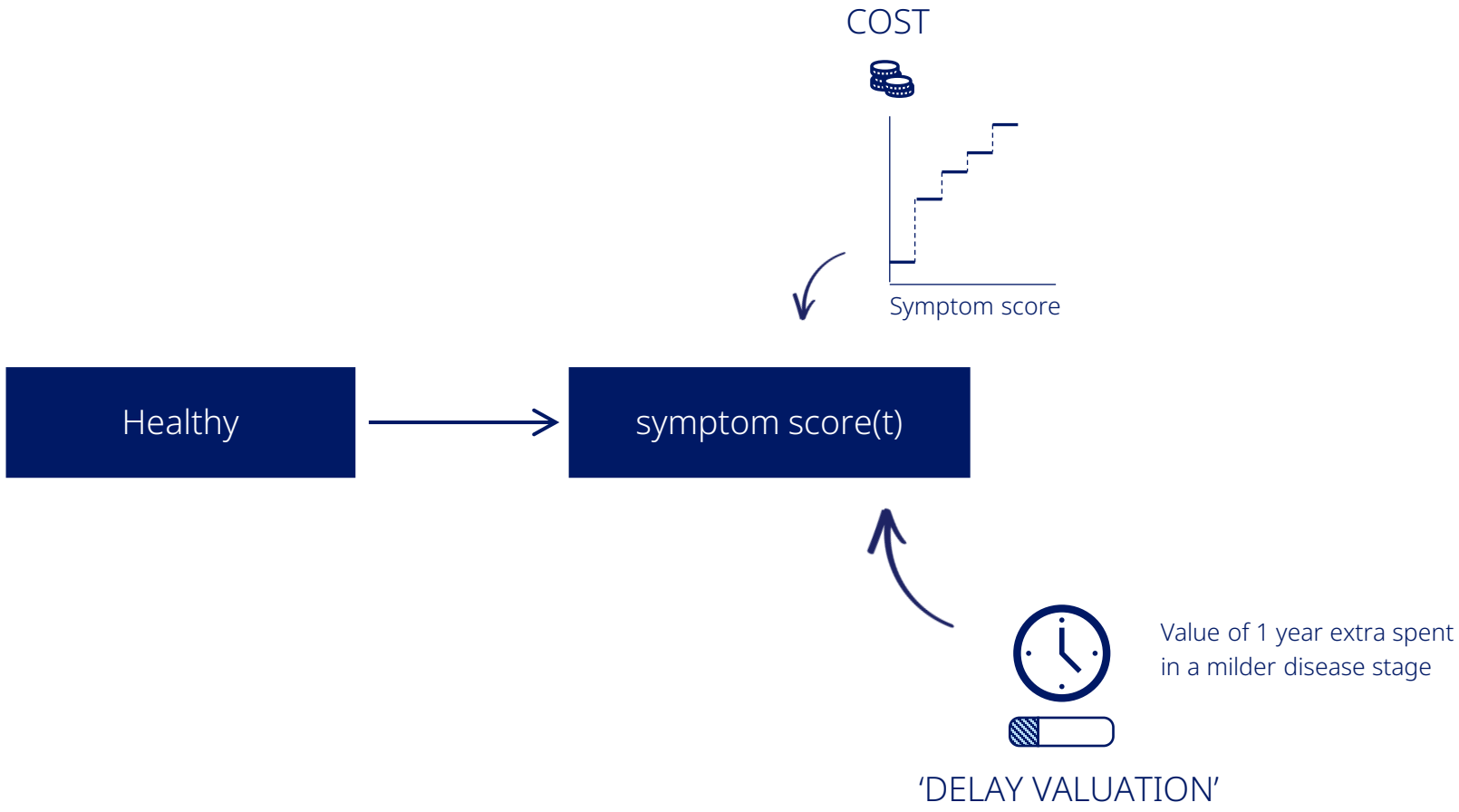
[1]Novo Nordisk A/S, Søborg, Denmark
[2]Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Lund, Sweden

Correspondence
Lars Lau Raket, Novo Nordisk A/S, Vandtårnsvej 108, 2860 Søborg, Denmark.
Email: llrk@novonordisk.com

Mixed models for repeated measures (MMRMs) are ubiquitous when analyzing outcomes of clinical trials. However, the linearity of the fixed-effect structure in these models largely restrict their use to estimating treatment effects that are defined as linear combinations of effects on the outcome scale. In some situations, alternative quantifications of treatment effects may be more appropriate. In progressive diseases, for example, one may want to estimate if a drug has cumulative effects resulting in increasing efficacy over time or whether it slows the time progression of disease. This article introduces a class of nonlinear mixed-effects models called progression models for repeated measures (PMRMs) that, based on a continuous-time extension of the categorical-time parametrization of MMRMs, enables estimation of novel types of treatment effects, including measures of slowing or delay of the time progression of disease. Compared to conventional estimates of treatment effects where the unit matches that of the outcome scale (eg, 2 points benefit on a cognitive scale), the time-based treatment effects can offer better interpretability and clinical meaningfulness (eg, 6 months delay in progression of cognitive decline). The PMRM class includes conventionally used MMRMs and related models for longitudinal data analysis, as well as variants of previously proposed disease progression models as special cases. The potential of the PMRM framework is illustrated using both simulated and historical data from clinical trials in Alzheimer's disease with different types of artificially simulated treatment effects. Compared to conventional models it is shown that PMRMs can offer substantially increased power to detect disease-modifying treatment effects where the benefit is increasing with treatment duration.

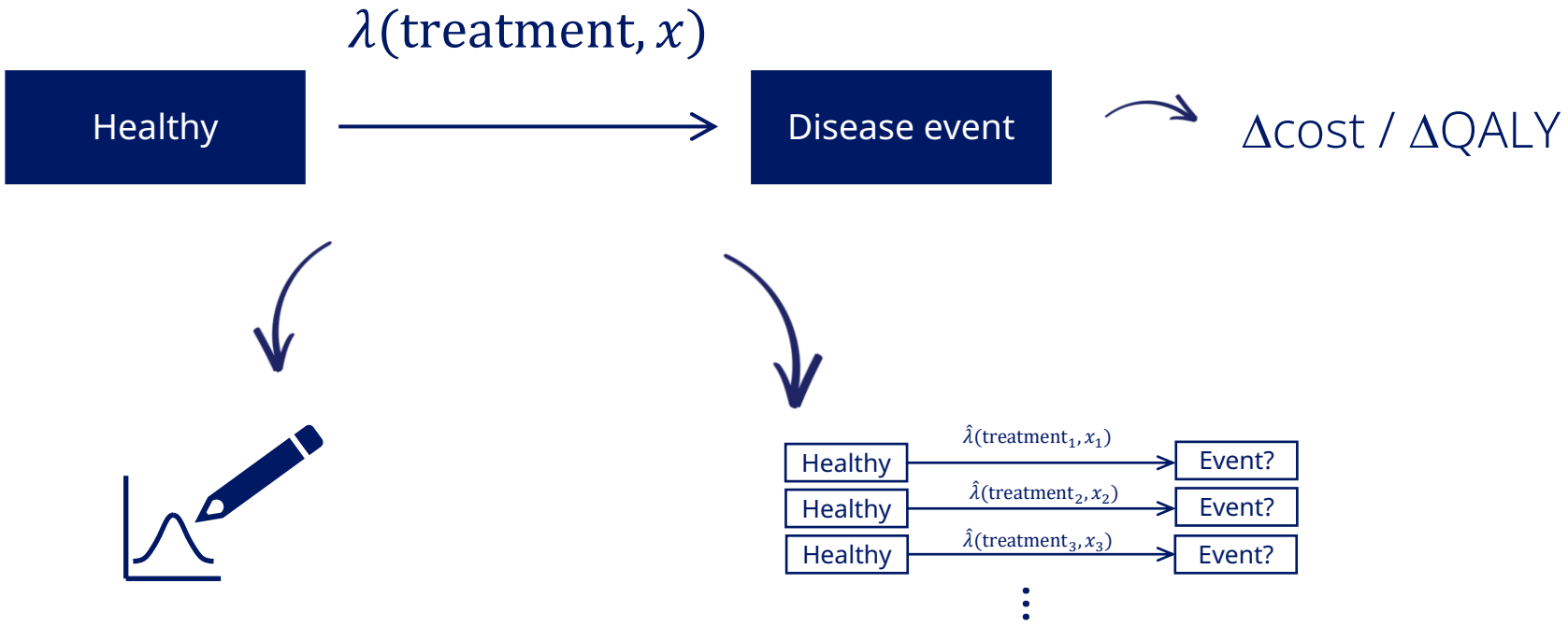
KEYWORDS
Alzheimer's disease, disease progression model, disease-modifying treatment effects, mixed model for repeated measures, mixed-effects model

Integrating progression model effect measures into health economic models



Hat #3

‘the data scientist hat’

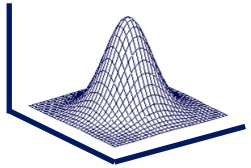


Derivation

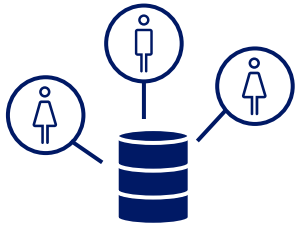
Discrete event simulation
(micro-simulation)

Feeding the micro-simulation

Multivariate normal simulations



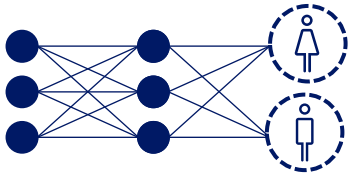
Real trial patient-level data



Least complex input

Most complex input

Independent normal simulations

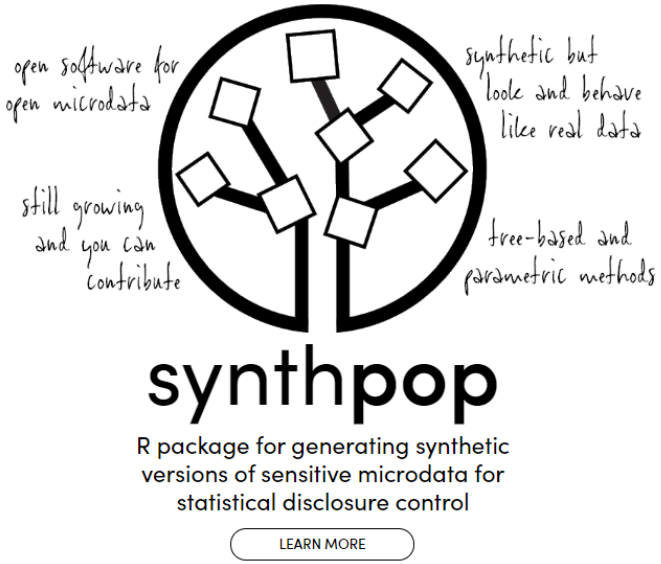


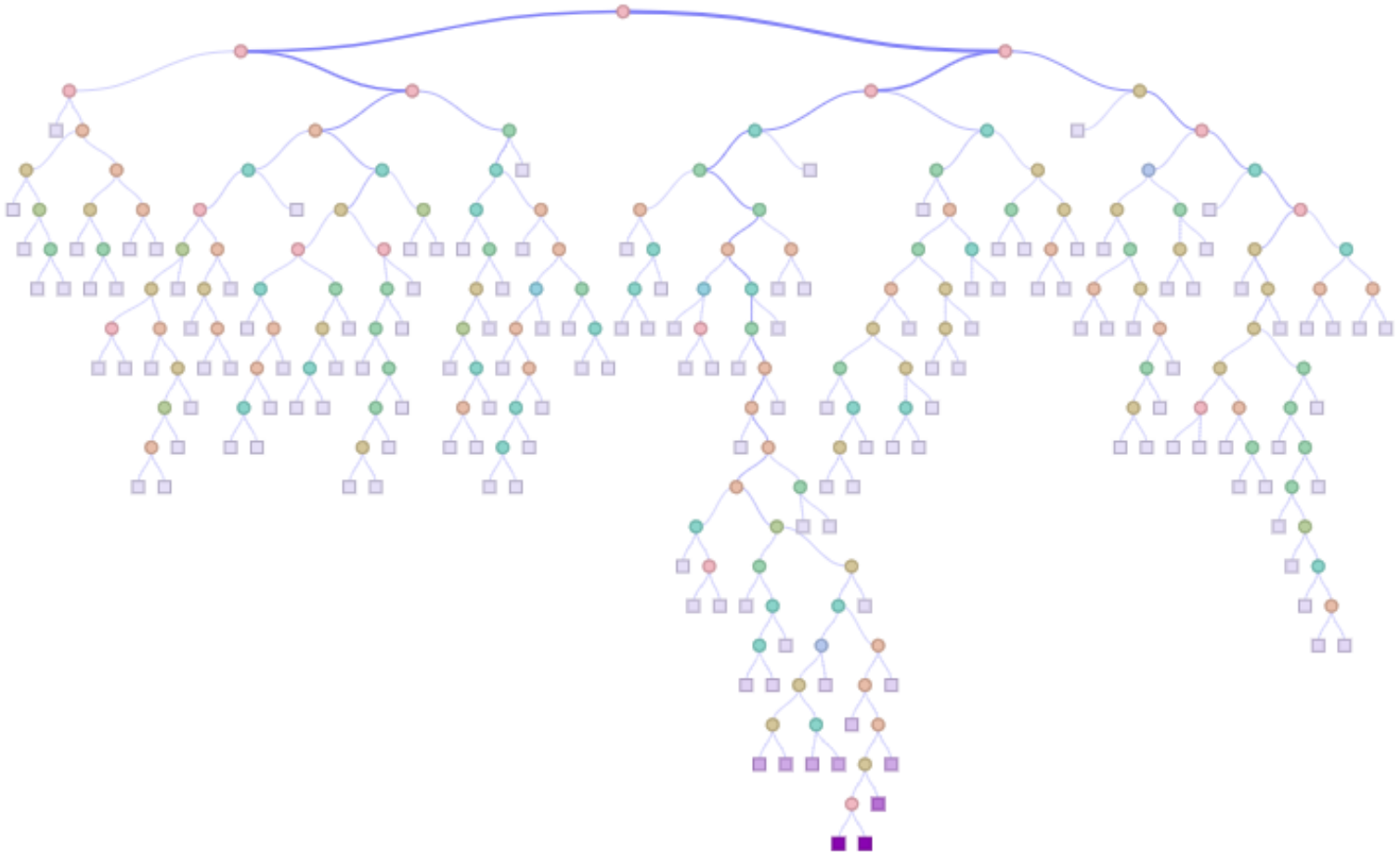
Machine-learning patient-level data

Real-world data

CART

(Classification And Regression Trees)

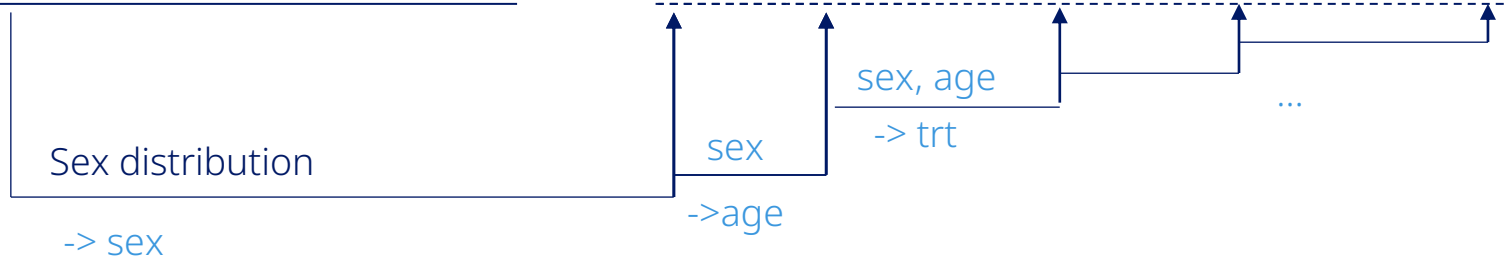




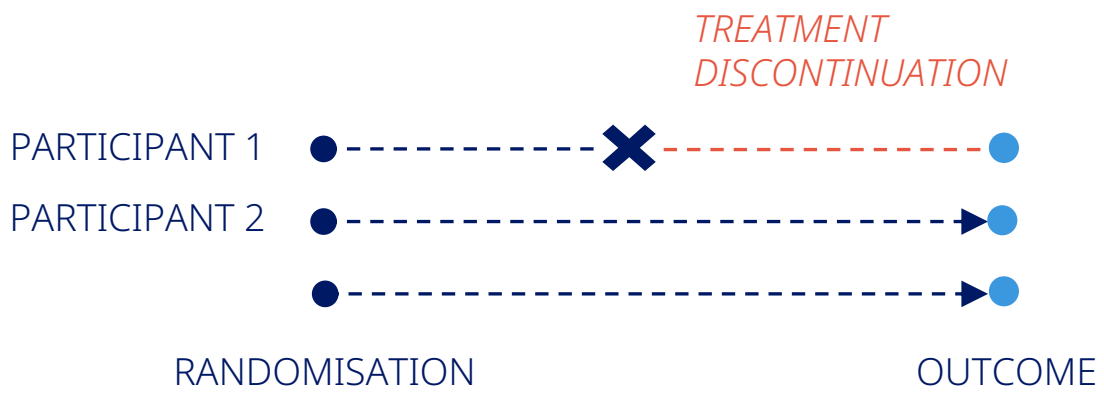
https://www.synthpop.org.uk/index.html

Sex	Age	Treatment	Body weight	Outcome
F	51	Active	92.2	89.1
F	43	Placebo	101.2	100.3
M	41	Placebo	99.7	98.3
F	64	Active	110.2	100.8
M	37	Placebo	96.4	95.3
F	54	Active	132.1	119.7
F	52	Active	105.3	104.1

Sex	Age	Treatment	Body weight	Outcome
M	49	Placebo	94.1	92.2
F	45	Active	99.2	95.1
M	40	Active	112.3	98.7
F	62	Active	88.3	85.6
F	37	Placebo	95.0	96.1
M	51	Active	127.4	105.2
F	55	Active	102.2	96.6



Collection of trial data *after* treatment discontinuation is important to address 'intention to treat' effect

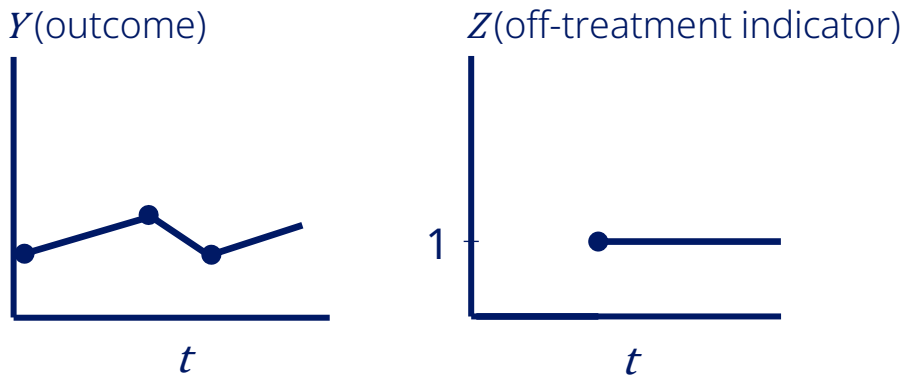


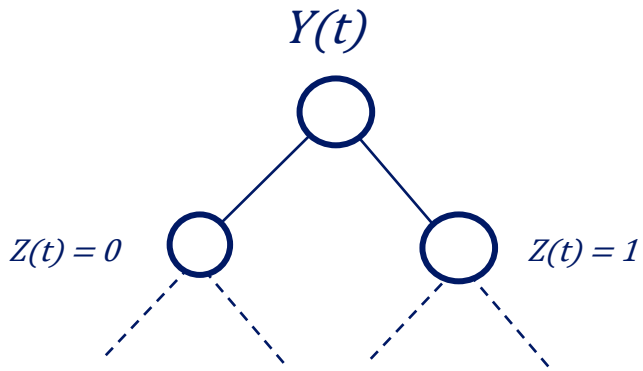
How can we synthesize realistic trajectories?

(i.e. that may include treatment discontinuation)

Synthesizing realistic trajectories

A quick-and-dirty CART solution (that's easy to set up in `rpart`)





- Synthesize $Z(t) \in \{0,1\}$
- Post-process $Z(t)$ to ensure non-decreasing step function
- When synthesizing $Y(t)$ with CART, force first tree split according to $Z(t)$
- Time treatment discontinuation $\rightarrow$ time of jump of $Z(t)$

There is a need for more skilled HTA statisticians!

Drug development → Marketing authorization → Availability to patients

REGULATORY ASSESSMENT

x 1

HEALTH TECHNOLOGY ASSESSMENT (HTA)

x 27

Joint Clinical Assessment

2025