Methodology: Realistic Estimates of prediction uncertainity from ML

zk: Can we derive composite measures to reduce uncertainty/cope with missingness?

Conformal Prediction looks an exciting approach - how well developed and accepted is this? or is this still a rapidly maturing area for active research?

HH: What is a relevant benchmarking dataset or synthetic dataset to test/validate the proposed methodology for "uncertainty from ML"

HH: Can we narrow-down what specific ML task the R-T partnership is interested in?

CHa : This paper : https://doi.org/10.1016/j.annonc.2020.07.013 may give an idea of an application. We would also be interested in doing the same concept with larger-p datasets (genomics, imaging etc)

HH: What expertise is on the panel using Bayesian + ML for uncertainty quantification? Could this person present state-of-the-art? Or case study?

MRB: Prediction uncertainty is likely to be driven by hidden biases in training, test and validation. How can these be minimised and bias detected?

AF: How do we propagate uncertainty downstream? How we deal with uncertainty in heterogenous ML pipelines with different ML models (eg statistical ML, deep learning, etc)

CHa : How do we deal with uncertainty of variables being incorporated downstream into other models?

CHa : How to deal with population (domain) shifts e.g. over time or between regions?

CHa : How do we deal with uncertainty inherent in our data (esp RWD) e.g. abstracted and extracted variables

AF: How do we identify whether epistemic vs aleatoric uncertainty dominates our problem? Best practices?

AF - Standards - distil relevant aspects for the modelling work we undertake in the partnership? e.g., ASME V&V 70 https://cstools.asme.org/csconnect/CommitteePages.cfm?Committee=103099834&Action=54642

CHa:What practice? Opportun influence Health Authority policy

Policy: Validation of Prognostic/Predictive Models

zk: how do we validate early prediction models in preclinical populations?

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CHa :What is best practice? Opportunity to influence Health Authorities?

MRB: Validation is probably dependent on Explainability, how can this be maximised? E.g. using Shapley plots to highlight areas for validation https://www.sciencedirect.com/science/article/pii/S0957417421002736

HH: Are there validation case-studies of prognostic/predictive models?

benchmark and challenges in predictive models. See for instance MICCAI https://grand-challenge.org/challenges/ but also https://pubmed.ncbi.nlm.nih.gov/32911207/ and https://pubmed.ncbi.n

HH: Is there a specific case study of interest?

HH: What type of data and/or model does the R-T have in mind?

MRB: Validation is probably dependent on Explainability, how can this be maximised? E.g. using Shapley plots to highlight areas for validation https://www.sciencedirect.com/science/article/pii/S0957417421002736

Methodology: Multi-Modal Data

AF - Multimodal data never gets all collected at once, but through a sequence of examinations to narrow down diagnostic/prognostic decision uncertainty. What is the optimal multimodal sequence?

AF - how do we build predictors that can make inferences even when some modalities are missing?

zk: Can we use multimodal data to identify/profile new disease subtypes?

zk: Can we optimise predictive assays for different disease stages?

GJ: "Deep" matching of patient profiles not just on clinical, but multimodal data. Does a multimodal approach allow us a more complete matching, so eg a hybrid control from RWE is "closer" to the trial population we are comparing to?

GJ: At individual patient level, can we predict risk of future events from currently available modalities earlier and/or more reliably than with single modalities?

GJ: Can we evaluate error propagation throughout the modalities into the final prediction eg of progression?

MRB: Lots of hype around multi-omics has not delivered. Can we perform a meta-analysis of multi-omic studies to define the most productive multi-modal interfaces?

MRB: Microarrays, Bulk tissue RNAseq and Single cell can all be used to study the same sample but differ widely in results, can we understand and normalise across such data types?

MRB: Can we define/generate gold standard multi-modal data sets for method development?

Dan: How do we integrate multimodal data so they can reinforce each others' evidence for/against a biological hypothesis (e.g. RNA/protein expression in pathways)?

CHa : How much value does multi-modal data add in addressing these questions? How much additional information does it need to add to overcoming the added complexity?

HH: It might be worth brainstorming together the specific questions to answer with multi-modal data?

HH: We used a tensor data structure in two different multi-modal datasets, I wonder if this is useful for the R-T partnership questions?

AKn: Can multi-modal data help us identify high/low risk patients and patients most likely to respond well to certain therapies?

AKn: Can multi-modal data help us overcome challenges associated with disease heterogeneity?

AKn: Can multi-modal data help us predict recurrence/progression patterns e.g. development of CNS metastases?

Methodology: Prognostic/Predictive Modelling (Health Status Metric)

HH: What type of models are best suited to prognostic predictive modelling (compare different methodologies)

HH: What is a suitable valideation/testing/benchmarking system for prognostic/predictive modelling?

AKn: Similar questions to those posed on board #3

AF - indeed, do not understand how this dfferes from board 3.

Tackling difficult issues in Computational Pathology

zk: Can predictive models help us understand disease pathology/make causative inferences?

HH: Can we create an end-to-end pipeline that highlights the different computational/metho dological/data reearch questions?

HH: the difficult issues are likely dependent on the system of interest. Can the R-T partnership pin down a concrete instead of abstract problem/dataset?

Dan: How can we integrate different modalities (e.g. H&E, IHC, spatial-omics) from the same patient?

Dan: Pathologists integrate info across scales, whereas end-to-end ML approaches typically work at one scale (pixel level). Would multi-scale approaches be advantageous? (e.g. U-Net)

MRB: Most computational pathology originates from the NHS. There are considerable barriers, including research environments and GDPR. Can technical solutions address this?

MRB: Pathology imaging depends on robust image patching, however public domain tools, like clam (http://clam.mahmoodlab.org/) struggle with some image/tissue types. Are other solutions available?

MRB: CAn we develop portable, standardised pipelines for pathology image analysis?

Dan: How important is color calibration/normalizati on to computational pathology?

Dan: How do we best integrate clinical variables (e.g. age, sex, cancer staging) with spatial data in deep learning architectures?

Early life predictions, following life trajectories

AKn: Are we thinking here about enhancing screening/surveillance approaches that currently exist?

AF - how do we update early life predictions as a patient's record gets "enhanced" with additional evidence/examinations? How we develop systems open not only to new data, but also to new modalities?

zk: how early can we predict? do the predictors/combinations of features change at different stages of disease?

zk: can we predict change in individual trajectories rather than clinical labels to reduce misdiagnosis?

HH: I have little experience in this domain, so I look forward to learning more about these questions.

MRB: Some promise with deep diffusion processes (DDP) to model the temporal relationships between disease onset expressed as a dynamic graph. http://proceedings.mlr.press/v108/qian20a/qian20a.pdf

MRB: EHR time course can be studied as a point process, using methods to Balance likelihood of already observed events with prediction of future events. See Work of Turing Fellow Mihaela van der Schaar,

Methodology: Knowledge Graphs

AF - How do we incorporate "prior mechanistic" information in prediction models. This is interesting justification of why you may want to do this https://www.nature.com/articles/s42256-019-0077-5

MRB: Lots of AI SMEs are using Knowledge graphs, how do these compare to other methodologies, what are the benefits and weaknesses?

What concrete question does the R-T partnership hope to answer with KG? This will then determine what are the nodes and edges of the KG.

MRB: Do open source knowledge graph frameworks exist?

Detecting Confounders/Matching populations

HH: I have little experience with this topic. I look forward to learning more and contributing once the questions are more concrete.

zk: how do confounders impact model generalisation across populations?

MRB: Do clinical trial methodologies like propensity score matching have a broad application in better matching populations for ML?

Creating virtual populations

AF - How do we quantify the coverage of a virtual population wrt to the target real population in typical RWE settings?

AF - How do we create generative virtual populations of digital twins based on large multimodal datasets of datasets?

MRB: Obvious opportunities to consider digital twins here? Can we use digital twins to maximise treatment arms of clinical trials?

Adam Knott

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Would be suitable to start a major research project in this area e.g may be suitable for our workshop/funding call model

'Deep' matching of patient profiles on multi-modal data (not just clinical). Does this approach allow us more complete matching e.g a hybrid control from RWE is 'closer' to the trial population we are comparing to?

Would developing multi-scale approaches/models be advantageous (e.g in pathology?)

How do we incorporate 'prior mechanistic' information into machine learning models?

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Can we use multi-modal data to address questions such as predicting recurrent regression patterns, identifying high or low risk patients?

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Can machine learning models help decipher disease mechanisms?

How do we best integrate clinical variables (e.g age, sex, cancer staging) with spatial data in deep-learning architectures?

Lower priority for Partnership/Roche

Medium priority for Partnership/Roche

High priority for Partnership/Roche

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* these may be related

Florian Markowetz

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