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Modern modelling of mortality and morbidity

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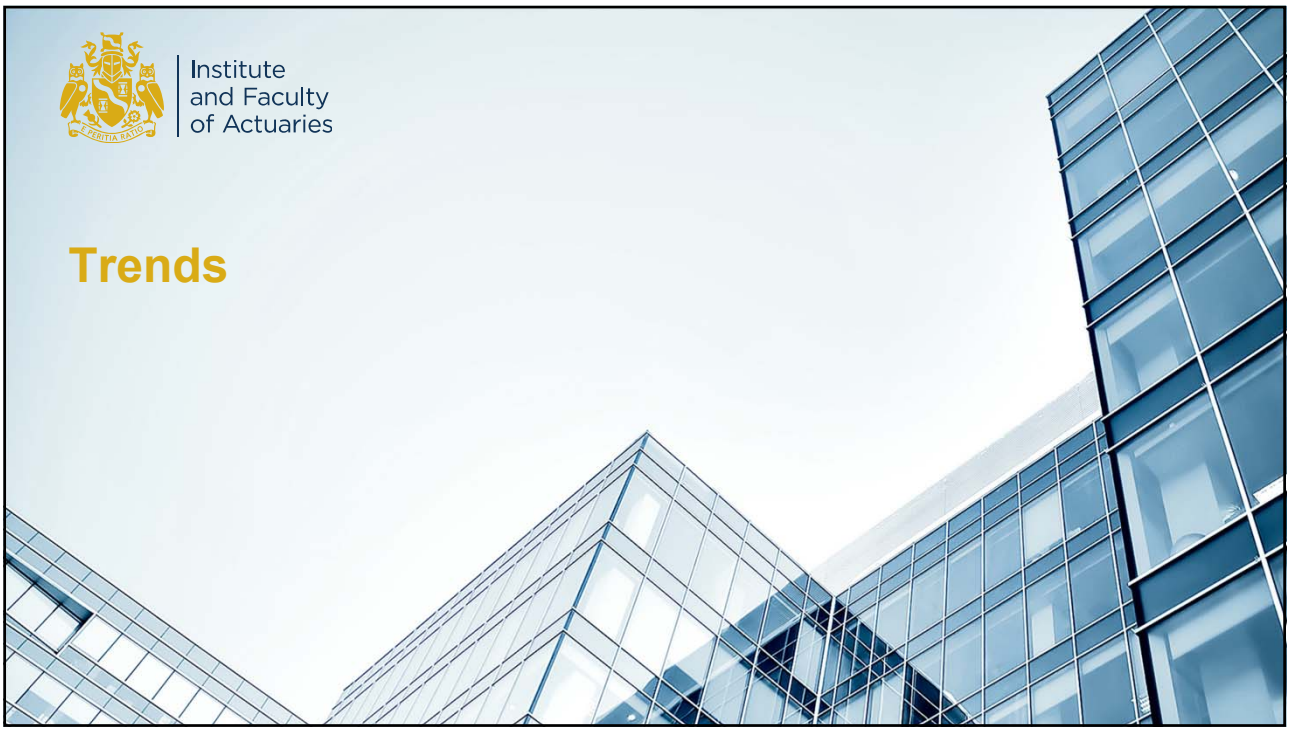
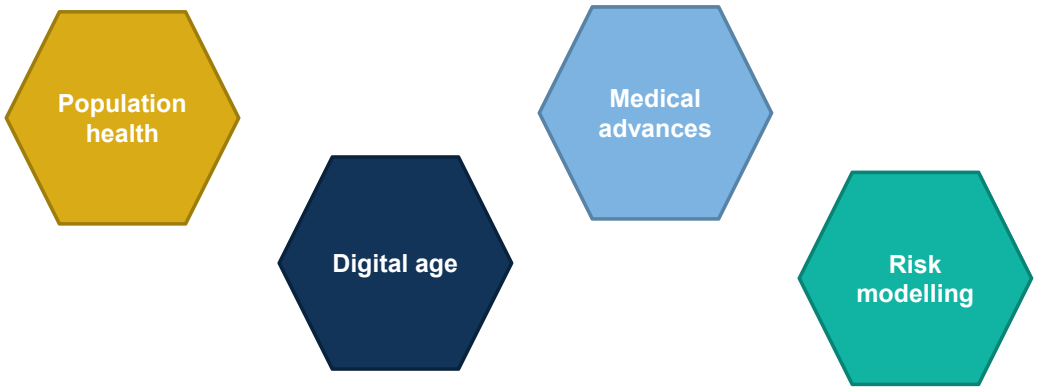
21 November 2019

Agenda

- Trends
- Survival analysis
- Applications



Trends



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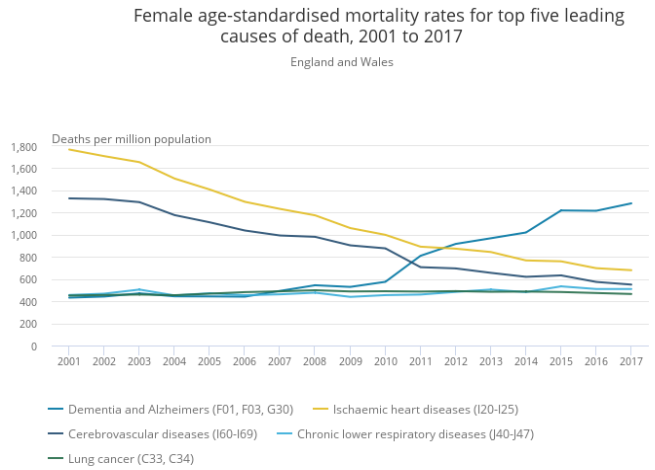
Overcoming old foes…



Source: Office for National Statistics

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..but making new ones

Cancer

1 in 2 will develop

Source: Cancer Research UK / Macmillan

Diabetes

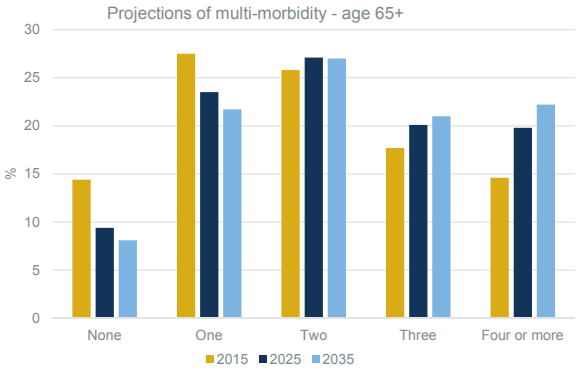
1 in 3 will develop

Source: Diabetes UK

Alzheimer's / Dementia

1 in 3 will develop

Source: Alzheimer's Research UK



Source: Andrew Kingston, Louise Robinson, Heather Booth, Martin Knapp, Carol Jagger, for the MODEM project, Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model, *Age and Ageing*, Volume 47, Issue 3, May 2018, Pages 374–380

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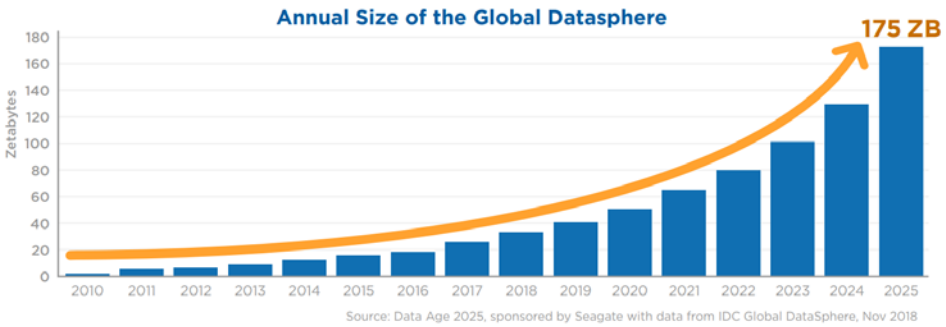
The data goldrush



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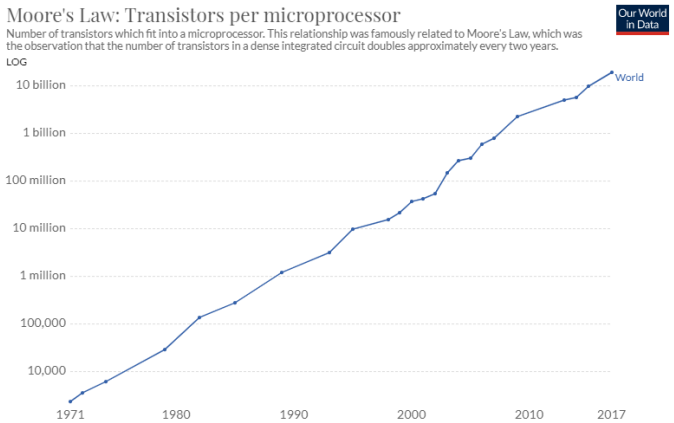
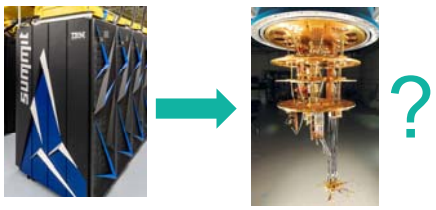
The rise of the machines





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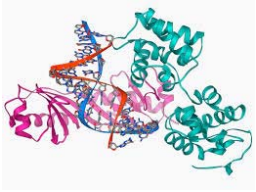
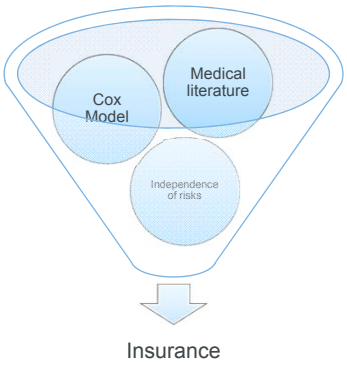
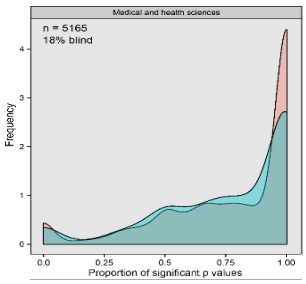
Precision medicine



Survival modelling – lagging behind?



Medical literature - Prone to bias?



Source: https://journals.plos.org/plosbiology/article/file?id=10.1371/journal.pbio.1002190&type=printable

Survival models - Outdated?

Kaplan and Meier 1958

Cox 1972

Fine & Gray 1999

AutoPrognosis 2017/18

Independence of risks - Real world limitation?

Survival analysis

What is it?

- Analysis of time until the event is of interest occurs (e.g. death, cancer, CVD, etc)
  - Probability of 'survival' up to time t (cumulative)
  - Conditional probability of the event (i.e. the hazard) at time t having survived to that time
    - Effect of key factor(s) on this occurring (rate of risk / hazard function)
    - Enables the difference between survival times of particular groups of patients to be tested while allowing for other factors

Traditional models

- Kaplan Meier
  - No underlying probability curve assumption needed
- Cox proportional hazards model
  - No assumption about the probability distribution of the hazard (i.e. risk of the event, e.g. dying)
  - Comparisons between groups gives the, commonly referenced, hazard ratio

The traditional cox model

- Ubiquitous in survival modelling of (single) risks, especially in medical literature
- Key assumptions:
  - **Non-informative / independent censoring**, i.e.
    - Individuals who are censored ("drop out" of the study) have the same future risk (of the event) as those who remain.
    - The reasons (i.e. other risks) for the censoring are independent (they do not affect the probability of the event of interest occurring)
  - **Relationship between rate and probability of event is the same (homogenous) in the population**
  - **Hazards are proportional - the effect of each risk (covariate) is time invariant**

✓ Easy to use

✓ No distributional assumptions

✓ Continuous or discrete time

× Proportional hazards
(effect of each covariate is time invariant, albeit model can be adjusted to allow for non-proportional hazards)

× Cannot identify independence of risks
(Tsiatis, PNAS, 1975; 72(1):20-22)

× Over-estimation in presence of competing risks

× Over-fitting in presence of multiple covariates

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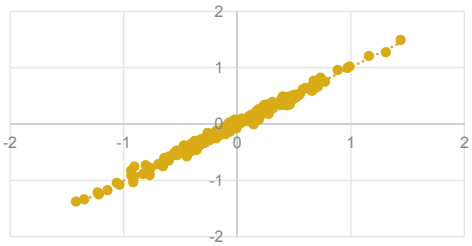
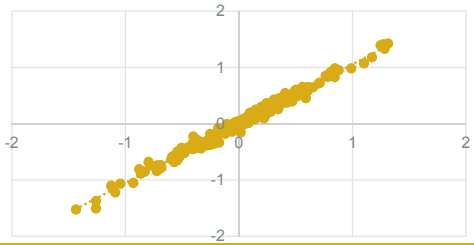
An aside on overfitting

- Using synthetic data to explore overfitting challenge in Cox models
- Interestingly find a **systematic** bias in association parameter estimates (vertical axis) versus their true values (horizontal axis)
- Holds promise of theoretically informed adjustments in use cases where there are a high proportion of risk factors to observations
- Observe similar systematic biases in base hazard rates

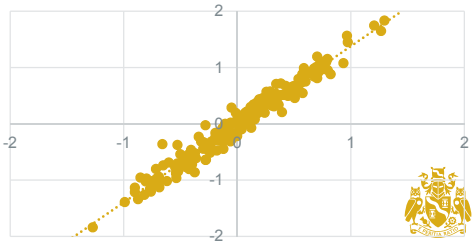
5 covariates, 400 observations



40 covariates, 400 observations



200 covariates, 400 observations



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The problem with models…the medical researchers know

- Competing risks: an event whose occurrence precludes the occurrence of the primary event of interest - **Assumed to not exist in traditional, commonly used, survival models**
- Reality invalidates all the key K-M and Cox assumptions

Because there is not a one-to-one correspondence between rate (how quickly people are suffering from a particular illness) and risk (how likely they will get it over time), you can have real world scenarios where the rate goes up and the risk goes down. E.g. if you get more obese your risk of dying of cancer decrease – because you are more likely to die of diabetes complications. If you model 'bottom' up, disease by disease, you could fail to model these interactions fully

P.K.Andersen et al 2012 (Competing risks in epidemiology: possibilities and pitfalls)

"It is tempting to also estimate the Cumulative Incidence function of a specific event of interest with the Kaplan-Meier method…While frequently uses, it is important to note that the logic of this modified estimator is flawed."

"The validity of this independence assumption cannot be statistically verified and is clinically implausible." *M. Wolbers et al 2014 (Competing risk analyses: Objectives and approaches)*

"…biology often suggests at least some dependence between competing risks, which in many cases may be quite strong. Accordingly, independent competing risks may be relatively rare…" *Austin et al, Circulation, 2016;133:601-609*

"…competing risks…in nephrology, it has only been acknowledged only recently in a few publications"

"This kind of interpretation is not realistic in clinical practice…the Kaplan-Meier method generally overestimates the probability of the event of interest and therefore yields misleading results in the presence of competing risks." *M.Nordzij et al 2013 (When do we need competing risks methods for survival analysis in nephrology?).*

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And so do the social sciences…

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Typical competing risk approaches

Prognostic models

How long people survive specific risk factors

"What is my risk of dying from lung cancer over the next 5 years?"

- Based on sub-distribution hazard function
- Hazard rate of a specific disease in a world where other diseases have no effect
- This means, for example, the "at risk" population for lung cancer includes those who have already died from all other causes.
- Hard to get good intuition as to what this really means, and so challenging to consider scenario analysis or changes in distributions over time

Etiological models

Causal effect of specific risk factors

"What impact will quitting smoking have on the chance of dying from lung cancer?"

- Based on cause-specific hazard function, i.e. the rate of incidence of a specific disease in the true at risk population.
- Easier to interpret, and for assessing which risk factors cause disease
- Not a good approach to measuring risk (e.g. the chance of someone dying of a particular cause over the next 5 years) as it only focussed on a single cause at a time.

A "fudge"…not tackling the issue

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Applying a Bayesian mindset

Accept you cannot identify model from maximum likelihood approach…

…but can seek the most likely model (from a range of models) given the observed data

- ✓ Model all risks simultaneously – rather than built up cause specific or sub-distribution hazard functions risk by risk – model their joint distribution
- ✓ Capture heterogeneity between individuals – i.e. different individuals with the same risk covariates (e.g. BMI, smoker status,..) can have distinct risk associations and base hazard rates
- ✓ Risks independent at individual level (or within classes of individuals) but that does not lead to independent risks overall
- ✓ Hazards are proportional within classes of individuals, but that does not lead to proportional hazards overall

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Success in practice

Prostate cancer risk

- Study of prostate cancer and type 2 diabetes mellitus
- Identified no relation between T2DM status and cancer risk
- Identified two distinct classes, with the smaller class representing 9% of population at higher risk. Hazard ratio for class membership of 16.4 (95% confidence interval of 7.1)
- Class membership more predictive of risk than any covariates captured (age, T2DM status, and Charlson comorbidity index1)
- Shows the ability to identify a class of individuals with much higher risk of prostate cancer.

Haggstrom et al, Int J Cancer (2018)143(8):1868-1875

Breast cancer risk

- Disorders in lipid and glucose metabolism have been suggested as a link between obesity and breast cancer
- Two classes identified, one with higher risk of breast cancer
- Impact of risk factors different between two classes.
- Class 1: Triglycerides level correlates to higher risks.
- Class 2: Cholesterol correlated to cardiovascular deaths and glucose to deaths from other causes.
- Shows the ability to identify different classes whose risk is materially differently correlated to different risk factors.

Wulaningsih et al, BMC Cancer (2015) 15:913-922

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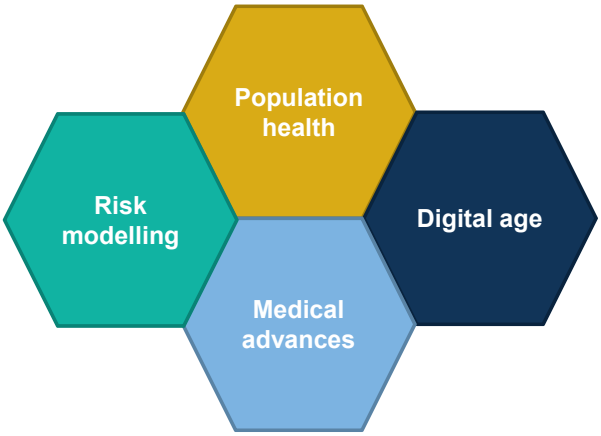
Where could this be used?



- Better risk stratification
- Better understanding of risk factors
- Accelerated underwriting
- Equity release mortgages
- Health & social care
  - Value based health care
- Financial (retirement) planning

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Profit boosting?

- Newer models have shown (vs K-M / Cox)
  - Completely different, at times opposite, risk markers
  - Chances of survival can be nearly HALF!
- What if new approach reduces claims by only 1% => +5%-10% increase in profits?

Source: a latent class model for competing risks: M. Rowley et al, 2017

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Conclusion

- We have the data & capabilities to better model individual morbidity and mortality
- Traditional modelling cannot reflect reality accurately enough
- New modelling approaches exist which are showing significantly different results (to traditional methods)
- Benefits, in theory, could be revolutionary
  - Insurance & underwriting; pricing, reserving, risk management
  - Individual planning
  - Health & care

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Questions

Comments

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