Dynamic predictions for repeated markers and repeated events
General Conclusion

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What we came here for

Over two days, this workshop will provide an opportunity for epidemiologists, biostatisticians and mathematicians, actors and researchers in the field of health to learn about innovative methods of data modeling, and the cancer prediction tools available to prevent the events of patients with cancer. Prediction models are used more and more to complement clinical reasoning, especially in the field of cancer. For this reason, the statistical models developed must provide accurate estimates and validated predicted probabilities on individuals targeted. However, even if the statistical and mathematical models have been widely developed and are still growing, methods of validating these approaches still require extensive research. Experts in the field have been solicited and have responded favorably. An important place is also left to the posters. The objective of this workshop

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Some general remarks

In 2004, during a NCI workshop [2], a major point was raised regarding issues in developing risk prediction : **Incorporating Risk Factor Changes Over Time Into Models**

Some of the Workshop recommendations for future cancer risk prediction research

1. Revise existing breast cancer risk assessment models and develop new models to improve predictive power
2. Encourage the development of new types of risk models
3. Obtain data to develop more accurate risk models
4. Support mechanisms and resources to validate risk models
5. Strengthen model development efforts and encourage coordination within large research and clinical centers
6. Promote effective cancer risk communication and decision-making

$\Rightarrow$ The present workshop follow these lines

[2] Cancer Risk Prediction Models: A Workshop on Development, Evaluation, and Application J Natl Cancer Inst 2005;97:715 – 23

Day 1 Feedback

INTRODUCTION ON PREDICTIVE ASSESSMENT FOR SURVIVAL MODELS
K. Moons

- Develop *vs.* use of myriad of risks predictions models
- Confess that he used to do some incorrect analysis but thanks to Franck Harell's work it 's over now
- Proper methodologies should be taught (Dissemination of good practice)
- Dynamic updated of our knowledge also for scientists
- Take home : Impact studies of using prediction models

Identifying Key Statistical Papers From 1985 to 2002 Using Citation Data for Applied Biostatisticians

Multivariable Prognostic Models, Issues in

Developing Models, Evaluating Assumptions and Adequacy, and Measuring and Reducing Errors

Table 3. Ranking of the top articles for applied biostatisticians, 1985–20

Rank #	First author	Journal, Year	Joinpoint fit[a]	Yrs	RAF[b]	E 2
1	Benjamini	*JRSS-B*, 1995	6.2; 7, 122.4; 10, 280.9	13	84	1
2	Higgins	*Stat Med*, 2002	48.6	6	100	
3	Liang	*Bmka*, 1986	7.3; 5, 29.9	22	72	
4	D'Agostino	*Stat Med*, 1998	10.2; 6, 28.4	10	100	
5	Kass	*JASA*, 1995	14.0; 11, 59.8	13	60	
6	Guo	*Bmcs*, 1992	16.7	16	96	
7	Spiegelhalter	*JRSS-B*, 2002	38.6	6	56	
8	Storey	*JRSS-B*, 2002	31.2	6	72	
9	Zeger	*Bmcs*, 1986	3.8; 4, 13.5	22	100	
10	Harrell	*Stat Med*, 1996	13.0	12	100	

Day 1 Feedback ctd

Janez $\star$: R^2 is not a measure of fit and suggested a versatile measure based on rank that can accommodate various survival setting
He also updated is PoV concerning past works

TAG *aka* Thomas Gerds : Recall the roadmap : Building $\rightarrow$ Udpating $\rightarrow$Evaluating predictions (using Brier Score)
Dynamic analysis recalculates coefficients

$$\text{Time origin} < \text{landmark time} < \text{time horizon}$$

MODELLING OF RECURRENT EVENTS AND COMPETING RISKS

Hein Putter

- Landmark originates from JCO , Condition on the future is wrong (for prediction at least)
- Exemplify dynamic prediction within the reversible illness-death-model
- Exemplify dynamic prediction with landmarking btw Nice Landmark data set (at risk) Caution
- Cumulative incidence is predicted following Cheng-Fine-Wei (Bcs, 1998)

Day 1 ctd

Vincent Couallier

- introduce dynamic intensity process that incorporate history of the recurrence
- Bridge between reliability and Biostatistics : Probably in the book *Survival and Event History Analysis, A Process Point of View* Aalen, Borgan and Gjessing.

Virginie Rondeau

- Joint model of 2 survival processes linked via frailty
- Recurrence timing + count
- Internal time dependent covariate is not appropriate for the recurrence
- Tale of Mr Martin's breast cancer
- Brier score + IPCW

Finally **Jeremy Taylor**

- Competing risks with a cure fraction
- Clustered data of 13 Trials
- Parametric hazard was used
- Various meaningful function of this event specific hazard were then computed (Residual lifetime)
- Connection with the landmarking

Basu and Tiwari . Breast cancer survival, competing risks and mixture cure model: a Bayesian analysis. Journal of the Royal Statistical Society: Series A (Statistics in Society) Volume 173, Issue 2, pages 307–329, 2010

LONGITUDINAL AND SURVIVAL DATA MODELING
Dimitris Rizopoulos

- Past and current issues with JM
- Recall Exogenous/endogenous covariates [3]
- Dynamic prediction needs Dynamic plots
- Refinements of the longitudinal sub model (within the LMM framework)
- Compare their impacts on the Dynamics Prediction with BMA machinery

[3] Must read : Cortese and Andersen, Biometrical J 2010

LONGITUDINAL AND SURVIVAL DATA MODELING

Cécile Proust Lima

- Presents Latent class mixed model framework for linking sub-models
- Give a fair comparison with JM
- Interest : Posterior distribution of the dynamic prediction
- Effective way of studying the Impact of initiation of a new therapy

Paul Blanche

- Assess the predictive accuracy in the context of joint model for longitudinal and competing events
- Derive a formal test of equality of $AUC(s,t)$ (or prediction errors) while the lad marking s is varying
- Versatile methodology

Donna Pauler Ankerst

- Realtime clinical epidemiology !
- Main issue : updating risk calculator for prostate cancer
- Incorporating medical innovation (here biopsy, SNPs)
- Automated manner
- Tackle the improvement of the AUC with new (costly) biomarker [4]

[4] Testing for improvement in prediction model performance. Pepe et al. 2013. Sim

MECHANISTICS MODELS AND PRECLINICAL ASPECTS

In short Biological knowledge is translated into a set of mathematical equations or a system of differential equations

Adeline Samson Short course : Toward a joint model of refinement of longitudinal process with NLMM?

Thierry Colin : Image-based simulation of tumor growth : a tool for improving the timing of Progression ?

Mélanie Prague : Feasible to use mechanistic model to (i) update time-dependent (longitudinal) covariate
(ii) simulate treatment intervention (that would affect the system of ODE) ?

Designing Clinical trial

Thomas Filleron : Provides a tool for planning and monitoring group sequential trial. This was also extended to competing risk (The use of group sequential designs withcommon competing risks tests. Lau, Zhang, MJ. Sim 2013)

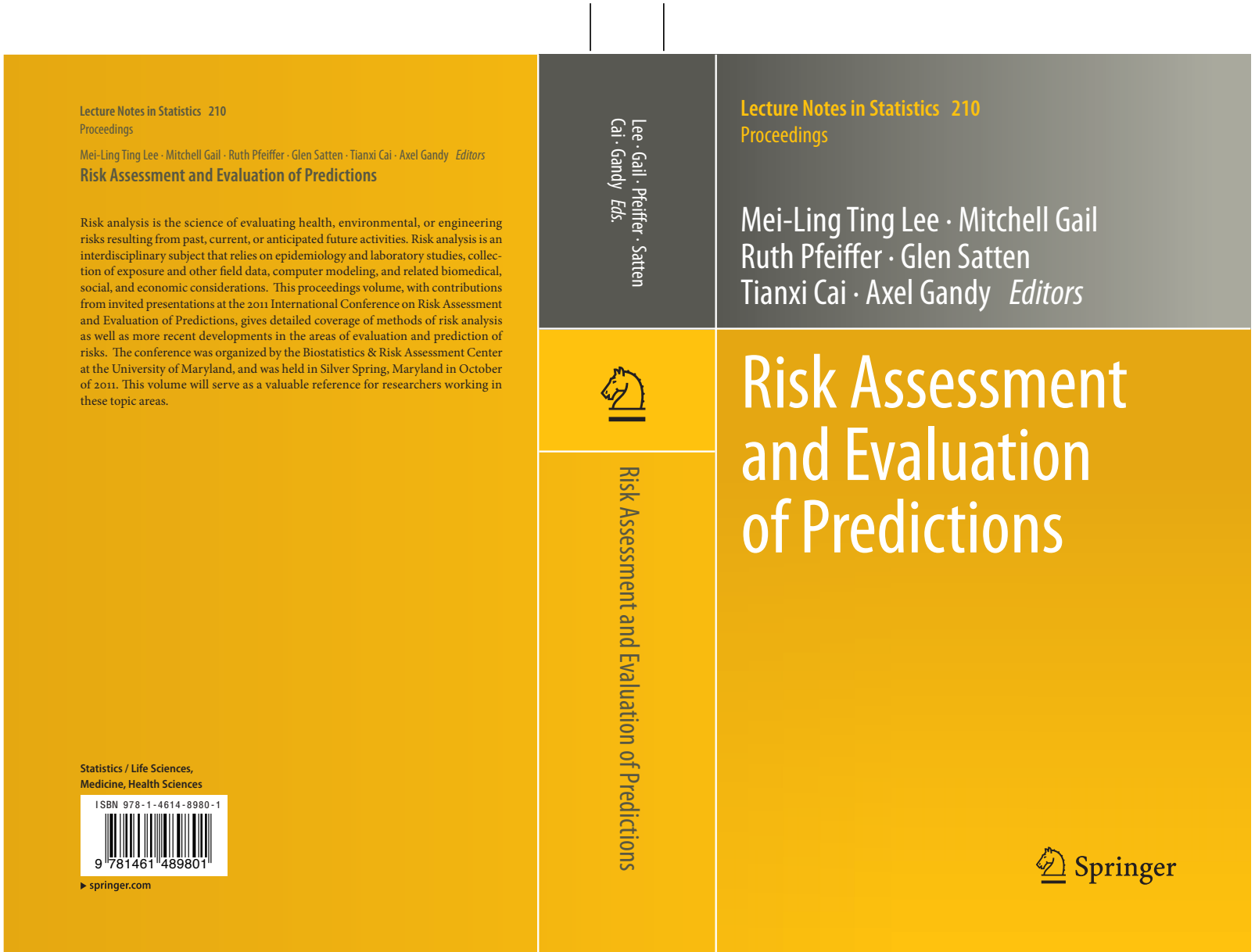
Use of a joint modeling analysis strategy leads to reduction of bias and increase in power in estimating the treatment effect. However, joint modeling is not yet commonly used in designing clinical trials. Most applications of joint modeling in the literature focus on estimating the effect of the longitudinal outcome on time-to-event.
[5]

[5] Chen, Ibrahim and Chu. Stat Med. 2011 ; 30(18): 2295–2309. doi:10.1002/sim.4263

Take home material

- R *arsenal* of dedicated packages
- Hopefully, this leads to dissemination (and misuse)
  example for jm : the longitudinal sub model is a model for an *internal* time dependent covariate
- Hopefully we are under surveillance : **Cochrane Prognosis Methods Group**
  http://prognosismethods.cochrane.org/

Readings


Lecture Notes in Statistics 210
Proceedings
Mei-Ling Ting Lee · Mitchell Gail · Ruth Pfeiffer · Glen Satten · Tianxi Cai · Axel Gandy Editors
Risk Assessment and Evaluation of Predictions
Risk analysis is the science of evaluating health, environmental, or engineering risks resulting from past, current, or anticipated future activities. Risk analysis is an interdisciplinary subject that relies on epidemiology and laboratory studies, collection of exposure and other field data, computer modeling, and related biomedical, social, and economic considerations. This proceedings volume, with contributions from invited presentations at the 2011 International Conference on Risk Assessment and Evaluation of Predictions, gives detailed coverage of methods of risk analysis as well as more recent developments in the areas of evaluation and prediction of risks. The conference was organized by the Biostatistics & Risk Assessment Center at the University of Maryland, and was held in Silver Spring, Maryland in October of 2011. This volume will serve as a valuable reference for researchers working in these topic areas.
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