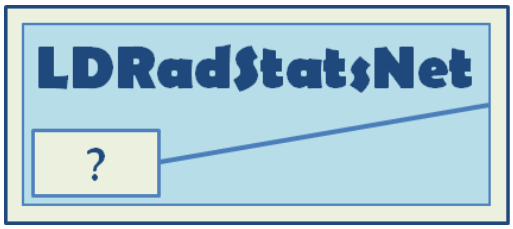

LD-RadStats: Workshop for statisticians interested in contributing to EU low dose radiation research statistical analysis

Introduction

Uncertainties, both quantitative and conceptual in nature, have been identified as key to addressing the remaining research questions in EU low dose radiation research. Sophisticated techniques are in use across the different disciplines, however, there seems to be little commonality and, furthermore, the proportion of individuals with formal mathematical and statistical training seems relatively low. In order to address this, DoReMi collaborators from PHE and CREAL, together with colleagues from Universitat Autonoma de Barcelona (UAB) and Durham University (DU), organized a workshop to bring together researchers from the low dose radiation fields and invited expert mathematicians and statisticians with an interest in applied uncertainty analysis. The meeting was funded with DoReMi internal members paying for themselves, and PHE's WP5 external experts budget paying for non-DoReMi participants to attend. In addition, UAB's Mathematics Research Centre (CRM) funded the attendance of three individuals.

Meeting agenda

The full timetable is attached – however, in brief, the DoReMi low dose radiation experts outlined the key research questions and the associated problems, together with the solutions that are currently being applied in DoReMi and the other EU low dose radiation research consortia, under the general headings of radiation biology, modelling and epidemiology research. The invited external statistical experts then outlined their own current research – the idea being to stimulate exchange of ideas. Focused discussions then took place to attempt to identify areas in which standard or indeed novel statistical methods can be applied to solve EU low dose radiation research questions going forward under MELODI and CONCERT.

Conclusions

1) Uncertainty analysis can contribute to solving the remaining low dose research questions, but certainly not solve the questions alone – multidisciplinary research is key. However, communication in interdisciplinary research can be supported by statistical expertise, e.g. in communication of what information is needed / what is available.
   Conceptualisation of uncertainties can help decision makers – for instance to provide definitions of uncertainty quantification for biological measurements. It helps to better delineate the possibilities of research and supports proper interpretation of evidence. Mathematical models should include mechanisms (knowledge of mechanisms required to eliminate or reduce uncertainty). A good, approximate model can be better than one with a lot of detail (operational vs research view).

Furthermore, quantitative uncertainty assessment is a necessary premise for any validation of techniques or hypothesis.

2) Specific areas to which we can contribute now include:
   - The inverse regression step should be revised. Translation of variability of the response variable to uncertainty of the exposure variable is currently rather primitive although the same problem is expected to be present in various scientific and engineering fields. Thus, it might be worthwhile spending more time in improving this step.
   - Defining biomarkers. In order to increase visibility and support utilization of biomarkers: What is a biomarker and what kind of a biomarker is it. Can we guide the act of producing biomarkers?
   - Including uncertainty in dose estimates into risk estimation, bias from confounding.

3) Training courses could be useful as there is still a need to understand the importance of proper, supportive, statistical analysis in many areas, but a dialogue between the researchers and statisticians is the first goal in contrast to the monologue of conventional training courses. If conventional trainings courses are planned, the target group should be young scientists who are already interested in statistical analysis (as all should be!) e.g. young bioengineers, non-radiation epidemiologists or biostatisticians with an interest in radiation and other potential recruits. Other topics could include uncertainty in cohorts (for modellers), radiation biology for non-biologists, frequently used software (+sharing).

4) Further general workshops similar to LDRadStats 2015 would be highly useful, but with an extended audience of both scientists already working in EU radiation research and new external attendees with statistical backgrounds – to aid networking in this field. In addition, focused workshops would be useful to bring together individuals from different fields, e.g. on measurement error (dose uncertainty) bringing together statisticians from nutritional and radiation epidemiology, for bioinformaticians (biologists who are interested in statistics!), to link to emergency preparadness, and perhaps to consider wider topics, e.g. models other than LNT.

5) The meeting participants all supported continuation of the informal network of scientists interested in the formal analysis of uncertainties in radiation research questions, rather than creation of a formal network at this stage. Ideas included creation of an internet forum where people can ask questions, mailing lists and a database of papers to share knowledge. However, for the network to have an impact, increased visibility of the availability of the informal network as a resource for EU radiation research will be needed – actions 2 – 5 result from this.

Actions

1) The meeting participants will contribute to a special issue of extended abstracts for Research Perspectives CRM Barcelona' subseries of the Birkhäuser's series Trends in Mathematics, to be guest edited by the meeting organisers (Ainsbury, Puig, Einbeck, Cardis). The due date for submissions is mid January, with publication expected in Spring 2016.

2) The informal network will henceforth be called LDRadStatsNet and will be given a logo to aid 'branding' and visibility. Liz Ainsbury (liz.ainsbury@phe.gov.uk) will manage the list of names of network members (one contact name per institute) and will act as an informal contact point through which questions from the community can be addressed to the network's members.
   Update 17/12/15 – Initial logo at the top of this report, to be reviewed at next meeting.

3) The meeting report will be sent to the DoReMi MB, presentations will be placed online, and Simon Bouffler (WP 5 lead) will give a brief report on the meeting during his WP5 presentation at the DoReMi final meeting. Update 17/12/15 – this action is complete.

4) The possibility to set up meetings on a semi-regular basis - for instance by teleconference once every 6 month – will be explored. In that case, meetings would be advertised and open to everyone interested (for instance scientists from DoReMi who have a statistical problem), but young scientists would be particular welcome.

5) Other possibilities to support communication and collaboration on a case-by-case basis will be further explored.

6) The possibility to set up another LDRadStats meeting in 2016 or 2017 will be explored. Update 17/12/15 – Meeting at Radiation Protection Week 2016 has been proposed.

7) The possibility to set up a training course under CONCERT will be explored (lead David Morina, CREAL). Update 17/12/15 – A course on epidemiological uncertainties has been submitted to the CONCERT E&T call.

8) The possibility to set up collaborative projects under CONCERT will be explored, the key point being that statistical development should be on the basis of formal project participation with participants receiving funding. Potential topics include:
- Guiding the translation of uncertainties in its pipeline/process from fundamental research towards radiation process.
- Guiding the translation of uncertainties from biomarkers towards epidemiology or other fields applying biomarkers.
- Ethical questions related to the prior elicitation in Bayesian analysis applied in emergency scenarios. How can users be trained in choosing priors and what are the risks?
- Biomarker development.
- Assessing the targets of low dose research.
- Uncertainty in doses.
- Developing measures to quantify and characterize the nature of uncertainties (this will support the identification of boundaries that can be excluded, potentially shed light on current disconnect non-linearity at high doses vs no evidence of non-linearity at low doses).
- Use of methods for interval censored covariates or cure models.
- Uncertainties in the Wismut cohort (already planned, extend).

9) Future work might include looking to formalize the network, perhaps as a named ‘infrastructure’ under CONCERT.

DoReMi LD-Radtat: Workshop for statisticians interested in contributing to EU low dose radiation research

CREAL, Barcelona - 26th to 28th October 2015

Timetable

Note on locations:

The workshop will take place in the Xipre Room at CREAL (www.creal.cat/enindex.html), which is on Barcelona Biomedical Research Park (http://www.prbb.org/), Carrer del Dr. Aiguader, 88 08003 Barcelona, Spain.

Registration, coffee breaks and lunch will take place on the first floor terrace.

Monday 26th October 2015 – DoReMi, Radiation biology and related applications

08:00 – 09:00: Registration and coffee

09:00 – 09:30: Welcome and introduction to DoReMi – Liz Ainsbury
09:30 – 10:00: Perspectives on low dose epidemiological studies - role of uncertainty – Elisabeth Cardis
10:00 – 10:30: Biological dosimetry – statistical challenges – Paco Barquinero/Pere Puig

10:30 – 11:00: Coffee

11:00 – 11:30: Bayesian solutions to biodosimetry count data problems, and software solutions – Manuel Higueras
11:30 – 12:00: Applications of count data distributions to radiation biology – Jochen Einbeck
12:00 – 12:30: Pitfalls of stochastic biomarkers: disregarding intrinsic variation – Daniel Samaga

12:30 – 13:30: Lunch

13:30 – 14:00: Heterogenous correlation of multi-level omics data for the consideration of inter-tumoural heterogeneity – Herbert Braselmann
14:00 – 14:30: Biophysical Monte Carlo modelling of irradiated cells – Krzysztof Fornalski
14:30 – 15:00: Semiparametric discrete kernel estimations for count data – Celestin Kokonendji

15:00 – 15:30: Coffee

15:30 – 16:00: Overview of topics related to model selection for regression - Riccardo De Bin
16:00 – 16:30: Data Integration in Early Drug Developments – Adetayo Kasim
16:30 – 17:00: A brief outlook of mathematical tools to deal with imprecise (quantitative or structural) knowledge – Eric Chojnacki

17:00 – 17:30: Overview of Day 1, discussion and questions

20:00: Dinner at Attic Restaurant, 120 Las Ramblas (http://www.atticrestaurant.cat/)

Tuesday 27th October 2015 – Epidemiology and modelling

09:30 – 10:00: Dose uncertainty, MCML and sampling density– Graham Byrnes
10:00 – 10:30: Statistical analysis of German uranium miners cohort – Christina Sobotzki

10:30 – 11:00: Coffee

11:00 – 11:30: EPI-CT – statistical challenges in a European study on radiation exposure from pediatric CTs and cancer risk– Michael Hauptmann
11:30 – 12:00: Dose-responses for cerebrovascular and heart diseases in atomic bomb survivors – an analysis involving multi-model inference techniques – Helmut Schöllnberger
12:00 – 12:30: Modelling radiation induced atherosclerosis in ApoE-/- mice– Fieke Dekkers

12:30 – 13:30: Lunch

13:30 – 14:00: Mechanistic analysis of lung cancer mortality in the Wismut cohort – Ignacio Zaballa
14:00 – 14:30: R implementation of the linear ERR model: applications to radiation epidemiology - David Morina
14:30 – 15:00: Bioinformatics Data Analysis in Radiation Epidemiology – Juan Ramon González

15:00 – 15:30: Coffee

15:30 – 16:00: Bayesian dose-response analysis for epidemiological studies with complex uncertainty in dose estimation - Deukwoo Kwon
16:00 – 16:30: MC modelling of initial radiation effects with PARTRAC – Elke Schmitt
16:30 – 17:00: Uncertainties in dose reconstruction and their impacts on radiotherapy late effects dose-response relationships - Rodrigue Allodji and Jeremy Bezin
17:00 – 17:30: Approaches for taking into account the heterogeneity of the dose-distribution in organs when estimating the risks – Florent De Vathaire
17:30 – 18:00: Overview of Day 2, discussion and questions

Wednesday 28th October 2015 – The way forward

09:00 – 13:00: Parallel breakout sessions to discuss how uncertainty analysis techniques in the context of each discipline can help solve DoReMi research questions going forward
Session 1: Radiation biology
Session 2: Epidemiology
Session 3: Modelling

Coffee will be available at 10:30.

12:30 – 13:30: Lunch

13:30 – 15:00: Reports from breakout sessions and group discussion on next steps – submission of extended abstracts to 'Research Perspectives CRM Barcelona;' formalisation of the network and/or a research proposal to CONCERT?

15:00: Close