Translational Statistics

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with thanks to

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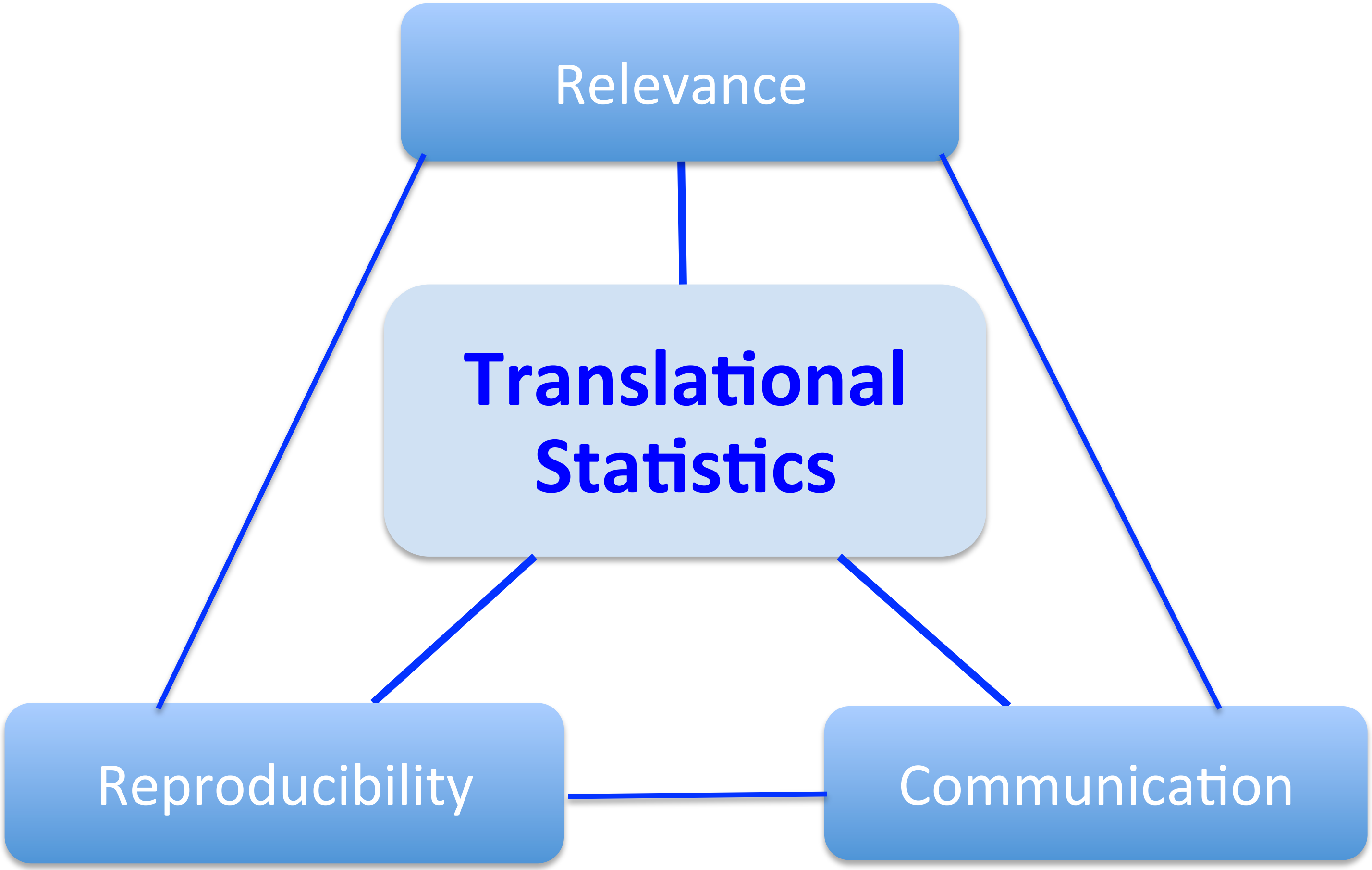
Outline


Relevance
Translational Statistics
Reproducibility
Communication

Translation

- **Translational Medicine**
  - promotes the convergence of basic and clinical research disciplines and the transfer of knowledge on the benefits and risks of therapies

bench to bedside

- **Translational Statistics**
  - facilitates the integration of Biostatistics within clinical research and **enhances communication** of research findings in an **accurate** and **accessible** manner to diverse audiences (e.g. policy makers, patients and the media)

desk to decision

Probability & Risk

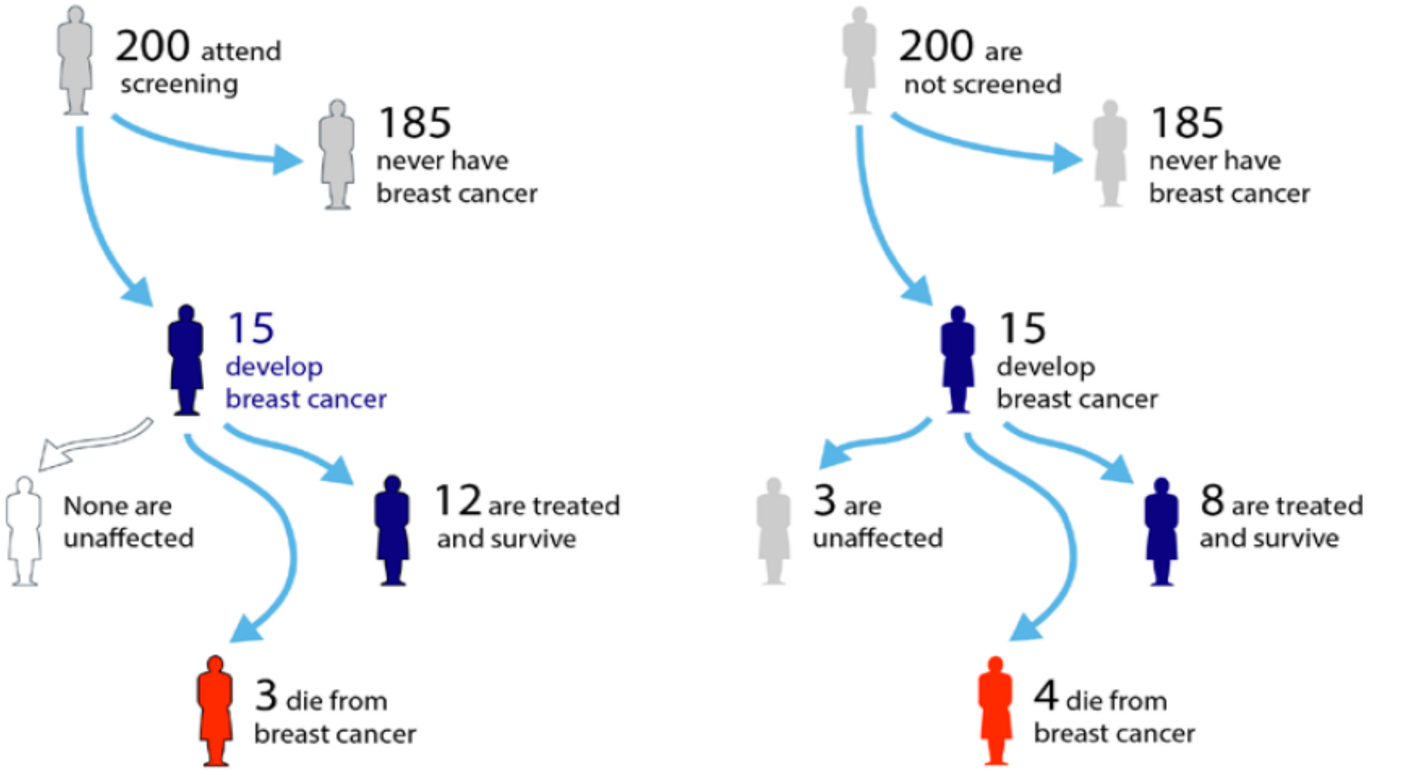
- Probability is tricky
  - Natural frequencies
  - *x out of N*

- Effect of Screening
  - Basic example in Bayes rule
  - Express as frequency tree using whole numbers
  - *women attending or not attending breast screening every 3 years between the ages of 50 and 70*

Breast Cancer Screening (UK)

200 women between 50 and 70 who attend screening

200 women between 50 and 70 who are not screened



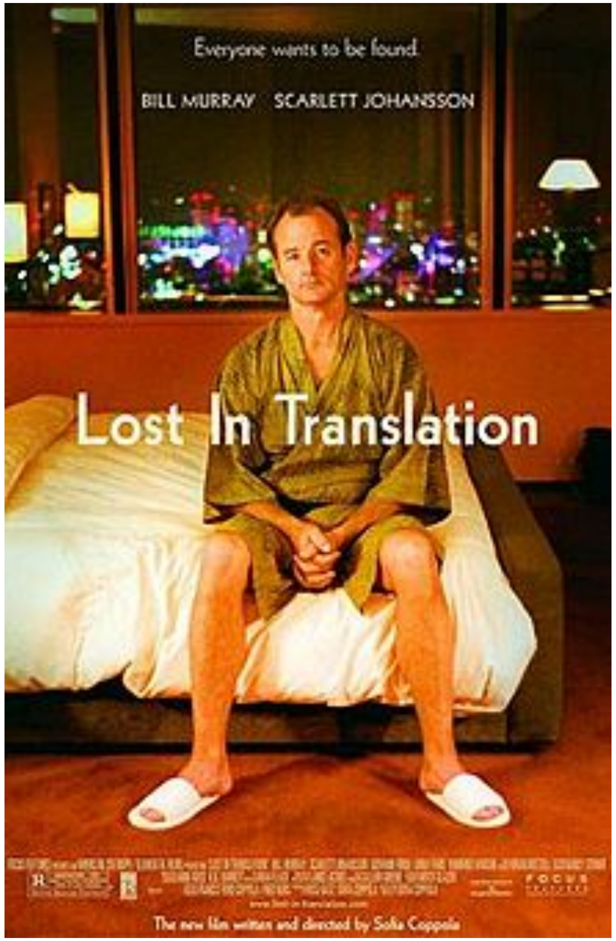
3 more treatments, 1 fewer death

3 fewer treatments, 1 extra death

Translating Odds is tricky

- Modelling a binary outcome – a common summary is an **odds ratio**

- It has been argued that a summary quoting the underlying probabilities is more informative than one based on ratios of odds or indeed of probabilities (relative risk)



Chance would be a fine thing

- Modelling the log(odds) is a mathematically attractive option

- Expressing the results as log(odds), odds or a ratio of odds isn't

- Symmetry in log(odds) useful $\hat{\beta}_j \rightarrow -\hat{\beta}_j,\ \hat{O}R_j \rightarrow \frac{1}{\hat{O}R_j}$

- Lack of symmetry of OR about 1 isn't

$\hat{O}R = 2.5$

$\hat{\beta} = 0.92$

$\hat{O}R = 0.4$

How can 2% become 20%?

Mail Online

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Statins can weaken muscles and joints: Cholesterol drug raises risk of problems by up to 20 per cent

- Statins are the most widely prescribed drugs in Britain
- However, many complain of muscle pain and joint weakness

By JENNY HOPE

PUBLISHED: 22:42, 3 June 2013 | UPDATED: 00:00, 4 June 2013

How can 2% become 20%?

- Table 4 of the paper reports:
  - risks with and without statins of **87%** vs **85%**
  - translate to odds of **0.87/0.13 = 6.7** and **0.85/0.15 = 5.7**
- The odds ratio is therefore **6.7/5.7 = 1.18 (*1.20*)**
- Alternatively
  - the risk ratio was **0.87/0.85 = 1.02**, a 2% relative change
  - the difference in absolute risks was **0.87 – 0.85 = 2%**

How can 2% become 20%?

- The authors reported an **‘odds ratio’** of **1.19** for muscular-skeletal problems, which the Daily Mail interpreted as a **20%** increased risk

10 best practice guidelines for reporting science & health stories

On health risks, include the absolute risk whenever it is available in the press release or the research paper - i.e. if ’cupcakes double cancer risk’ state the outright risk of that cancer, with and without cupcakes.

abpi

Bringing medicines to *life*

CODE OF PRACTICE

for the

PHARMACEUTICAL

INDUSTRY

2012

- ***reference to absolute risk and relative risk.*** *Referring only to relative risk, especially with regard to risk reduction, can make a medicine appear more effective than it actually is. In order to assess the clinical impact of an outcome, the reader also needs to know the absolute risk involved. In that regard relative risk should never be referred to without also referring to the absolute risk. Absolute risk can be referred to in isolation*

Ovarian Cancer & HRT *(Feb 2015)*

The Telegraph

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HRT nearly doubles the risk of ovarian cancer, experts warn

Large study finds that risk remains ten years after stopping treatment

Ovarian Cancer & HRT

- ***Telegraph:*** Women who undergo hormone replacement therapy, even for a short time, nearly double their risk of developing ovarian cancer

- ***The study:*** conducted by a team at Oxford University and involving 100 researchers worldwide, found that women who take HRT to combat symptoms of the menopause are 40 per cent more likely to get one of the two most common types of ovarian cancer.

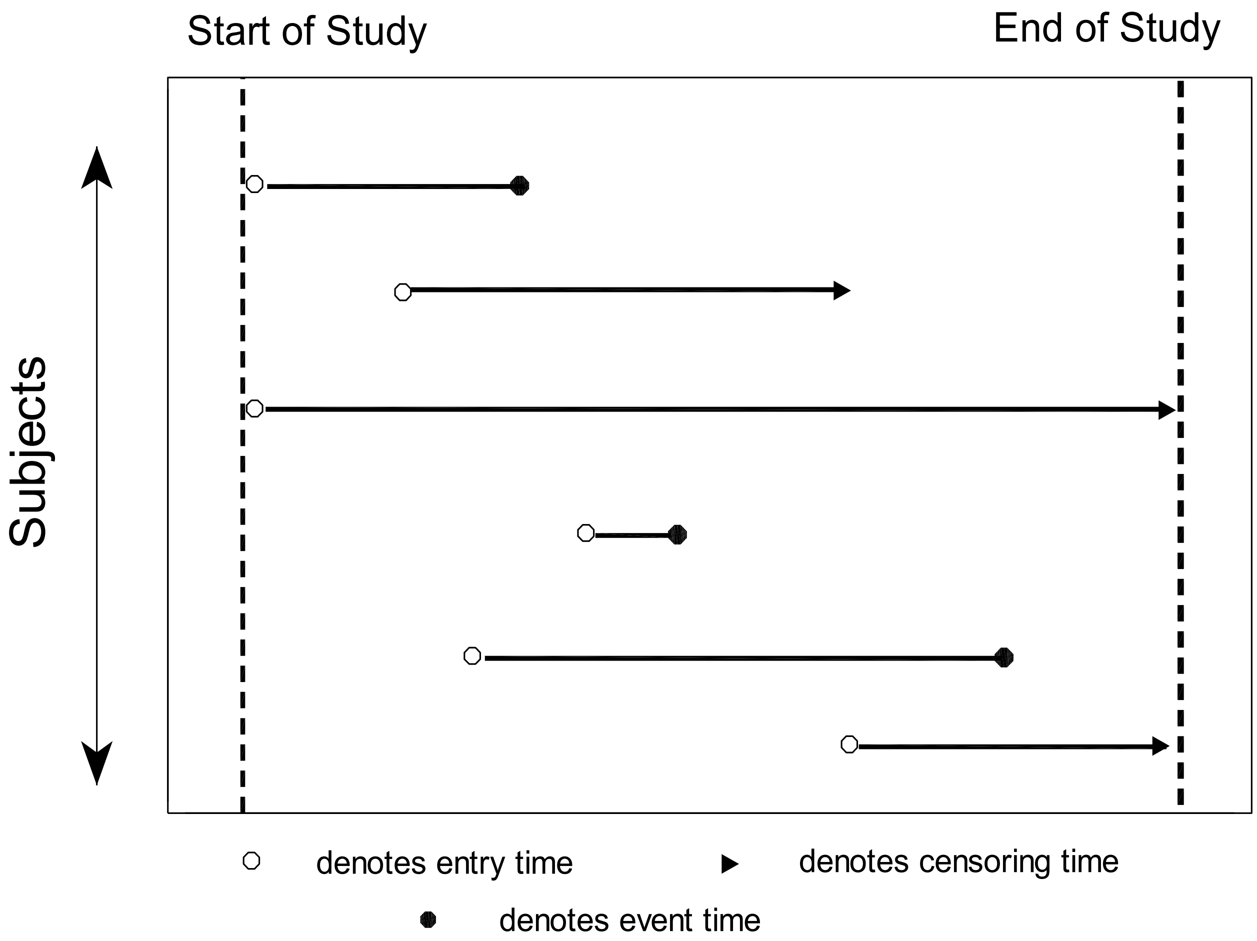
- ***Prof Sir Richard Peto (co-author):*** "For women who take HRT for five years from around age 50, there will be about one extra ovarian cancer for every 1,000 users and one extra ovarian cancer death for every 1,700 users."

Time to Event Data

- Time to event data arise when there is interest in the length of **time** until a particular event occurs.

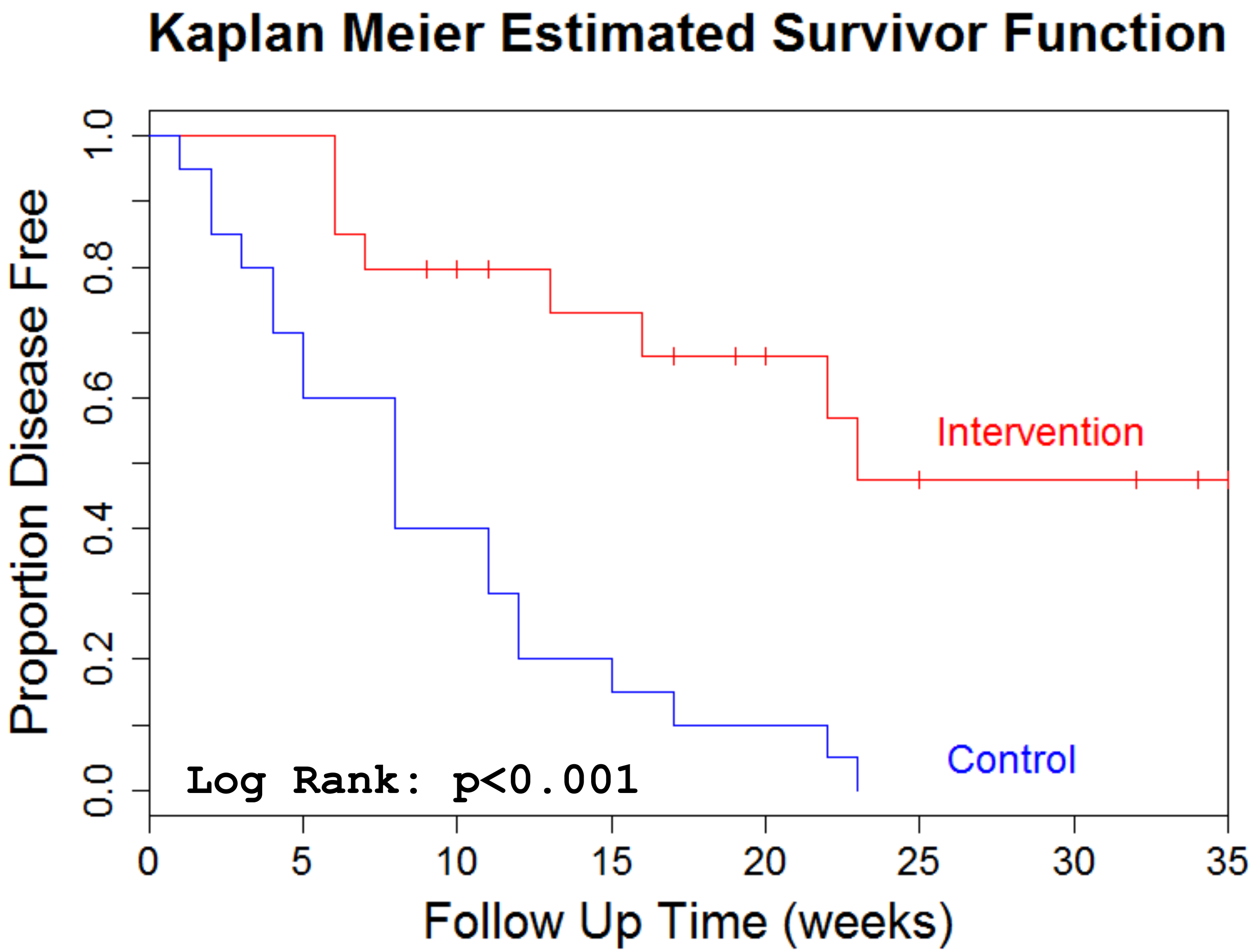
- An important characteristic of survival data is the presence of **censoring**.

Typical Time Profile of a Survival time study



The length of a line denotes 'observation time'

6MP LeukaemiaTrial (1963)



Freireich E J, Gehan E A,Frei E II, et al. 1963

Mean Residual Life

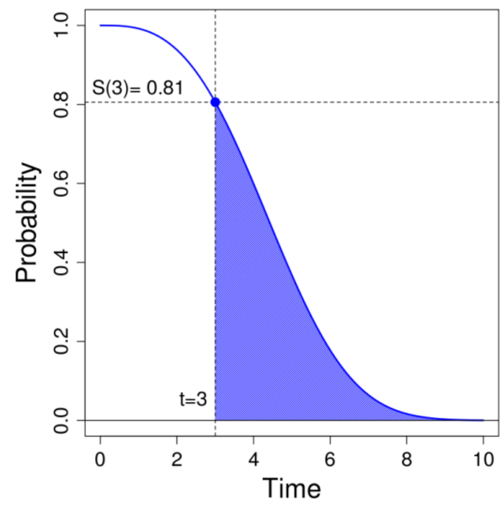
- Alternative summary

Mean residual life – *how long do I have left?*

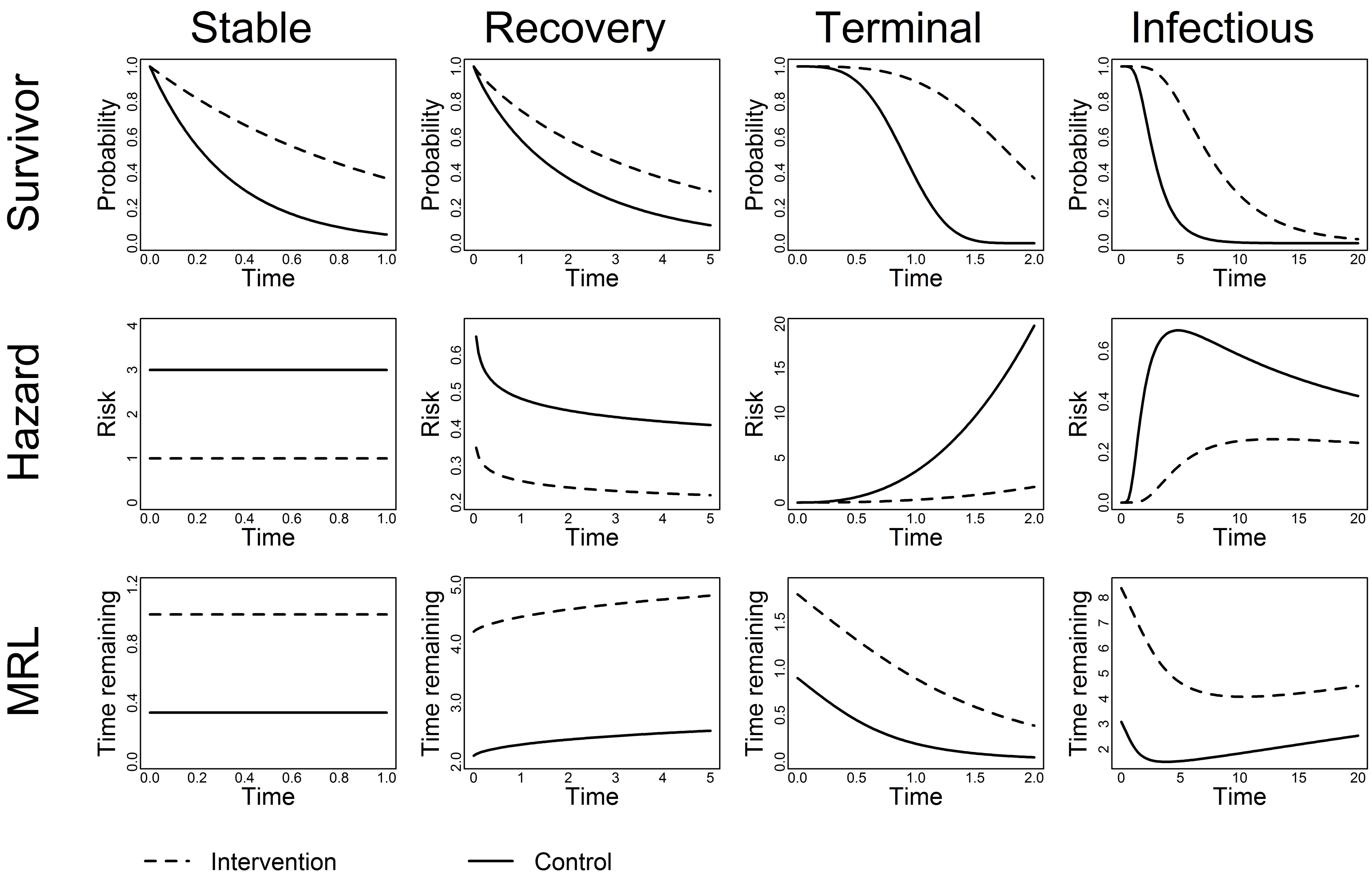
$$m(t) = E(T - t \mid T > t) = \frac{1}{S(t)} \int_t^\infty S(s)ds$$

MRL Often used in Engineering problems

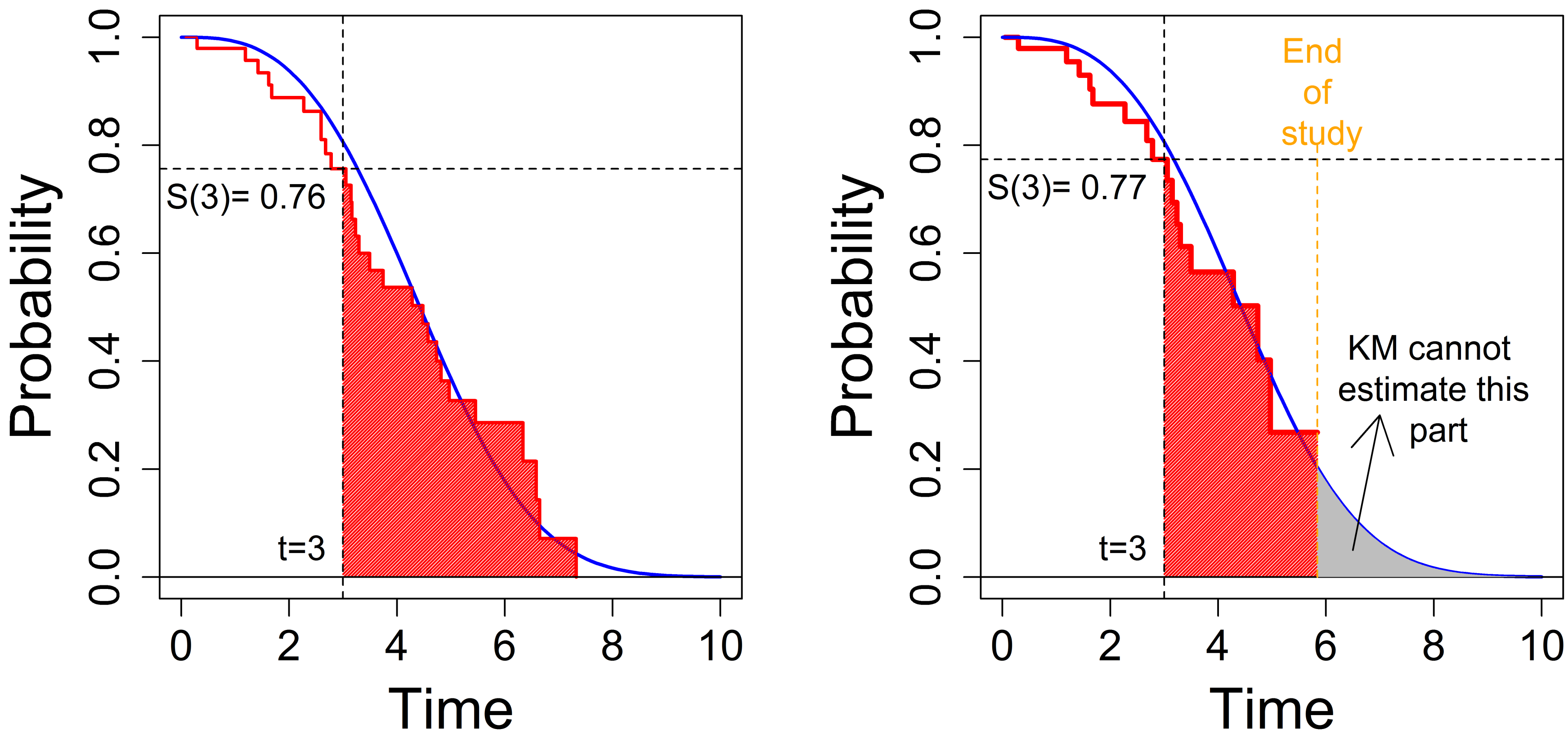
Right censoring a problem in clinical trials



Survival Patterns



MRL: Calculation



Problems with Censoring

Estimation under right-censoring, particularly studies with fixed endpoint?

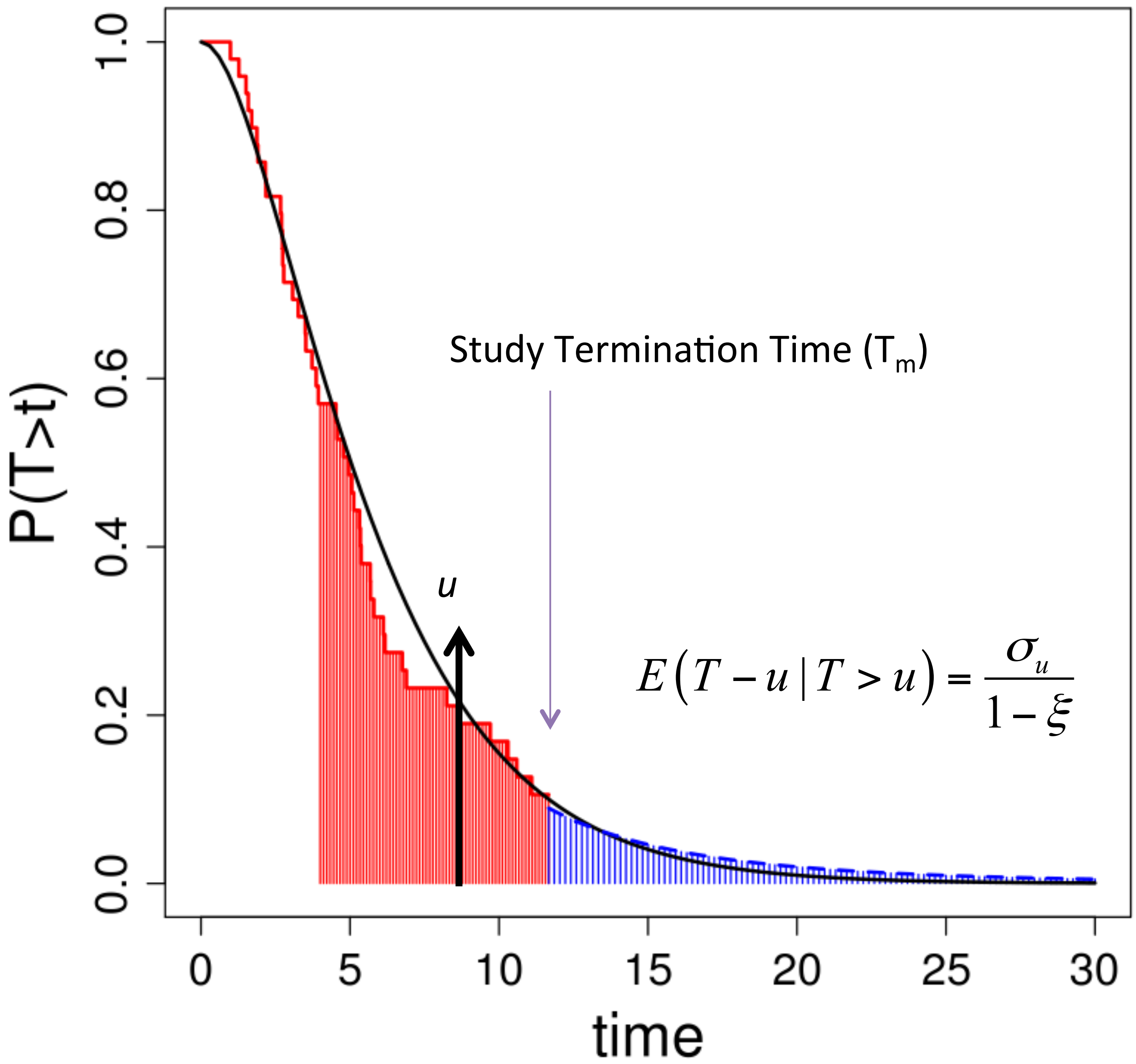
- Non-parametric approach based on kernel density estimators
- Extrapolation
- Combined Kaplan-Meier & parametric model (exponential,...)

Extreme Value Approach

Hybrid estimator combines

- Kaplan-Meier
- Parametric model for tail using Generalised Pareto Distribution – based on extreme value theory

Flexible model for the tail



P(T>t)
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
time
Study Termination Time (T_m)
u
$E(T-u \mid T>u)=\frac{\sigma_u}{1-\xi}$

Research Article

Statistics in Medicine

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(wileyonlinelibrary.com) DOI: 10.1002/sim.6431

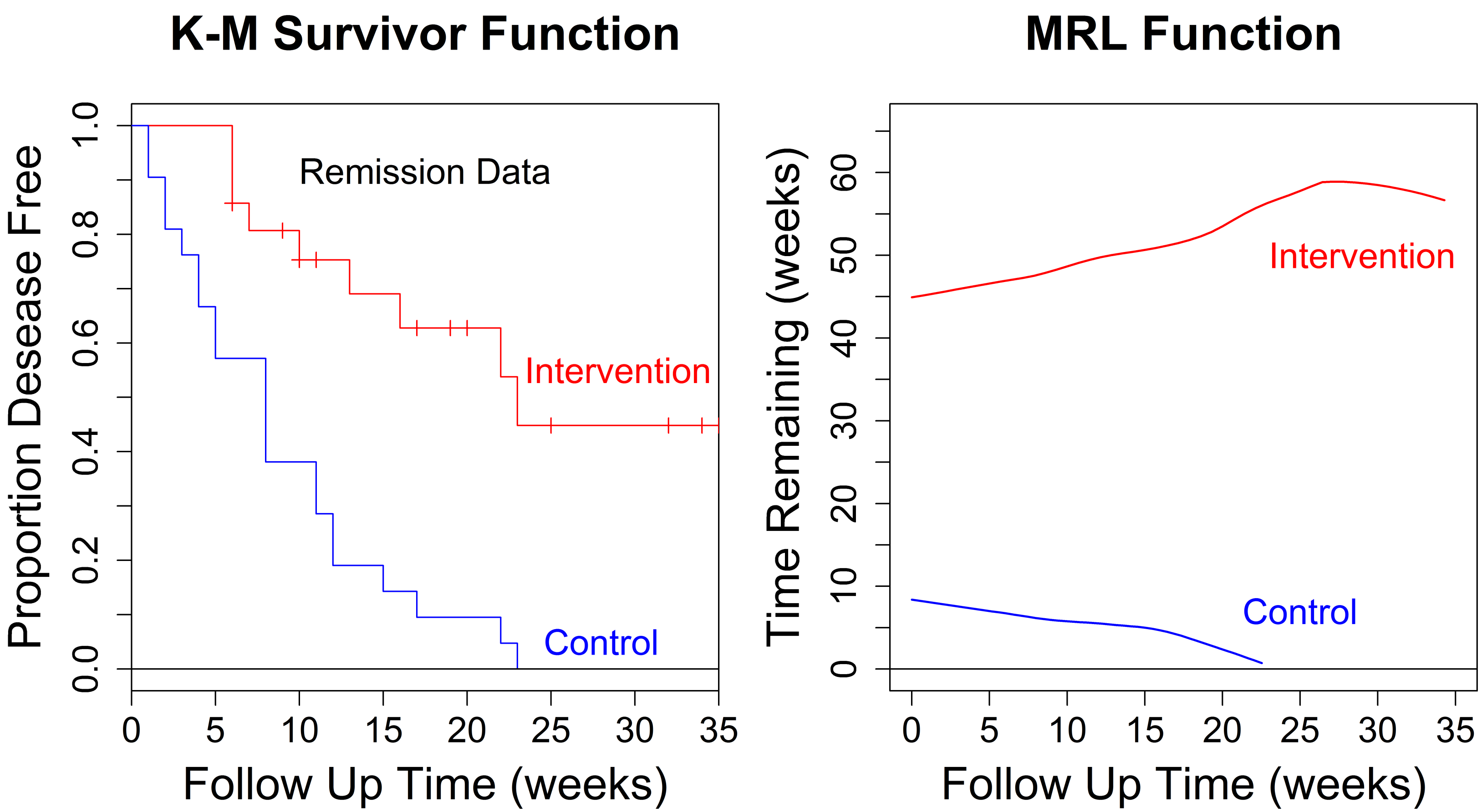
Summarising censored survival data using the mean residual life function

Alberto Alvarez-Iglesias,[a*†] John Newell,[a] Carl Scarrott[b] and John Hinde[a,c]

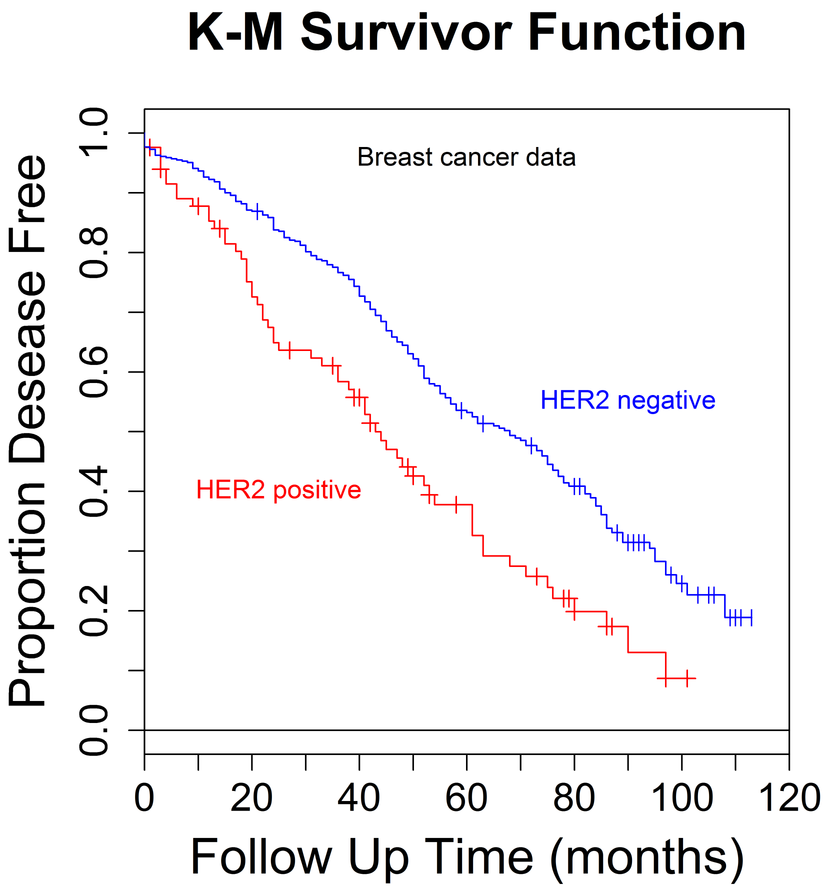
The mean residual life function provides a clear and simple summary of the effect of a treatment or a risk factor in units of time, avoiding hazard ratios or probability scales, which require careful interpretation. Estimation of the mean residual life is complicated by the upper tail of the survival distribution not being observed as, for example, patients may still be alive at the end of the follow-up period. Various approaches have been developed to estimate the mean residual life in the presence of such right censoring. In this work, a novel semi-parametric method that combines existing non-parametric methods and an extreme value tail model is presented, where the limited sample information in the tail (prior to study termination) is used to estimate the upper tail behaviour. This approach will be demonstrated with simulated and real-life examples.

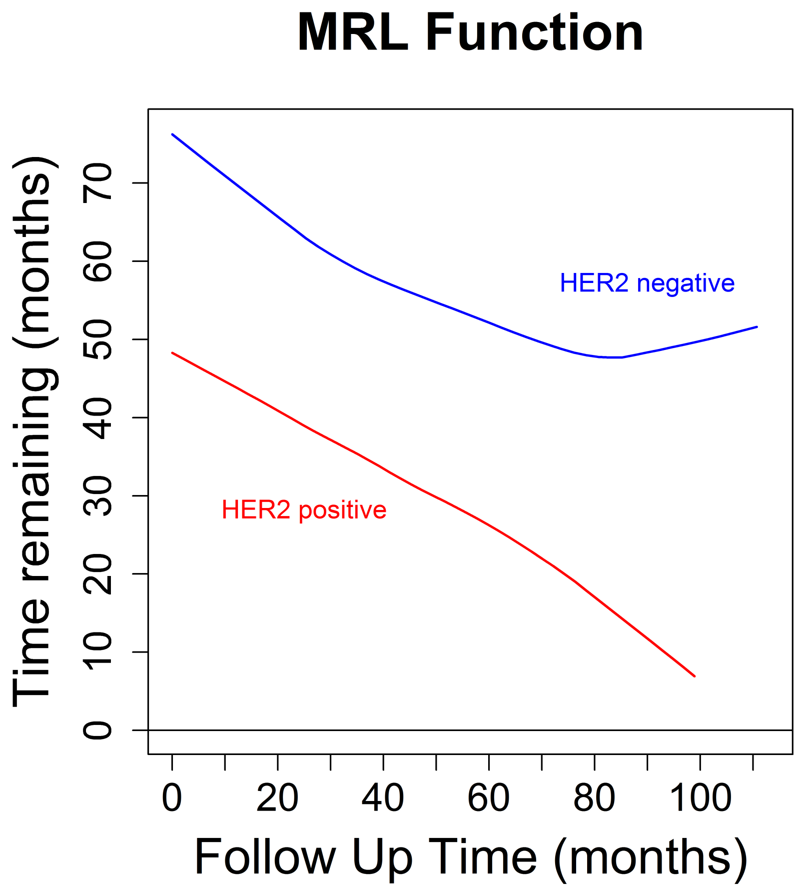
Keywords: extreme value theory; generalised Pareto distribution; mean residual life; survival analysis

Acute Leukaemia: 6MP Study



Galway Breast Cancer Study





Reproducible Research

- Replication of results
- Validation of analyses
- Quality control

- Dynamic reports
- Extension to
  - new data
  - new settings

Dynamic Report Generation (Rstudio)

R code

Latex code

OUTPUT (pdf)

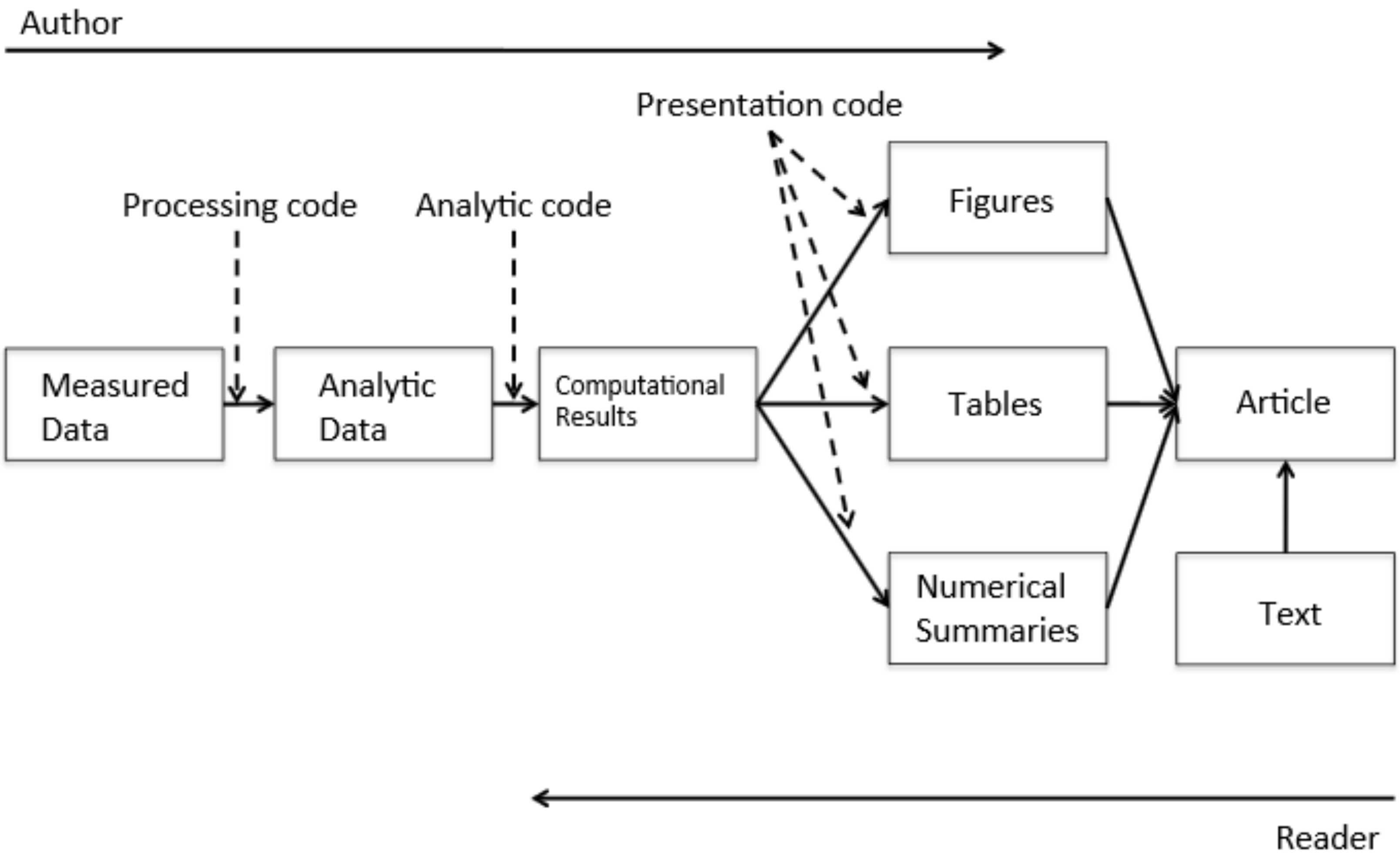
Table DEMO-2 *Baseline characteristics*
Demographics (Gender)
Screening Population

Gender	Total Subjs	%
Male	36	83.7% (36/43)
Female	7	16.3% (7/43)
Total	43	

Reproducible Data Analysis

- `Weaved' document is run through Sweave.
- All data analysis output (text, tables and graphs) inserted into report document.
- Do not need to copy and paste results and/or type them by hand.
- Statistical report is completely **reproducible**.
- Report is **dynamic** and can be easily regenerated when the data or analyses change (all of the results/tables/figures are automatically updated).

Research Pipeline

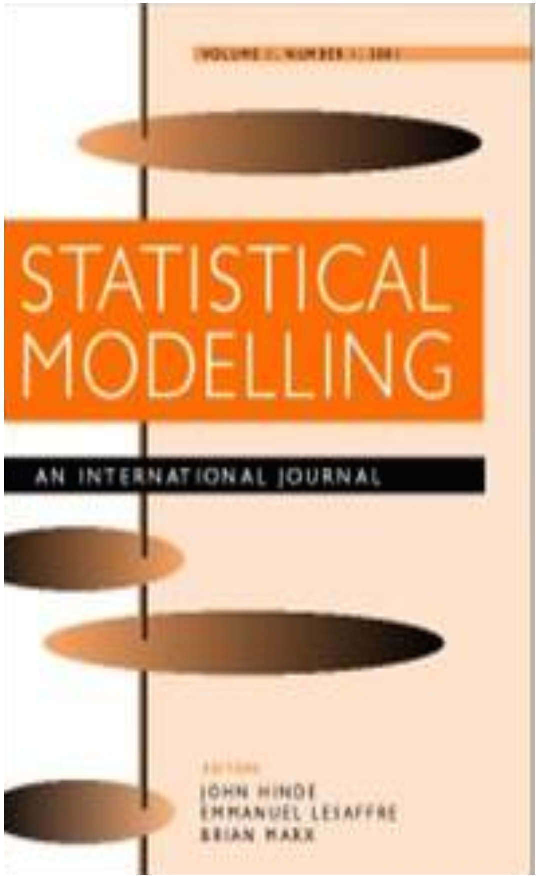


Biometrical Journal

Editorial (2009): ***Biometrical Journal and Reproducible Research***

*It is our aim to increase the quality, usefulness and scientific impact of Biometrical Journal articles through **reproducibility**.*

Statistical Modelling Journal

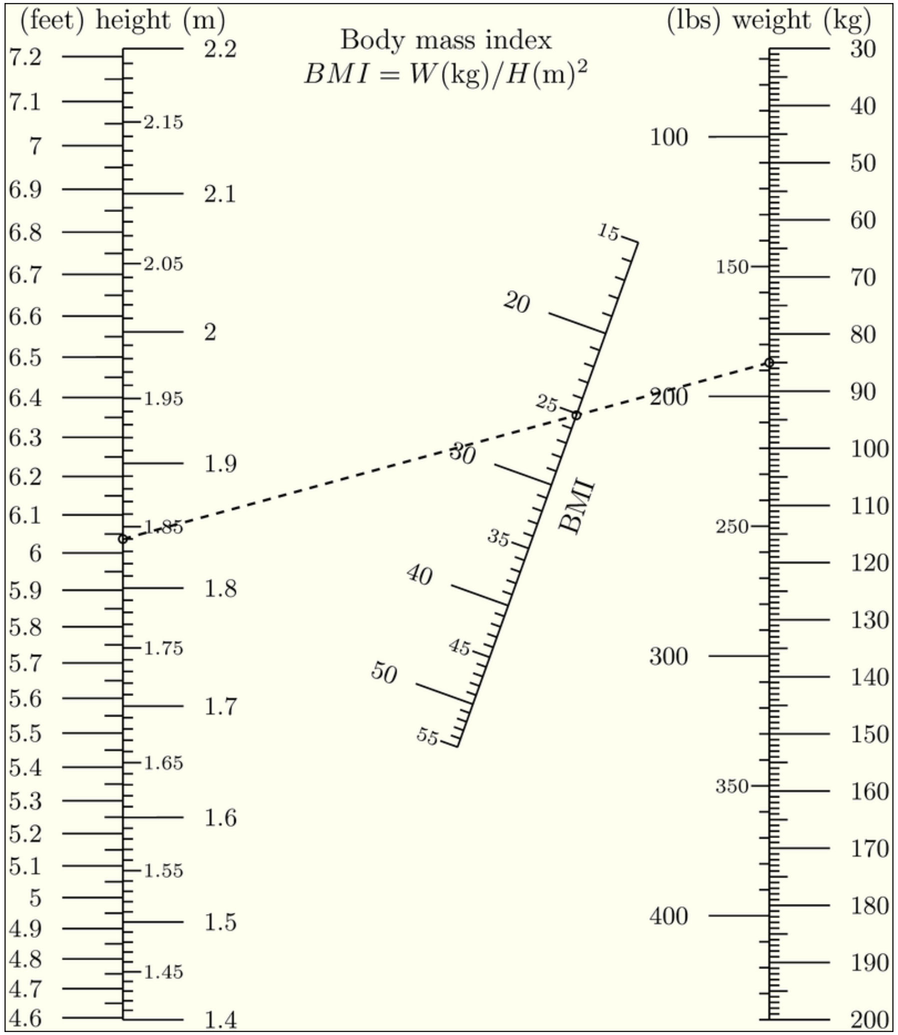


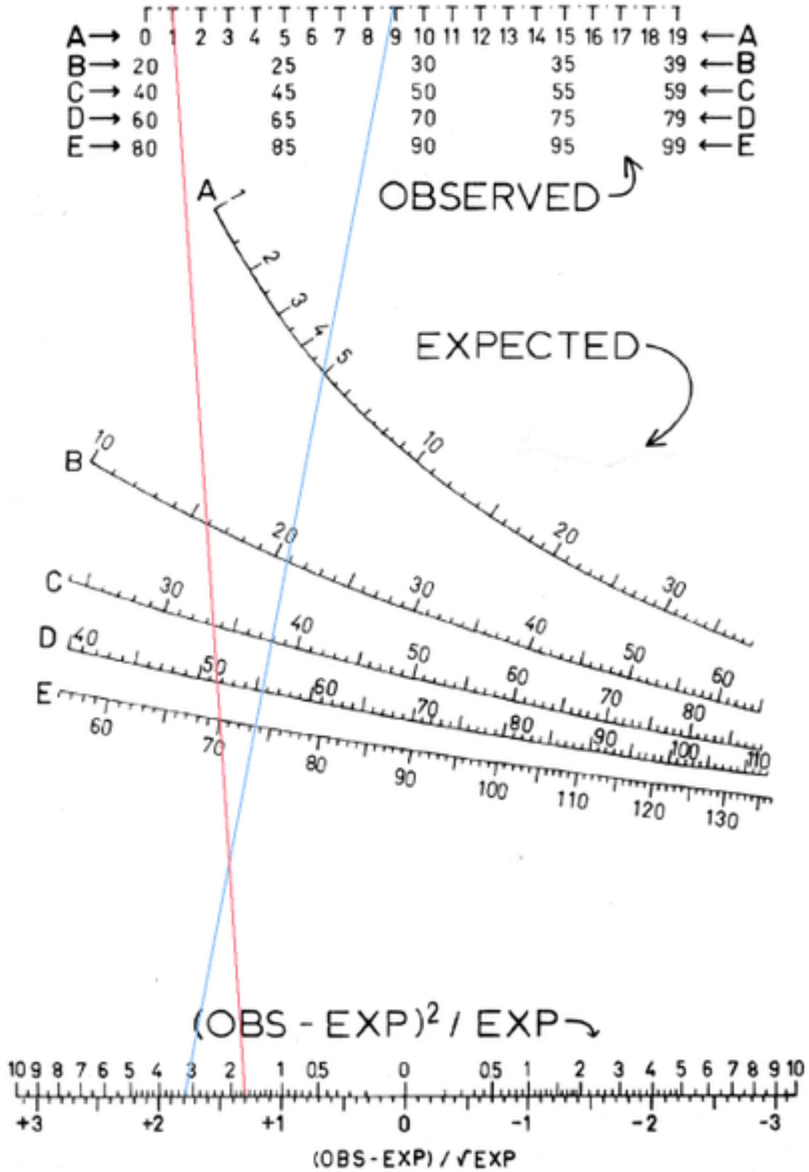
From outset in 2001:

Free public availability of data & code a ***condition*** *for publication*

Nomograms

graphical analog computing devices of complicated formulas





A→ 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 ←A
B→ 20 25 30 35 39 ←B
C→ 40 45 50 55 59 ←C
D→ 60 65 70 75 79 ←D
E→ 80 85 90 95 99 ←E
OBSERVED
EXPECTED
A
B
C
D
E
$(OBS - EXP)^2 / EXP$
10 9 8 7 6 5 4 3 2 1 0.5 0 0.5 1 2 3 4 5 6 7 8 9 10
+3 +2 +1 0 -1 -2 -3
$(OBS - EXP) / \sqrt{EXP}$

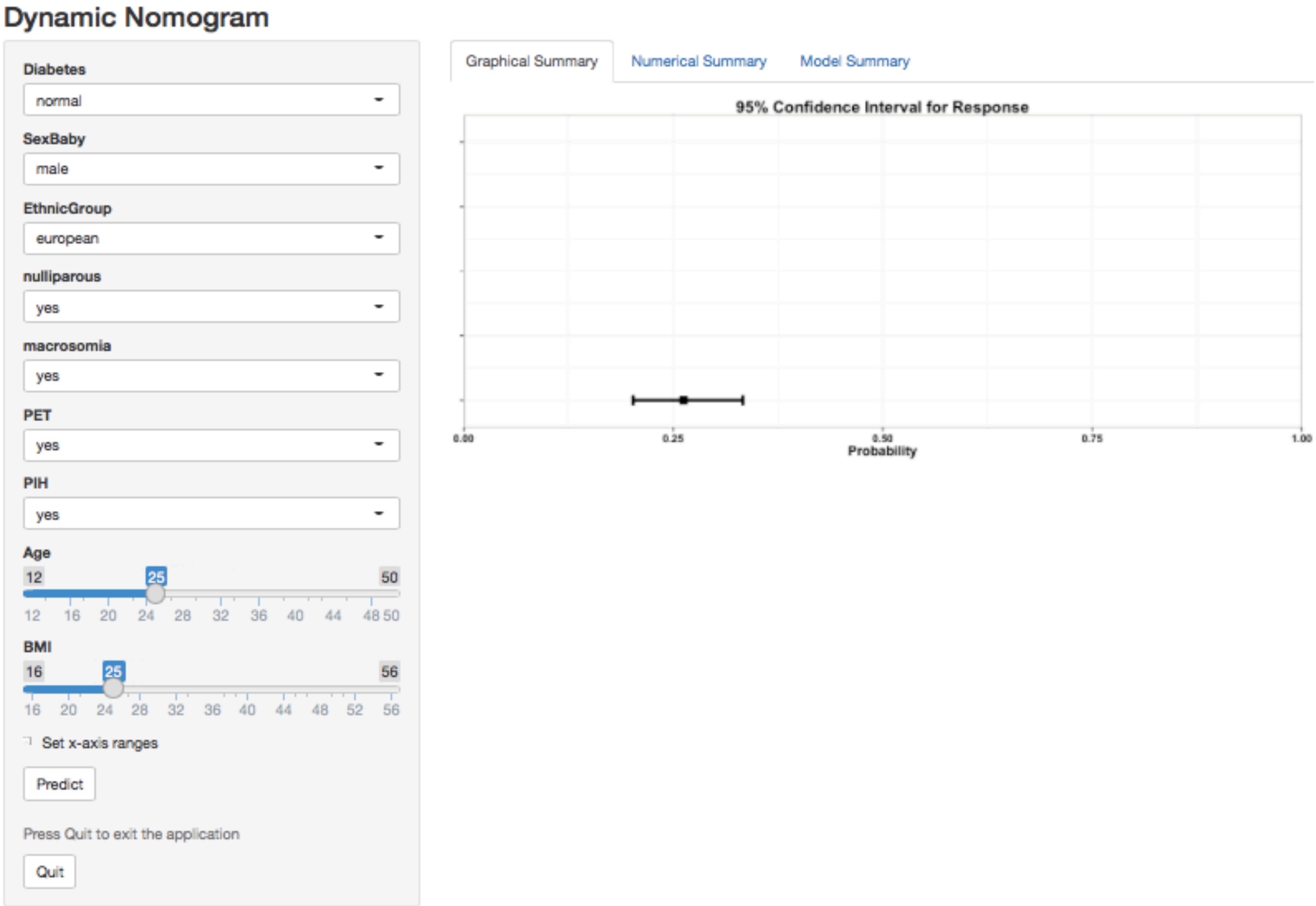
Nomograms

In Statistics, a ***nomogram*** is a **graphical representation** of a statistical model providing a point estimate of the response variable for a particular set of values for the explanatory variables

Risk of Caesarean Section (n=6526)

Variables	Coefficient	Odds ratio	Lower Interval	Upper Interval	p-value
Intercept	-4.413	0.012	0.007	0.020	<0.001
Glucose gestational Diabetes (Non-Diabetic)	0.238	1.269	1.091	1.476	0.002
Glucose Pre gestational Diabetes (Non-Diabetic)	1.597	4.937	3.710	6.569	<0.001
Age	0.050	1.051	1.038	1.064	<0.001
BMI	0.067	1.069	1.057	1.081	<0.001
Nulliparous status=yes (Nulliparous status=no)	-0.401	0.669	0.586	0.765	<0.001
Macrosomia status =yes (Macrosomia status=no)	0.055	1.056	0.902	1.236	0.498
Preeclampsia=yes (PET=no)	0.699	2.011	1.449	2.791	<0.001
pregnancy included hypertension=yes (PIH=no)	0.010	1.010	0.791	1.291	0.936
Baby sex =Male (Female)	0.110	1.117	0.987	1.264	0.080
Ethnic group = non-European (European)	0.277	1.319	1.064	1.636	0.012

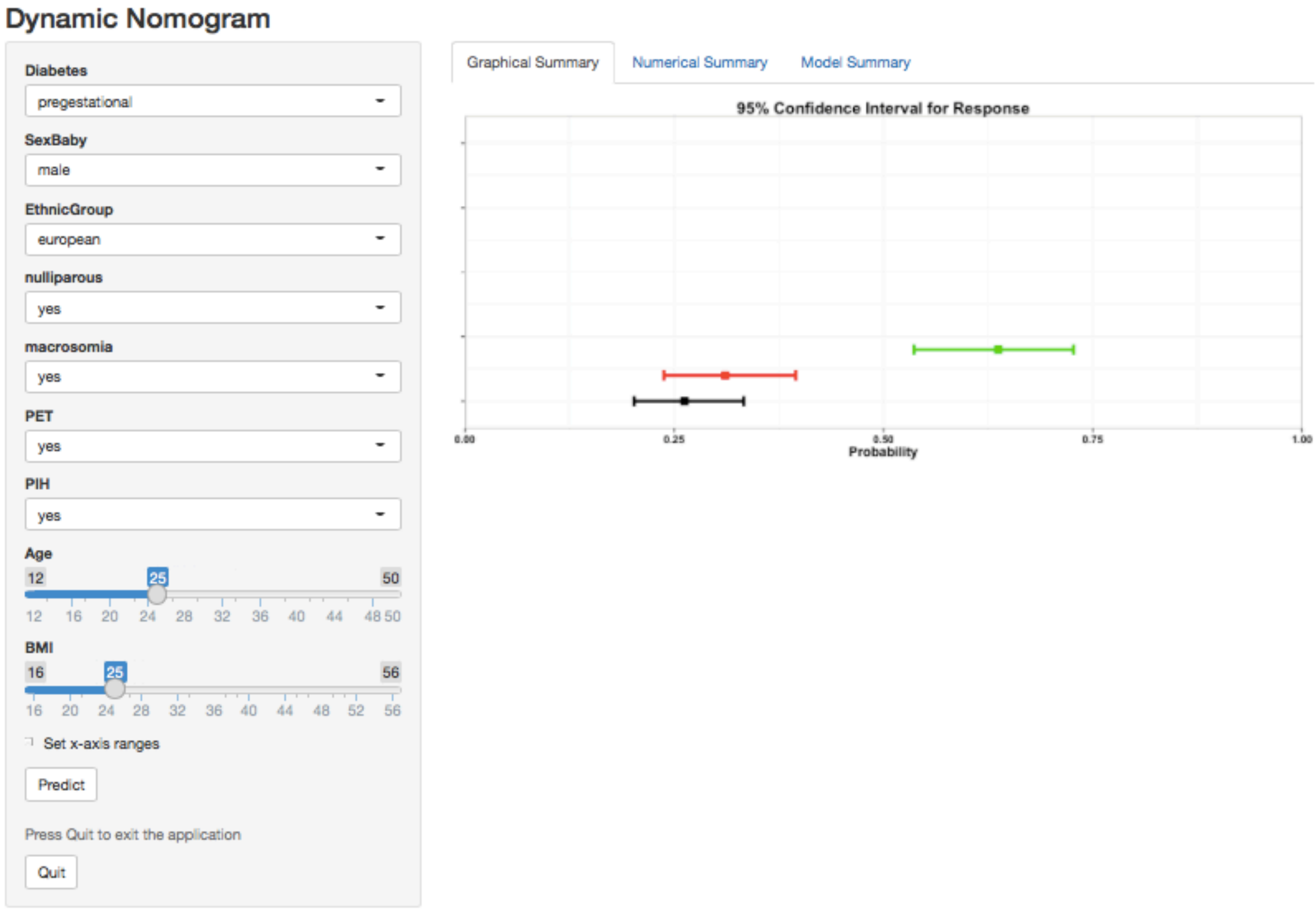
Click here for model nonogram



Dynamic Nomogram
Diabetes
normal
SexBaby
male
EthnicGroup
european
nulliparous
yes
macrosomia
yes
PET
yes
PIH
yes
Age
12
25
50
12 16 20 24 28 32 36 40 44 48 50
BMI
16
25
56
16 20 24 28 32 36 40 44 48 52 56
Set x-axis ranges
Predict
Press Quit to exit the application
Quit
Graphical Summary
Numerical Summary
Model Summary
95% Confidence Interval for Response
0.00
0.25
0.50
0.75
1.00
Probability

Dynamic Nomograms

- A Shiny application in R
- DynNom function
  - `DynNom(model, data)`
  - Supports: `lm, glm, rms, coxph`
- Delivered as a webpage or Rstudio window
- DynNom available from CRAN


Dynamic Nomogram
Diabetes
pregestational
SexBaby
male
EthnicGroup
european
nulliparous
yes
macrosomia
yes
PET
yes
PIH
yes
Age
12
25
50
12 16 20 24 28 32 36 40 44 48 50
BMI
16
25
56
16 20 24 28 32 36 40 44 48 52 56
Set x-axis ranges
Predict
Press Quit to exit the application
Quit
Graphical Summary
Numerical Summary
Model Summary
95% Confidence Interval for Response
0.00
0.25
0.50
0.75
1.00
Probability

Summary of Displayed Models

Graphical Summary | Numerical Summary | Model Summary

	Age	BMI	Diabetes	SexBaby	EthnicGroup	nulliparous	macrosomia	PET	PIH	Prediction	Lower.bound	Upper.bound
2	25	25	normal	male	european	yes	yes	yes	yes	0.262	0.202	0.333
3	25	25	gestational	male	european	yes	yes	yes	yes	0.311	0.238	0.395
4	25	25	pregestational	male	european	yes	yes	yes	yes	0.637	0.536	0.727

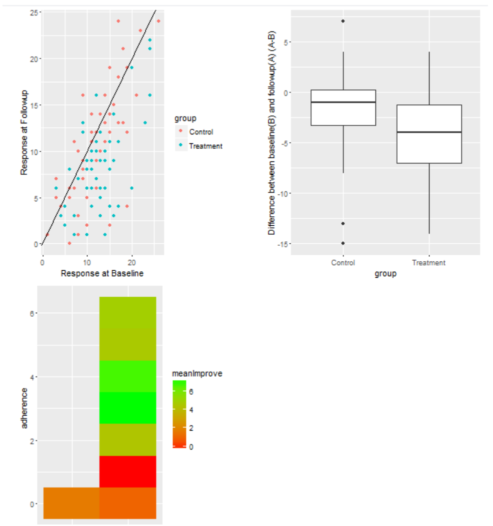
Fitted Model Summary

Graphical Summary | Numerical Summary | Model Summary

```
binomial regression (logit): CaesareanSection ~ Age + BMI + Diabetes
 + SexBaby + EthnicGroup + nulliparous + macrosomia + PET + PIH
==================================================
                          Dependent variable:
                      ---------------------------
                           CaesareanSection
--------------------------------------------------
Age                       1.051*** (1.038, 1.063)
BMI                       1.069*** (1.058, 1.080)
Diabetesgestational       1.269*** (1.118, 1.420)
Diabetespregestational    4.937*** (4.651, 5.223)
SexBabyfemale             0.895*** (0.772, 1.019)
EthnicGroupnoneuropean    1.319*** (1.104, 1.534)
nulliparousyes            0.669*** (0.536, 0.803)
macrosomiayes             1.056*** (0.899, 1.213)
PETyes                    2.011*** (1.683, 2.339)
PIHyes                    1.010*** (0.765, 1.255)
Constant                   0.014 (-0.487, 0.514)
--------------------------------------------------
Observations                       5,395
Akaike Inf. Crit.                6,053.293
==================================================
Note:                      *p<0.1; **p<0.05; ***p<0.01
```

Lorem ipsum dolor sit amet, consectetur adipiscing elit. Morbi tincidunt libero turpis, vel dictum dolor rutrum vitae. Curabitur finibus massa ut velit commodo, eget laoreet erat mattis. Donec efficitur purus quis sollicitudin mollis. Phasellus vitae ex est. Morbi nec aliquam odio, in rhoncus tellus. In hac habitasse platea dictumst.

Quisque tempus ligula nec ligula scelerisque, eget condimentum lorem lacinia. Ut euismod nec risus quis semper. Aliquam egestas condimentum magna ut dapibus. Sed faucibus turpis id posuere pharetra.



Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	-3.08024	3.89764	-0.790	0.431094
Response.at.Base	0.71233	0.08017	8.886	1.57e-14
GroupTreatment	-3.01056	0.78997	-3.811	0.000231
Age	0.01363	0.03660	0.373	0.710224
SmokerYes	-1.04456	1.63362	-0.639	0.523908
GenderMale	0.30119	0.82006	0.367	0.714131
Resting.Pulse	0.05892	0.03373	1.747	0.083505

Donec et auctor risus, vel dignissim ante. Donec pretium massa tellus, ut facilisis leo lobortis tincidunt. Aliquam consequat quis mi pellentesque imperdiet. Vestibulum eu cursus odio. Vivamus a turpis ligula. Phasellus aliquet leo in odio laoreet, eu molestie eros auctor. Morbi lacus leo, faucibus sed facilisis quis, scelerisque sed nisl. Vestibulum finibus laoreet imperdiet. Fusce urna ligula, varius in hendrerit vitae, dapibus ac ante. Duis consequat in enim non auctor. Nunc id purus nec ipsum blandit fermentum id ut arcu.

Aenean quis euismod justo. Nam pulvinar rutrum elit ut eleifend. Proin luctus blandit justo, a congue elit scelerisque eget. Mauris viverra, nunc eget lacinia malesuada, ante mauris egestas ligula, vitae elementum neque sapien in sem. Nam at eros vulputate turpis congue maximus. Pellentesque mauris risus, feugiat id feugiat ut, egestas vel lacus.

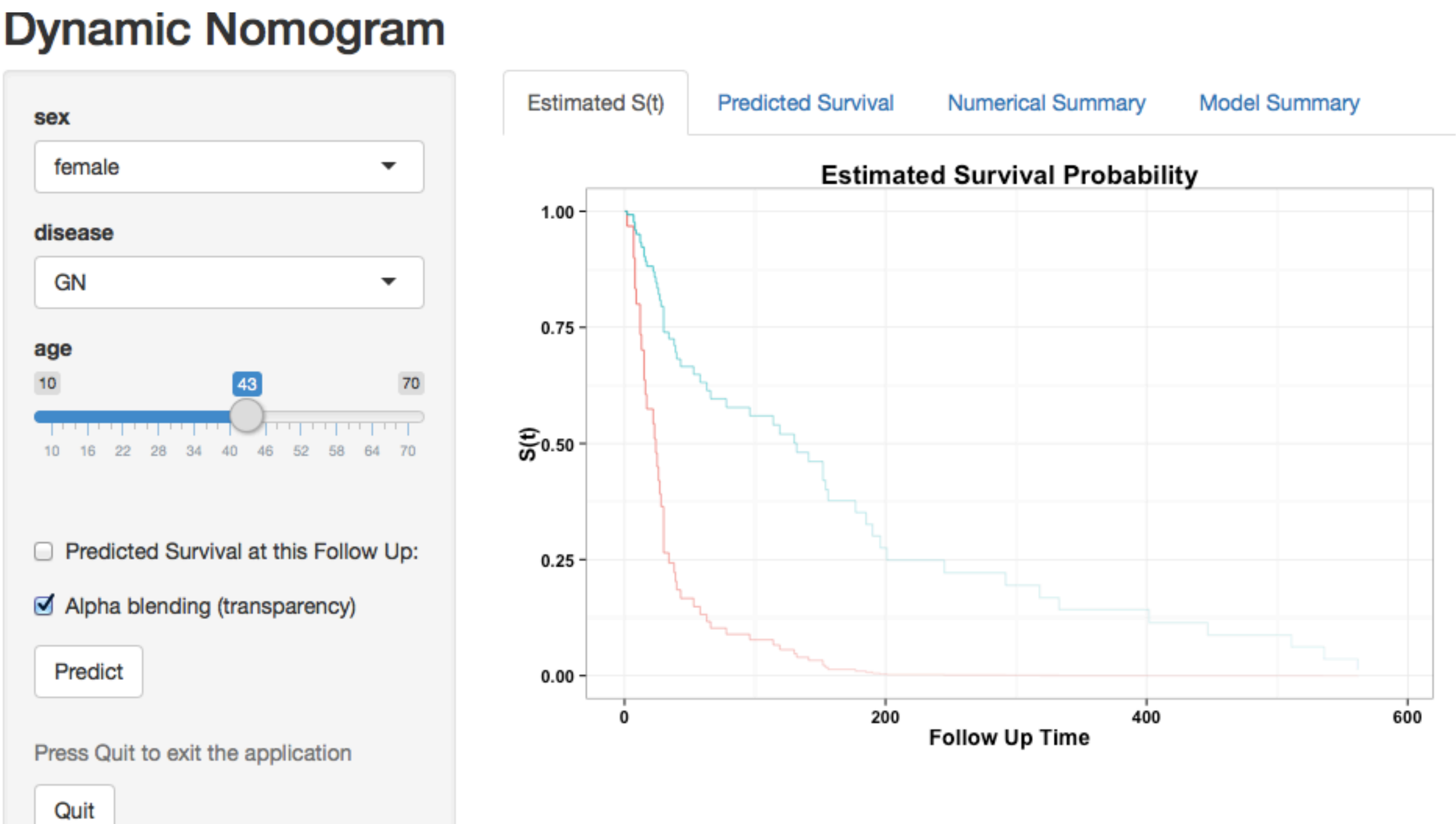
Dynamic Nomograms in Survival Analysis

- Display the estimated survivor function ?
  - Use alpha blending ?

- Display the estimated mean residual life function?
  - Use alpha blending ?

- Report the probability of survival beyond fixed time points (e.g. 5 years) or the hazard relative to the mean ?

Dynamic Nomograms in Survival Analysis



Conclusions

- Translational statistics has a key role to play in design and analysis and in translating the results in an accurate and understandable manner

- Dynamic nomograms: *a useful tool?*

- The most truthful analysis may not be the one that best translates the truth .....