

The Challenge of Precision Medicine in Oncology: Bayesian Solutions for a Changing Landscape in Health Technology Assessment

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- Focus of drug development on targeting specific mutations or biomarkers is leading to challenges for health technology assessment (HTA):
 - Sparse or disconnected evidence networks in network meta-analysis (NMA)
 - Limited sample sizes and growing use of single-arm phase-II trials with external control arms in HTA submissions[1]
 - Reliance on immature overall survival data for survival extrapolations used in economic modelling[2]
- Goal of this talk will be to outline some of the ways that Bayesian methods are being used to leverage limited and disparate data sources to address these challenges
- Loosely based on our paper Mackay EK, Springford A. Evaluating treatments in rare indications warrants a Bayesian approach. *Frontiers in Pharmacology*. 2023.

Motivation for Bayesian Approaches (1 / 2)

- In many rare cancer settings strong structural assumptions need to be made to draw inferences due to
 - ① small sample sizes,
 - ② lack of a concurrent control arm,
 - ③ lack of a common comparator for indirect treatment comparisons, and
 - ④ limited follow-up for survival endpoints
- Bayesian approaches are well-suited to synthesizing information across **multiple disparate data sources** under **flexible structural modelling assumptions**, including incorporation of **aggregate data** or **elicited information** from experts

Motivation for Bayesian Approaches (2 / 2)

- Bayesian approaches have seen uptake in many areas related to HTA:
 - For constructing hybrid or fully-external control arms
 - To synthesize aggregate and individual patient data for population-adjusted indirect comparisons
 - In network meta-analysis (NMA), including newer approaches to network meta-regression and incorporation of non-randomized studies into NMA
 - Incorporation of external information to inform long-term survival extrapolations for economic modelling
- Potential motivators:
 - **Ease of implementing complex structural models** in Bayesian computational/software tools
 - Posterior inference allows for **nuanced decision making** in post-hoc analyses for HTA
 - **Ease of propagating uncertainty** through to economic modelling via posterior sampling
 - **Priors may be used as regularizers** to mitigate overfitting and **allow for scenario analysis** in very small sample settings

Information Borrowing to Improve Survival Extrapolations

- Challenge of estimating long-term survival for economic modelling when extrapolating from immature overall survival (OS) data in oncology trials
- Growing use of methods to incorporate external information into parametric survival models, including via Bayesian approaches[4]
 - Constructing priors for model parameters using historical trials / real-world data (RWD)
 - Partial pooling of information across trials/data sources via Bayesian hierarchical models
 - Constructing priors via expert elicitation

Example 1: Prior Informed by Historical Trial Data

- Soikkeli et al.[5] sought to improve OS extrapolations from the 30-month data cut of the VISTA trial
- RCT comparing bortezomib plus melphalan and prednisone (VMP) vs. melphalan and prednisone alone (MP) in previously treated transplant-ineligible multiple myeloma patients
- They model OS for patient i under a Weibull proportional hazards model:

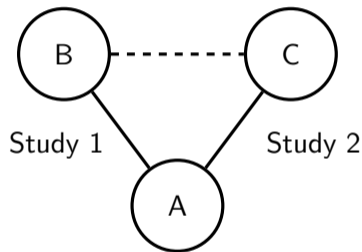
$$T_i \sim \text{Weibull}(\lambda_i, \alpha)$$
$$\ln(\lambda_i) = \mu + \delta \cdot a_i$$

where $a_i \in \{0, 1\}$ is a treatment arm indicator, and μ and δ parameters.

- They construct an informative gamma prior for the α shape parameter by moment matching the shape parameter posterior for a Weibull model fitted on historical trial data for MP, and use diffuse priors for μ and δ

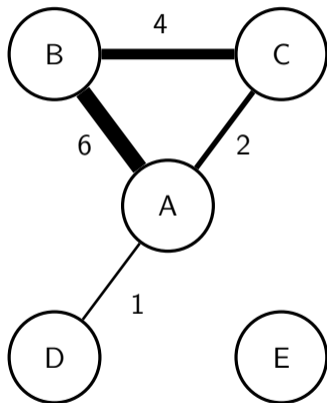
Incorporating Disparate Data Sources into Network Meta-analysis

- Network meta-analysis (NMA) is routinely applied to synthesize evidence from both **direct (within-trial)** and **indirect (between-trial)** comparisons
- E.g. suppose we have two RCTs comparing treatments B vs. A and C vs. A



- Assuming **constancy of relative treatment effects**, we can estimate the treatment effect for C vs. B (e.g. the log odds ratio) as $d_{BC} = d_{AC} - d_{AB}$ (**fixed effects** model)
- We can slightly relax the constancy of relative treatment effects under an exchangeability assumption (**random effects** model)

Incorporating Disparate Data Sources into Network Meta-analysis



- However, with very narrowly defined indications in oncology we can easily end up with sparse or disconnected networks
- Without a common comparator to anchor an indirect comparison, we need to make the very strong assumption that all prognostic factors are balanced between trials (rather than effect modifiers alone)

- Potential for incorporation of non-randomized studies (NRS) into NMA to address challenges of sparse or disconnected networks[6], including:
 - Use of informative priors based on NRS
 - Hierarchical models which allow for partial pooling across study designs (RCT vs. NRS)
 - Incorporation of an adjustment for systematic and/or non-systematic bias for NRS
- Partial pooling of information across different drugs within the same class in a NMA[7]

Example 2: NMA with Hierarchical Borrowing within a Drug Class

- Heeg et al.[7] conduct a Weibull mixture-cure model (MCM) network meta-analysis (NMA) in second-line non-small cell lung cancer (NSCLC)
- The Weibull MCM is a mixture model that assumes that a subset of the population is cured (or at least long-surviving)

- With survival function

$$S(t|\pi, \lambda, \alpha) = \pi + (1 - \pi)S^{weib}(t|\lambda, \alpha) \quad \lambda > 0, \quad \alpha > 0, \quad 0 \leq \pi \leq 1$$

- MCMs have seen uptake in modelling survival for immunotherapies as a subset of patients appear to achieve durable response
- Difficult to estimate cure fraction parameter π with immature data

Example 2: NMA with Hierarchical Borrowing within a Drug Class

- They estimate their Weibull MCM NMA model on a network of RCTs comparing docetaxel chemotherapy vs. the immunotherapies pembrolizumab, nivolumab, and atezolizumab
- As the tails of the survival curve (and consequently the cure fraction π) have a major impact on mean survival and economic evaluations, they allow for information borrowing across immunotherapies to improve estimates for the cure fraction via an exchangeability assumption
- Cure fraction estimates for atezolizumab increase when more within-drug-class borrowing is allowed

Multilevel Network Meta-Regression (ML-NMR)

- In relapsed or refractory multiple myeloma (rrMM) the disease can become more treatment resistant to various drug classes with subsequent lines of therapy, and PD-L1/PD-1 immunotherapy drugs can be expected to be more beneficial in patients with greater PD-L1 expression
- This can introduce potential challenges of effect modification, compromising anchored indirect treatment comparisons and NMA
- Phillippo et al.[8] have developed a generalization of network meta-regression methods to incorporate partial or complete individual patient data—called multilevel network meta-regression (ML-NMR)—which can be used to adjust for imbalances in effect modifiers across studies

Multi-level Network Meta-Regression (ML-NMR)

- The model incorporates both a likelihood for the IPD:

$$y_{ijk} \sim \pi_{ind}(\theta_{ijk})$$
$$g(\theta) = \eta(\mathbf{x}_{ijk}) = \mu_j + \mathbf{x}_{ijk}^T(\beta_1 + \beta_{2,k}) + \gamma_k$$

and a study-level aggregate data (AgD) likelihood:

$$y_{\cdot jk} \sim \pi_{agg}(\theta_{\cdot jk})$$
$$\theta_{\cdot jk} = \int_{\mathcal{X}} g^{-1}\{\eta(\mathbf{x})\} f_{jk}(\mathbf{x}) d\mathbf{x}$$

- With a reasonable assumption on the underlying distribution of the covariates $f_{jk}(\mathbf{x})$ and a numerical integration marginalization step, adjustment can be made for imbalances in effect modifiers while avoiding aggregation bias (a type of ecological bias)

Example 3: Two Approaches to Unanchored Population-Adjusted Indirect Comparisons for Basket Trials

- Maciel et al.[9] perform an unanchored population-adjusted indirect comparison of adagrasib vs. sotorasib in KRAS^{G12C}-mutation positive NSCLC, CRC, and PDAC tumours using an unanchored ML-NMR approach.
- They estimate an odds ratios (OR) of response for adagrasib vs. sotorasib under a hierarchical model which allows for partial pooling of information across histologies
- As their data only comprises 3 tumour types, their choice of random effect heterogeneity parameter is based on another basket trial (albeit for another drug class)
- The estimated OR for PDAC under a borrowing scenario (Model 1a) is 2.02 (95% CrI 1.14 to 4.05) in contrast with a naive comparison which yielded considerably less precise estimates—OR = 2.15 (95% CrI 0.58 to 8.76)

Example 3: Two Approaches to Unanchored Population-Adjusted Indirect Comparisons for Basket Trials

- Mackay et al.[10] apply a 2-level Bayesian hierarchical model to estimate the OR of response for larotrectinib vs. entrectinib while accounting for differences in histology composition for an unanchored comparison of more than a dozen NTRK-fusion positive solid tumour types
- We found that the posterior probability of superiority for larotrectinib exceeded 80% for all of the included histologies

External or Hybrid Control Arms

- Bayesian borrowing approaches like power priors[11] and meta-analytic predictive (MAP) priors[12] can be used to augment small concurrent control arms in RCTs through dynamic or static borrowing from historical trials or RWD
- Bayesian borrowing has also been applied to augmenting an external control arm constructed from RWD. For example, Strübing et al.[13] used a static power prior to partially borrow information from published aggregate data for a historical trial to supplement a matched external control arm.
- Methods which combine propensity score weighting, matching, or standardization approaches with Bayesian borrowing methods are an active area of research—e.g. propensity-score-based MAP priors[13]

- Bayesian approaches are well-suited to addressing some of the challenges of synthesizing information from disparate data sources that are arising due to a growing focus on precision oncology in drug development
- As a result we are seeing the application of new methods and modelling approaches in health technology assessment settings
- Nuanced quantification of the amount of evidence in favour of a conclusion and the ability to assess sensitivity of results to potentially strong priors under a Bayesian approach can be of particular value for precision oncology settings

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Thank You!

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