Adaptive Platform Trial Scientific Meeting

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CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

Identifying Patient Subgroups with Treatment Effect Heterogeneity

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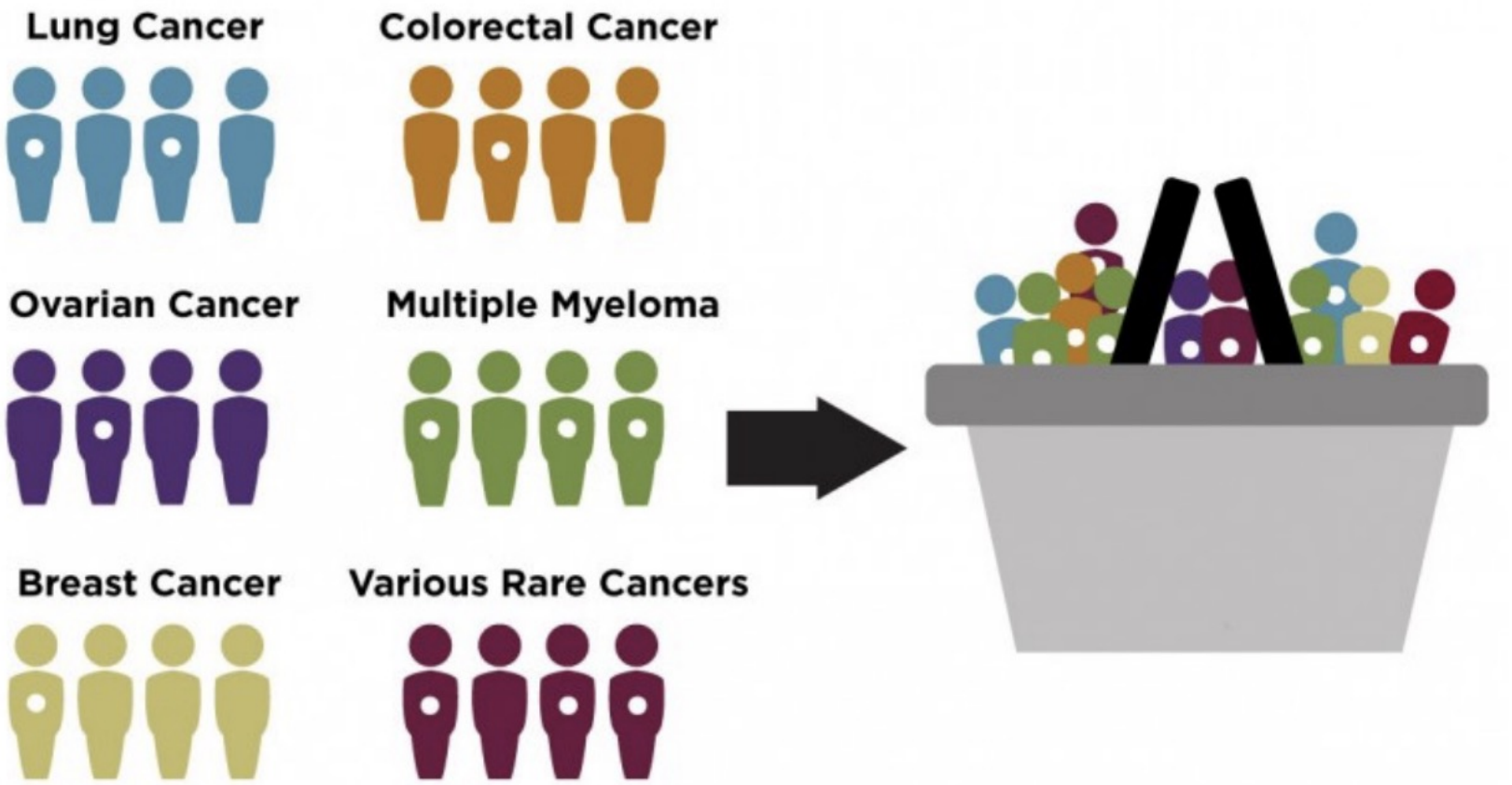
Background

Response Heterogeneity

Response Heterogeneity

Response Heterogeneity



Basket Trials

Response Heterogeneity

- Data:
  - Population can be divided into subgroups
  - Investigated regimen might not be effective in all subgroups
  - Level of response might differ between subgroups
- Goal:
  - Identify for which subgroups the treatment is effective (response rate $\xi_k \geq x$ some threshold)

Aim

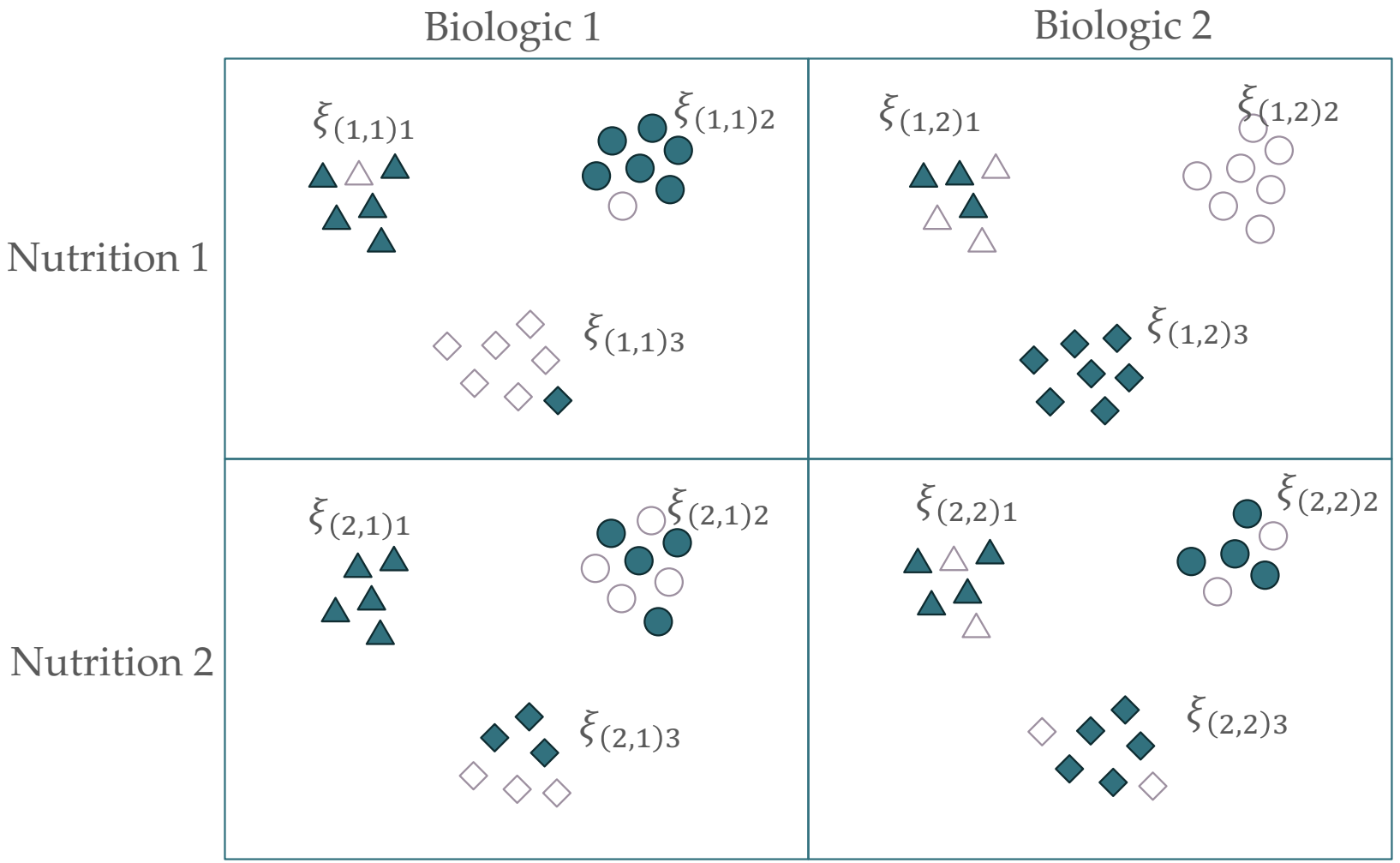
Factorial Design

Factorial Design

- Aim:
  - Identify patient subgroups with heterogeneity in APTs with factorial design
- Motivation:
  - For rheumatoid arthritis, combined therapies from various domains *(biologics/corticosteroids/nutritional supplements):* effective in some subgroups with different levels of effectiveness
  - Identify the predictors determining the effectiveness of combined therapies
- *Example:*
  - *REMAP-CAP explored 240 (=5 antibiotics * 3 extended macrolides * 4 steroids * 4 antiviral therapies) potential regimens with a factorial design on different patient strata*

Factorial Design

Example: 2*2 regimens on 3 biomarker groups



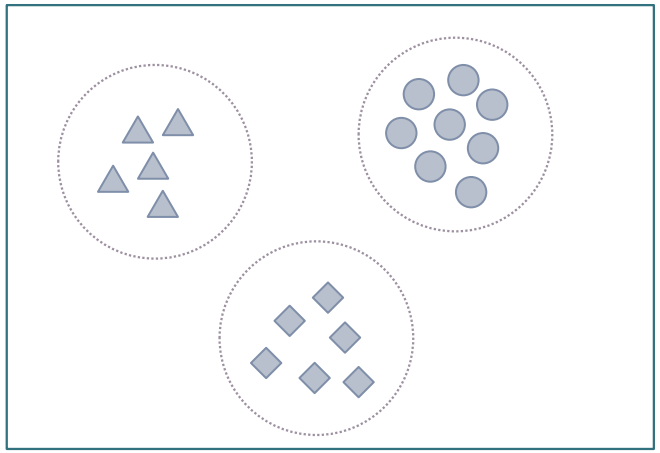
Approach

Bayesian Model Averaging

One regimen
Full Model

- Suppose we only have 1 available treatment on 3 biomarker subgroups
- logistic regression with 1 categorical variable (biomarker group)
- k = 1,2,3

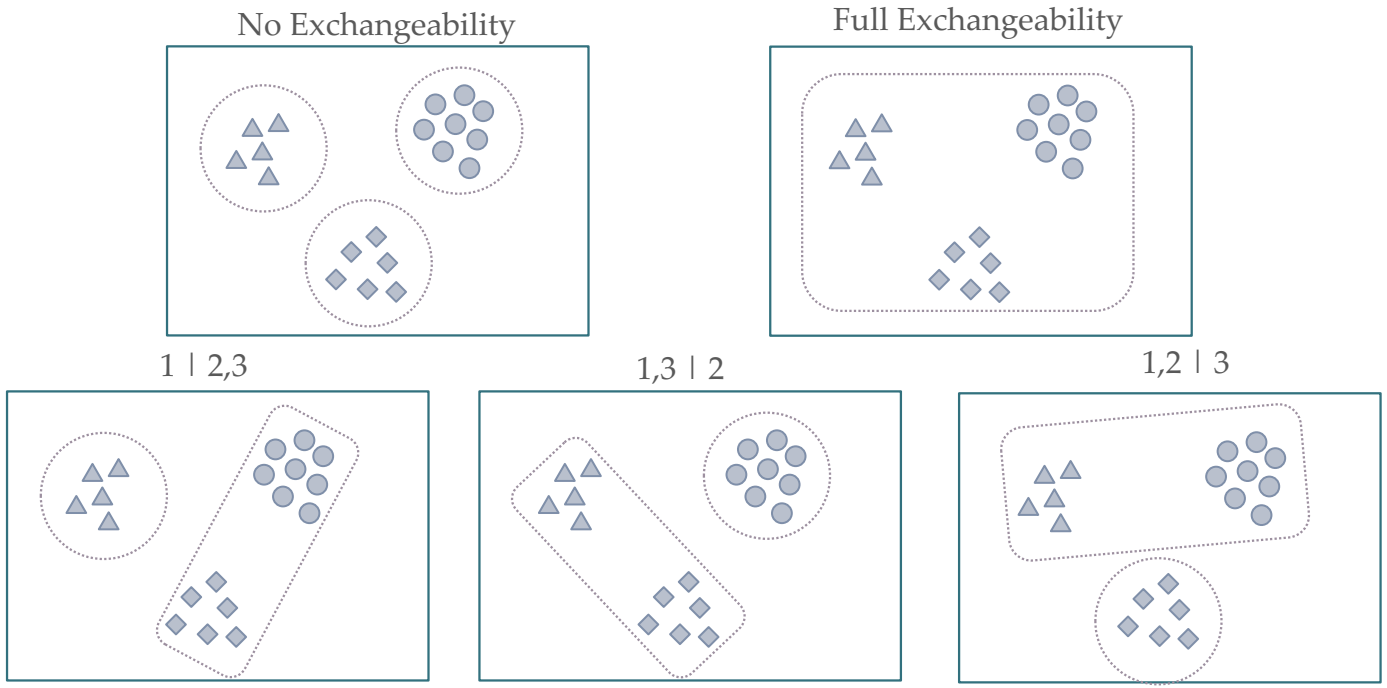
$$logit(\mathbb{E}(Y_{k,i})) = logit(\xi_k)$$
$$= \beta_0 + \beta_2 \mathbb{1}_2 + \beta_3 \mathbb{1}_3$$



One regimen
Full Model

- If we treat subgroups separately, the power might be low
- Allow for information sharing between subgroups
- Uncertainty about scope and strength of information sharing
- Psioda *et al* (2021) proposed Bayesian Model Averaging
  - Synthesizes information from different models
  - Compatible with adaptive design

One regimen
Model Space



- K=3: Complete model space contains 5 models
- Each model partitions population into exchangeable sets
- For each set we estimate one common response rate

One regimen
Model Space

$$logit(\mathbb{E}(Y_{k,i})) = logit(\xi_k)$$
$$= \beta_0 + \beta_2 \mathbb{1}_2 + \beta_3 \mathbb{1}_3$$

$$\eta_2 - \eta_1 = \beta_2 = 0$$
$$\eta_3 - \eta_1 = \beta_3 = 0$$
$$\eta_3 - \eta_2 = \beta_3 - \beta_2 = 0$$

- 0 restrictions
  - Full model
  - No exchangeability
  - 1 possible way to select
- 1 restrictions
  - Reduced model
  - Pool 2 biomarker groups to be exchangeable
  - 3 possible way to select
- 2 restrictions
  - Minimal reduced model
  - Full exchangeability
  - 1 possible way to select
- 1+3+1=5 models

One regimen
Model Averaging

- Prior in the model space:

$$p(\mathcal{M}_m)$$

- Posterior in the model space:

$$p(\mathcal{M}_m|\mathbf{D}) \propto p(\mathbf{D}|\mathcal{M}_m)p(\mathcal{M}_m)$$

- Conditional on model m, posterior probability of efficiency:

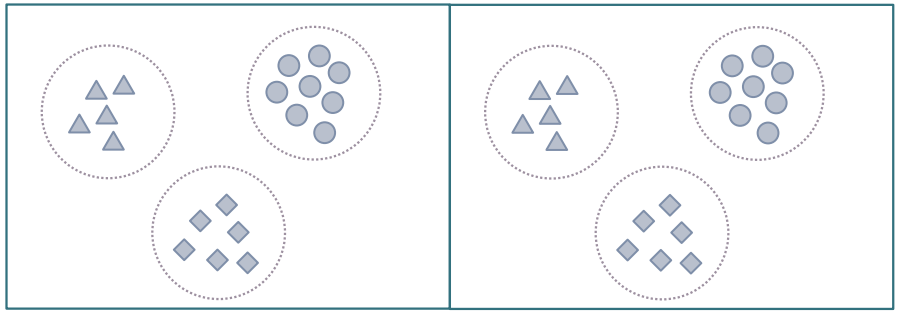
$$P(\xi_k > x|\mathcal{M}_m, \mathbf{D})$$

- Averaging across the model space, posterior probability of efficiency

$$P(\xi_k > x|\mathbf{D}) = \sum_m P(\xi_k > x|\mathcal{M}_m, \mathbf{D})p(\mathcal{M}_m|\mathbf{D})$$

1*2 regimens
Full Model

- Full Model: logistic regression
  - 2 categorical variables: regimen, biomarker
  - Main effect and interaction
- Regimen index j = 1,2
- Biomarker group index k = 1,2,3



$$logit(\mathbb{E}(Y_{(j)k,i})) = logit(\xi_{(j)k})$$
$$= \beta_0 + \beta_2 \mathbb{1}_2 + \beta_3 \mathbb{1}_3 + \beta_{(2)} \mathbb{1}_{(2)} + \gamma_{(2)2} \mathbb{1}_{(2)2} + \gamma_{(2)3} \mathbb{1}_{(2)3}$$

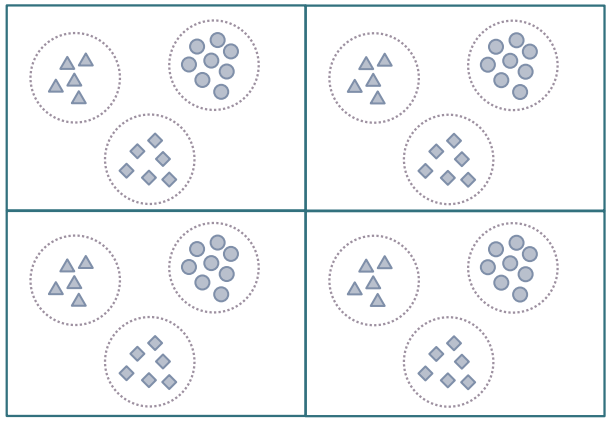
$\mathbb{1}_{k'} = 1$ if the patient is in subgroup k'.

$\mathbb{1}_{(j')} = 1$ if patient is randomized to accept regimen j'.

$\mathbb{1}_{(j')k'} = \mathbb{1}_{(j')} * \mathbb{1}_{k'}$.

2*2 regimens
Full Model

- logistic regression
  - 3 categorical variables
  - 2-way & 3-way interactions
- Regimens: (1,1) (1,2) (2,1) (2,2)
- Biomarker group index: k=1,2,3



$$
\begin{aligned}
logit(\mathbb{E}(Y_{(u,v)k,i})) &= logit(\xi_{(u,v)k}) \\
&= \beta_0 + \beta_2\mathbb{1}_2 + \beta_3\mathbb{1}_3 + \beta_{(\cdot,2)}\mathbb{1}_{(\cdot,2)} + \beta_{(2,\cdot)}\mathbb{1}_{(2,\cdot)} + \delta_{(2,2)}\mathbb{1}_{(2,2)} \\
&+ \kappa_{(2,\cdot)2}\mathbb{1}_{(2,\cdot)2} + \kappa_{(2,\cdot)3}\mathbb{1}_{(2,\cdot)3} + \kappa_{(\cdot,2)2}\mathbb{1}_{(\cdot,2)2} + \kappa_{(\cdot,2)3}\mathbb{1}_{(\cdot,2)3} \\
&+ \gamma_{(2,2)2}\mathbb{1}_{(2,2)2} + \gamma_{(2,2)3}\mathbb{1}_{(2,2)3}
\end{aligned}
$$

$\mathbb{1}_{k'} = 1$ if the patient is in subgroup k'.

$\mathbb{1}_{(u',\cdot)} = 1$ if patient is randomized to accept treatment u' from domain A.

$\mathbb{1}_{(\cdot,v')} = 1$ if patient is randomized to accept treatment v' from domain B.

$\mathbb{1}_{(u',\cdot)k'} = \mathbb{1}_{(u',\cdot)}\mathbb{1}_{k'}$, $\mathbb{1}_{(\cdot,v')k'} = \mathbb{1}_{(\cdot,v')}\mathbb{1}_{k'}$, $\mathbb{1}_{(u',v')k'} = \mathbb{1}_{k'}\mathbb{1}_{(u',\cdot)}\mathbb{1}_{(\cdot,v')}$

$u = 1, 2; v = 1, 2; k = 1, 2, 3.$

2*2 regimens
Model Space

- (2*2 regimen) * 3 biomarker groups
- Each regimen cell has 5 possible partitioning configurations
- Complete model space contains 5^4 models

$$\eta_{(1,1)2} - \eta_{(1,1)1} = 0 \quad \eta_{(1,2)2} - \eta_{(1,2)1} = 0$$
$$\eta_{(1,1)3} - \eta_{(1,1)1} = 0 \quad \eta_{(1,2)3} - \eta_{(1,2)1} = 0$$
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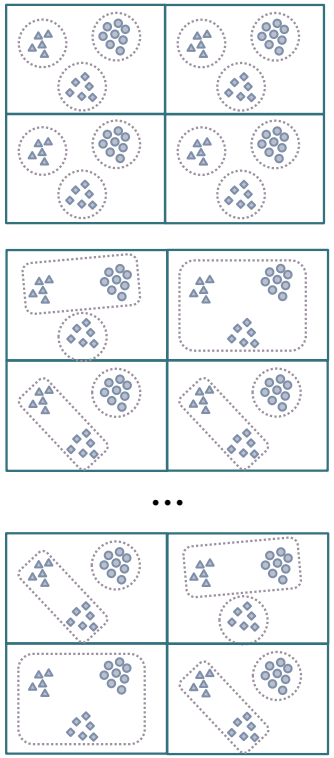

Discussion

Challenges and Plans

Discussion

- BMA was proposed to borrow information dynamically, which performed well for binary (Psioda et al 2021) and continuous outcomes (Bean et al 2023)
  - Conjugate priors: Beta-binomial; Gamma-Normal
  - Averaged the complete model space
- Challenges to expand the method to factorial platform trials
  - No conjugate prior; factorial structure
  - Impossible to explore complete model space
- Plans
  - Used MCMC to estimate one factorial model
  - Next step: reduce computational burden; use specialized MCMC to sample from model space

Thank you

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References

- Angus, Derek C., et al. "The REMAP-CAP (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study. Rationale and design." Annals of the American Thoracic Society 17.7 (2020): 879-891.
- Psioda, Matthew A., et al. "Bayesian adaptive basket trial design using model averaging." Biostatistics 22.1 (2021): 19-34.
- Bean, Nathan W., Joseph G. Ibrahim, and Matthew A. Psioda. "Bayesian multiregional clinical trials using model averaging." Biostatistics 24.2 (2023): 262-276.