The Perils and Pitfalls of Complex Clustering in Pragmatic Trials

November 3, 2023

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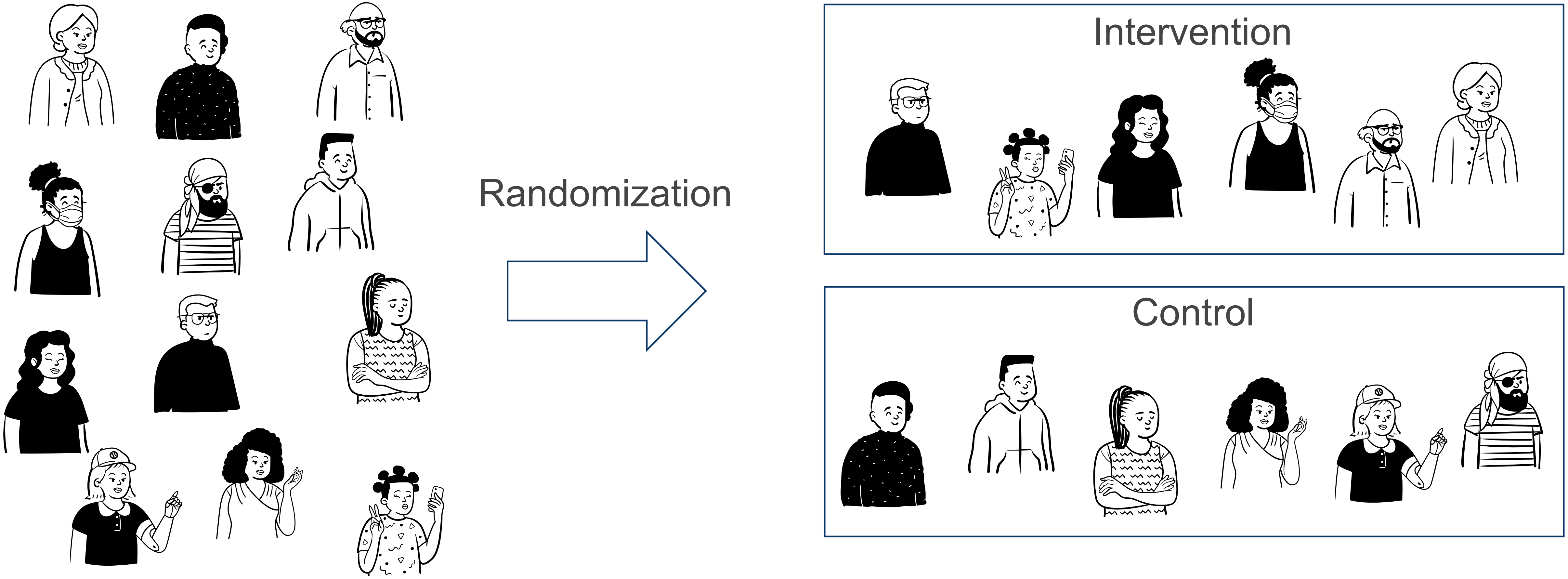
Today’s Presentation

- Introduction
  - Individually Randomized Group Treatment Trials
- Nesting and Membership Structures
- Complex Clustering Simulation Study
  - Methods
  - Results
- Conclusions

- Disclaimer: The views expressed in this presentation are those of the speaker and do not necessarily reflect the position or policy of funding agencies or the U.S. government.

Individually Randomized Trials

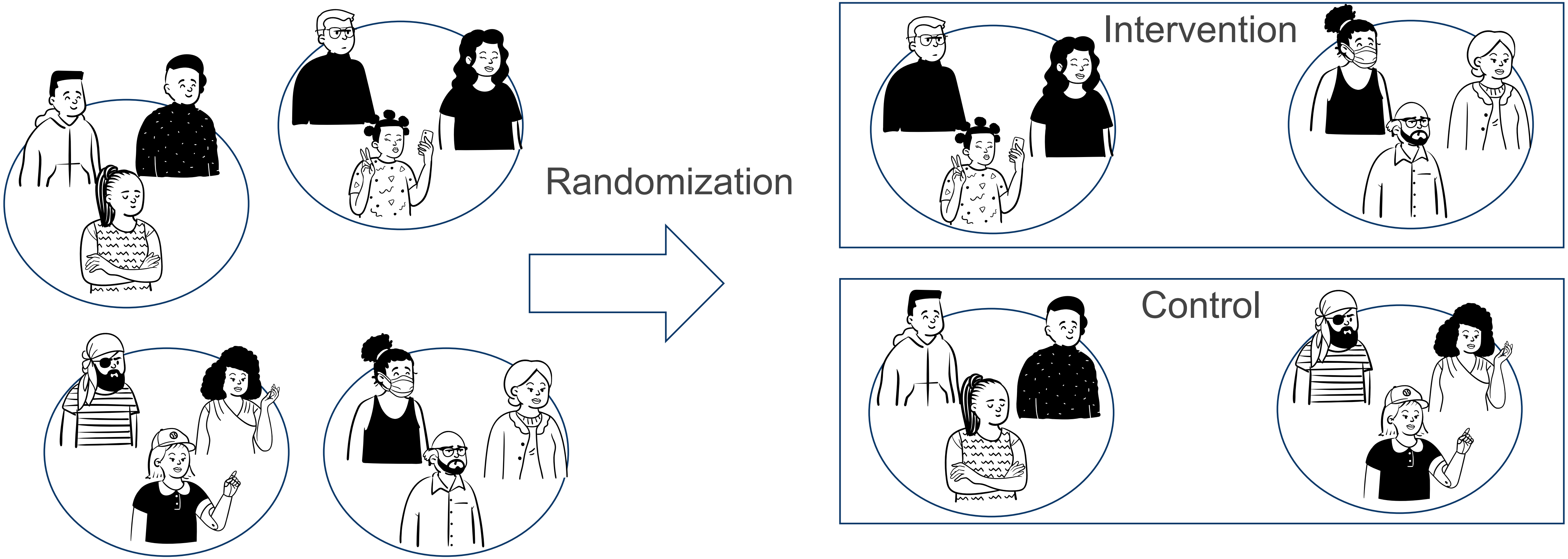
- Individuals are randomized to either control or intervention arms.



- Observations are independent before and after randomization.

Group- or Cluster-Randomized Trial (GRT)

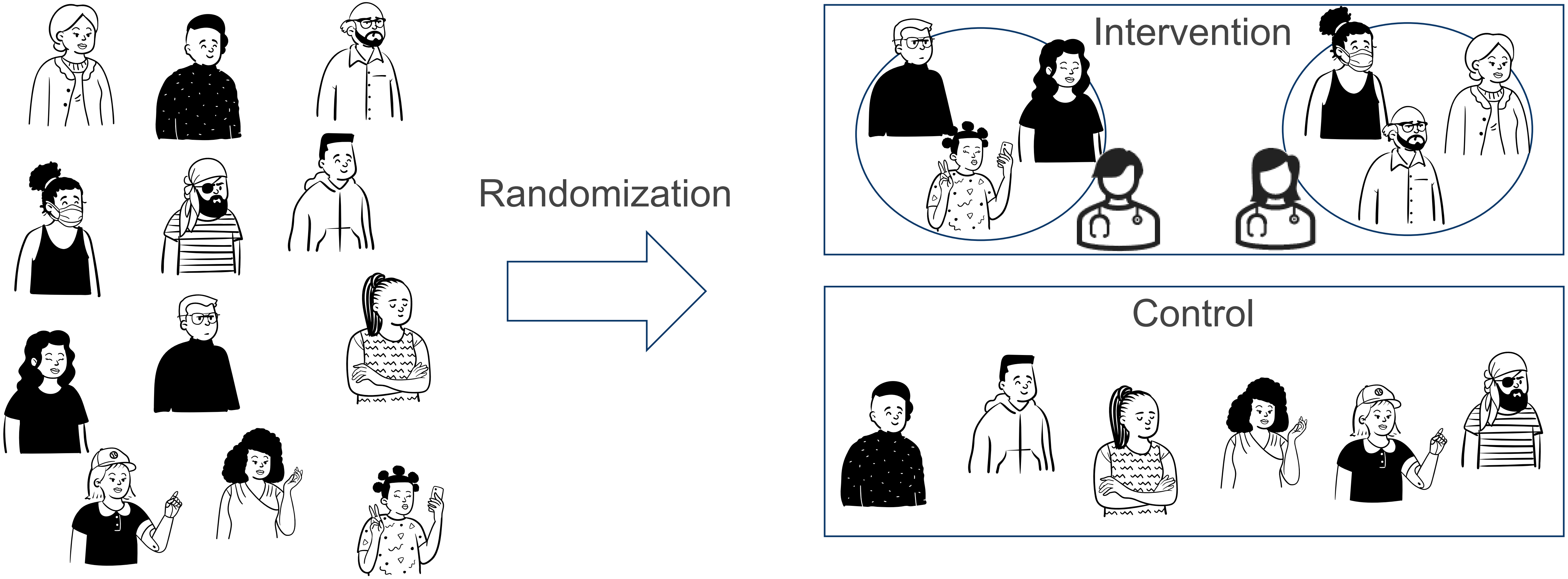
- Pre-existing groups are randomized to either control or intervention arms.



- Observations are correlated before and after randomization.

Individually Randomized Group Treatment (IRGT) Trials

- Individuals are randomized to either control or intervention arms.



- Treatments delivered in groups or via shared intervention agents

Impact on the Analysis in an IRGT Trial

- Connections between participants in the same group or sharing the same agent will create a positive intraclass correlation (ICC) that reflects extra variation attributable to the group or shared intervention agent.
- Failing to account for ICC is well understood to inflate type I error rates in the context of group- or cluster-randomized trials (Murray, 1998).
- Similar type I error rate inflation may be observed with IRGT trials (Pals et al., 2008; Baldwin et al., 2011).
- The potential impact of correlation is acknowledged less frequently in the context of IRGT trials (Pals, et. al. 2011).

- Murray DM. Design and Analysis of Group-Randomized Trials. New York: Oxford University Press; 2018.
- Baldwin SA, et al. Evaluating models for partially clustered designs. Psych Methods. 2011;16(2):149-65. PMID21517179.
- Pals SL, et al. Individually randomized group treatment trials: a critical appraisal of frequently used design and analytic approaches. Am J Public Health. 2008;98(8):1418-24. PMID18556603. Erratum: Am J Public Health. 2008;98(12):2120.
- Pals SL, et al. Ignoring the group in group-level HIV/AIDS intervention trials: A review of reported design and analytic methods. AIDS 2011;25(7):989–96. PMID: 21487252.

Prior Advice for Analysis of IRGTs

- Mixed models are the most common approach, Candlish et al. (2018) provide SAS, R, and STATA code for analyzing IRGT trials.
  - Candlish J et al. Appropriate statistical methods for analysing partially nested randomised controlled trials with continuous outcomes: a simulation study. BMC Med Res Methodol. 2018;18(1):105. PMID: 30314463.
- Methods for sample size estimation for IRGTs have been published.
  - Pals SP, et al. Individually randomized group treatment trials: a critical appraisal of frequently used design and analytic approaches. Am J Pub Health. 2008;98(8):1418-24. PMID18556603.
  - Roberts C, Walwyn R. Design and analysis of non-pharmacological treatment trials with multiple therapists per patient. Stat Med. 2013;32(1):81-98. PMID22865729.
  - Moerbeek M, Teerenstra S. Power analysis of trials with multilevel data. Boca Raton: CRC Press; 2016.
  - Hemming K, et al. A tutorial on sample size calculation for multiple-period cluster randomised parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. Int J of Epi. 2020;49(3):979-95. PMID32087011.
  - Teerenstra S, et al. Sample size for partially nested designs and other nested or crossed designs with a continuous outcome when adjusted for baseline. Stat Med. 2023;42(19):3568-92. PMID: 37348855.

Prior Advice for Analysis of IRGTs

- The initial literature assumed that each participant interacted with only one agent and that agents were independent.
  - These patterns may not hold in practice and failure to model the correct pattern can lead to an inflated type 1 error rate.
  - Several authors have since described models that address some of these complex design features.

- Roberts C, Walwyn R. Design and analysis of non-pharmacological treatment trials with multiple therapists per patient. Stat Med. 2013;32(1):81-98. PMID22865729.
- Luo W, et al. Modelling partially cross-classified multilevel data. Br J Math Stat Psychol. 2015;68(2):342-62. PMID25773173.
- Cafri G, et al. An introduction and integration of cross-classified, multiple membership, and dynamic group random-effects models. Psychol Methods. 2015;20(4):407-21. PMID: 26237504.
- Sterba SK. Partially nested designs in psychotherapy trials: A review of modeling developments. Psychother Res. 2017;27(4):425-36. PMID26686878.
- Candlish J, et al. Appropriate statistical methods for analysing partially nested randomised controlled trials with continuous outcomes: a simulation study. BMC Med Res Methodol. 2018;18(1):105. PMID30314463.
- Brown CH, et al. Accounting for Context in Randomized Trials after Assignment. Prevention science. 2022;23(8):1321-32PMID: 36083435.

Questions about Complex Clustering in IRGT Trials

- What happens when participants interact with multiple intervention agents?
- Does it matter if the multiple agents are nested within arm or if the same agents interact with participants in both arm?
- If limited resources allow for only one agent to deliver treatments, what is the impact?
- What is the performance of simpler analytic models when applied to data with complex clustering?

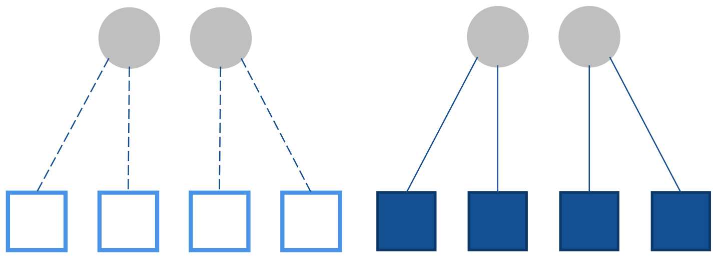
Limitations of the Existing Literature

- The literature for IRGT trials has continued to assume:
  - Intervention agents operate only within the intervention arm.
  - There are several agents implementing the intervention.
- There are other structures that the existing literature has addressed in isolation, but not in a comprehensive way.
  - Nesting Structure: Fully Nested, Partially Nested, Crossed
  - Membership Structure: Multiple Membership, Single Membership, Single Agent
- We undertook an extensive simulation study to evaluate the impact of ignoring or misrepresenting agents in a variety of settings.
  - Evaluate models for Fully Nested, Partially Nested, and Crossed designs.
  - Evaluate models for Multiple Membership, Single Membership, and Single Agent.
  - Evaluate fixed effects vs random effects for agents in a Crossed design.
- Our focus was assessing type I error rates for various configurations.

Nesting Structures

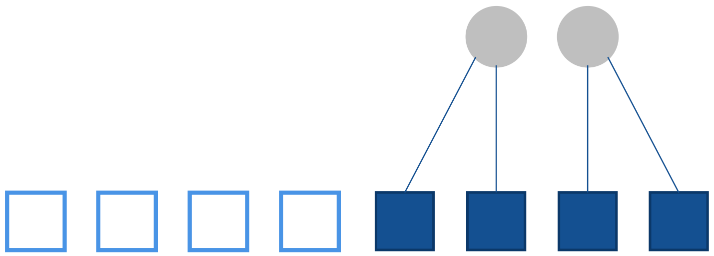
- Three data structures that are present in IRGT trials.

Fully Nested



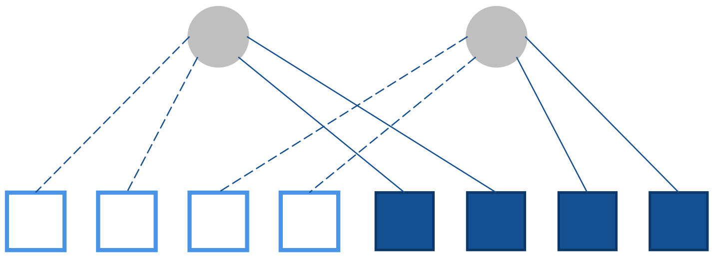
Agents are present in both arms, each agent only interacts with participants in a single arm.

Partially Nested



Agents are present in one arm only.

Crossed

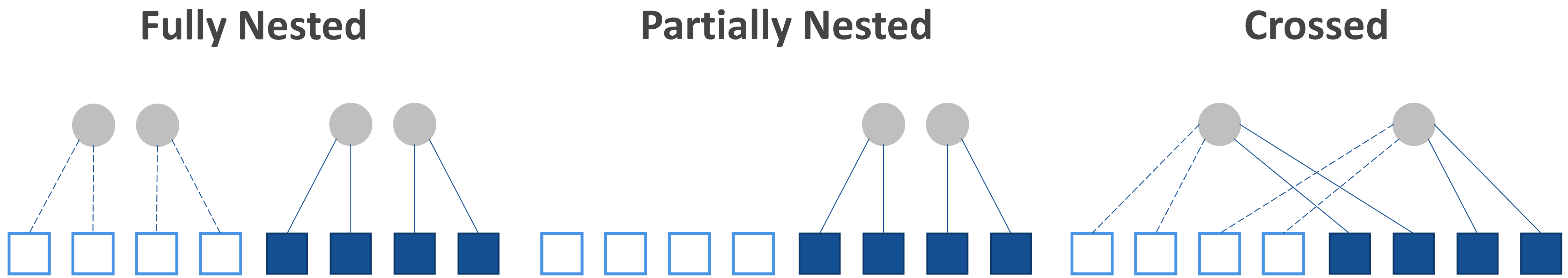


Same agents interact with participants in both arms.

Intervention Agent ● Control Participant □ Intervention Participant ■

Membership Structures

- Participants may interact with one or more agent.

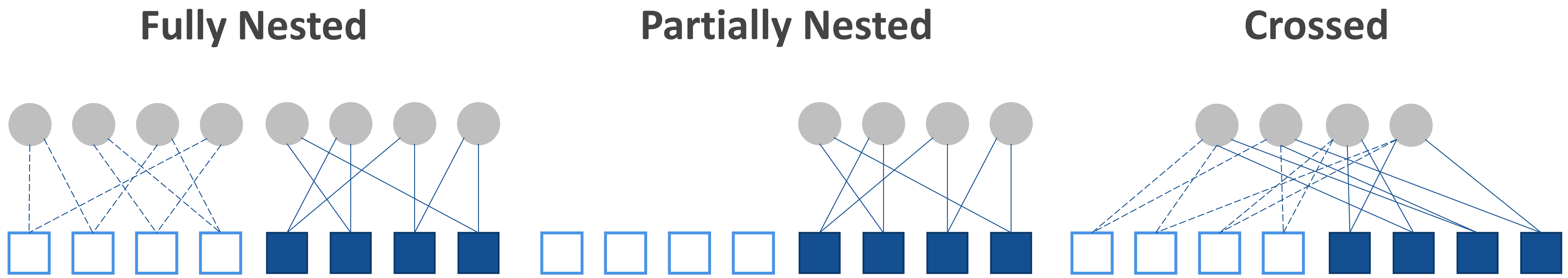


- **Single Membership:** Each participant interacts with one agent.
- Corresponds to conventional methods for IRGT trials (and GRTs).

Intervention Agent ● Control Participant □ Intervention Participant ■

Membership Structures

- Participants may interact with one or more agent.

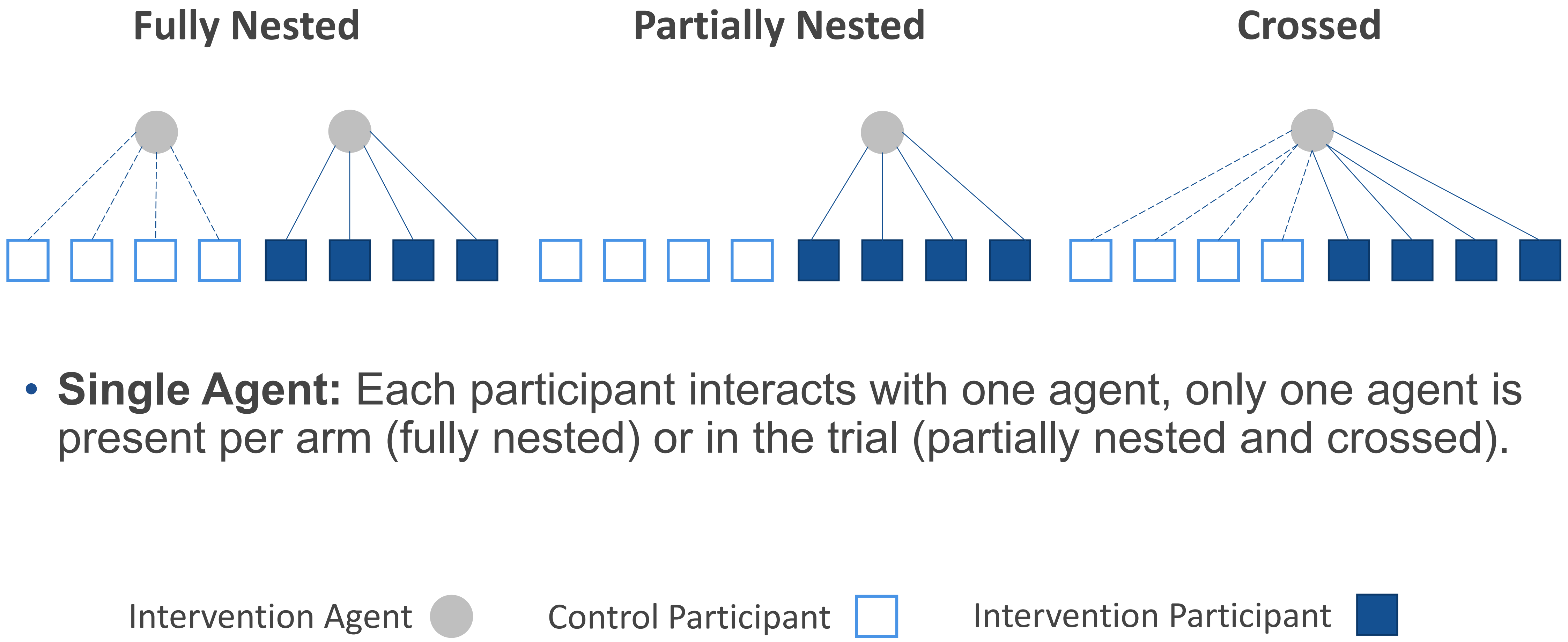


- **Multiple Membership:** A participant may interact with more than one intervention agent.

Intervention Agent ● Control Participant □ Intervention Participant ■

Membership Structures

- Participants may interact with one or more agent.



- **Single Agent:** Each participant interacts with one agent, only one agent is present per arm (fully nested) or in the trial (partially nested and crossed).

Statistical Models

- Intervention agents are traditionally represented with random effects in linear mixed models.
  - Representing nested agents with fixed effects can result in inflated type I error rate (Zucker, 1990).
- In Multiple Membership structures, random effects for agents are weighted.
  - Reflects the proportion of treatment a participant receives from an agent.
  - Agent weights are between 0 and 1, and for a given participant, all weights sum to 1.
  - Exogenous Weights: Weights are specified using some external factor with strong theoretical justification.
  - Endogenous Weights: Weights are determined empirically by assessing several different possibilities and choosing the best set based on some criterion.
- Expressions for ICC are more complicated with Multiple Membership structures.
  - ICCs found for pairs of agents, value of each ICC depends on the agent weights.

- Zucker DM. An analysis of variance pitfall: The fixed effects analysis in a nested design. Educ and Psych Measurement. 1990;50(4):731-8.

Complex Clustering Simulation Study - Methods

- Five data generation mechanisms (DGMs):
  - **Fully Nested**: Agents nested in both arms.
  - **Partially Nested**: Agents nested in one arm.
  - **Crossed**: The same agents working in both arms.
  - **Crossed-Interaction**: Added an agent x arm random effect.
  - **Crossed-Imbalanced**: Agents worked primarily with participants in one arm.
- Multiple agents: 2, 6, 10, or 20 agents per arm (Nested) or total (Crossed).
- Participants per agent: Nested DGMs - 5 or 20, Crossed DGMs - 10 or 40.
- Crossed-Imbalanced: 80% of an agent’s participants were in one arm.
- Same sample size for a given number of agents and participants per agent.
- ICCs under a Single Membership model were set to 0.05, 0.10 or 0.20.
- For power, the intervention effect was set to 0.20 sd units

Complex Clustering Simulation Study - Methods

- Multiple Membership Structure
  - Agents per participant: 2, 3, 4, or 5
  - Weight for the primary agent: 0.5, 0.75, 0.85, or 0.95
  - For 3 or more agents per participant, the remaining weight was randomly distributed among the secondary agents.
  - We also examined a case in which the weights for the agents were equal.
- Single Membership Structure
  - Weight for the primary agent: 1
  - For the case in which Multiple Membership analytic models were applied to Single Membership data, we generated Multiple Membership data but calculated the outcome using only the largest magnitude agent random effect; this provided Single Membership data based on the most influential agent.
- Single Agent Structure
  - A single agent per arm (Nested) or in total (Crossed).

Complex Clustering Simulation Study - Methods

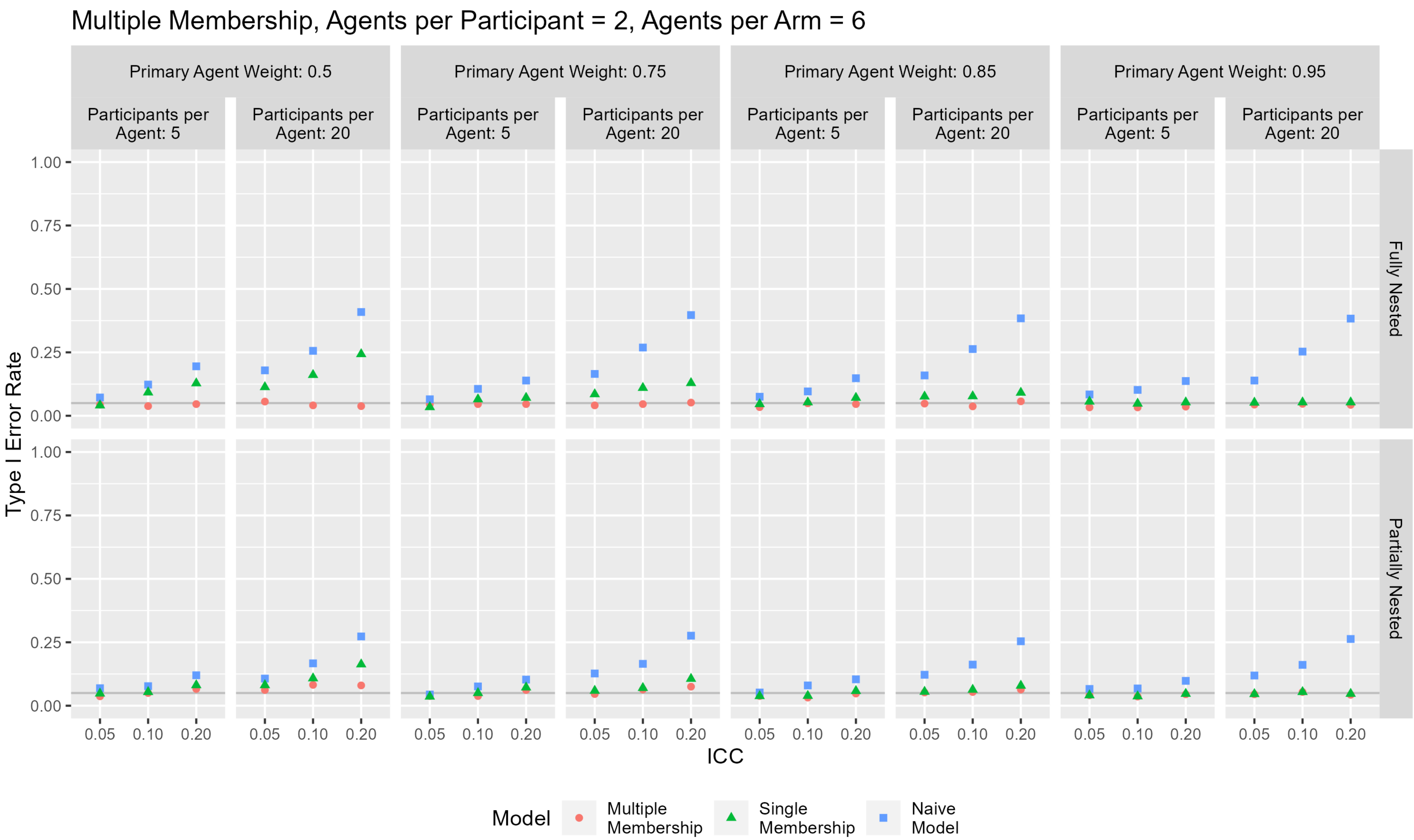
- Several analytic models were used.
- Multiple Membership data:
  - Multiple Membership model with random effects for agents
  - Single Membership model using a random effect for the primary agent
  - Naive Model ignoring agent effects altogether
  - Agent weights were assumed to be known (i.e. exogenous)
- Single Membership data:
  - Single Membership model with a random effect for the agent
    - Equivalent to GRT analysis for Fully Nested and to IRGT analysis for Partially Nested
  - Naive Model ignoring agent effects altogether
- Single Agent data:
  - Naive Model ignoring agent effects altogether
    - It is not possible to estimate agent effects

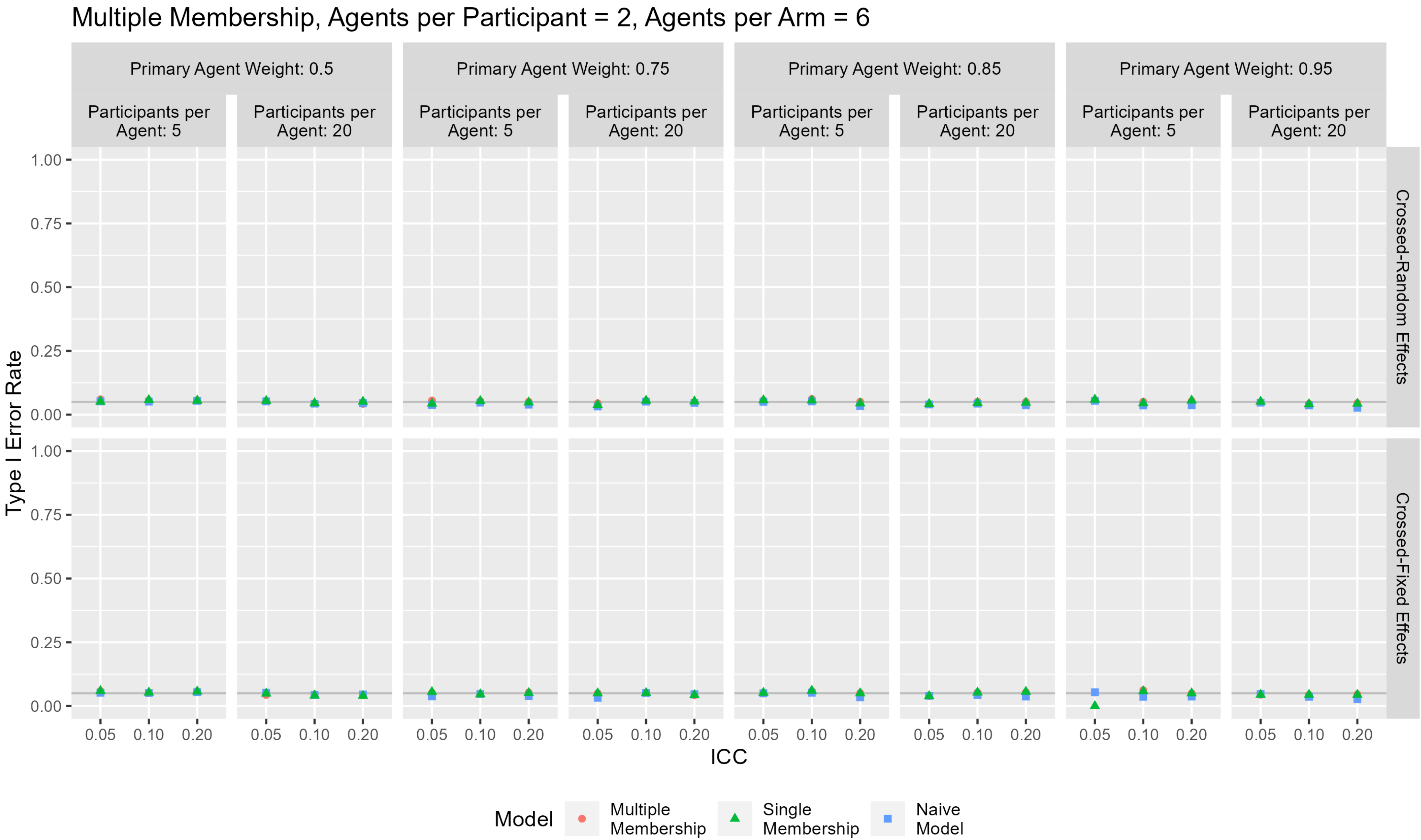
Complex Clustering Simulation Study - Methods

- Additional analytic models:
  - For Crossed and Crossed-Imbalanced data, we examined models that represented agents as fixed effects.
  - For Multiple Membership data, we pursued two variations
    - The data were unchanged, but in the analysis, we permuted the agent weights so that we used incorrect weights – “Permute”
    - Generated the data based only on the most influential agent but analyzed using all agents – “Max”
- Data were generated in R version 4.2.3.
- Analytic software
  - SAS PROC MIXED for Single Membership models, KR2 df
  - SAS PROC GLIMMIX 9.4 for Multiple Membership models, KR2 df
  - R package lme4’s `lmer` function modified to fit Multiple Membership was used for the Crossed with interaction models, KR df

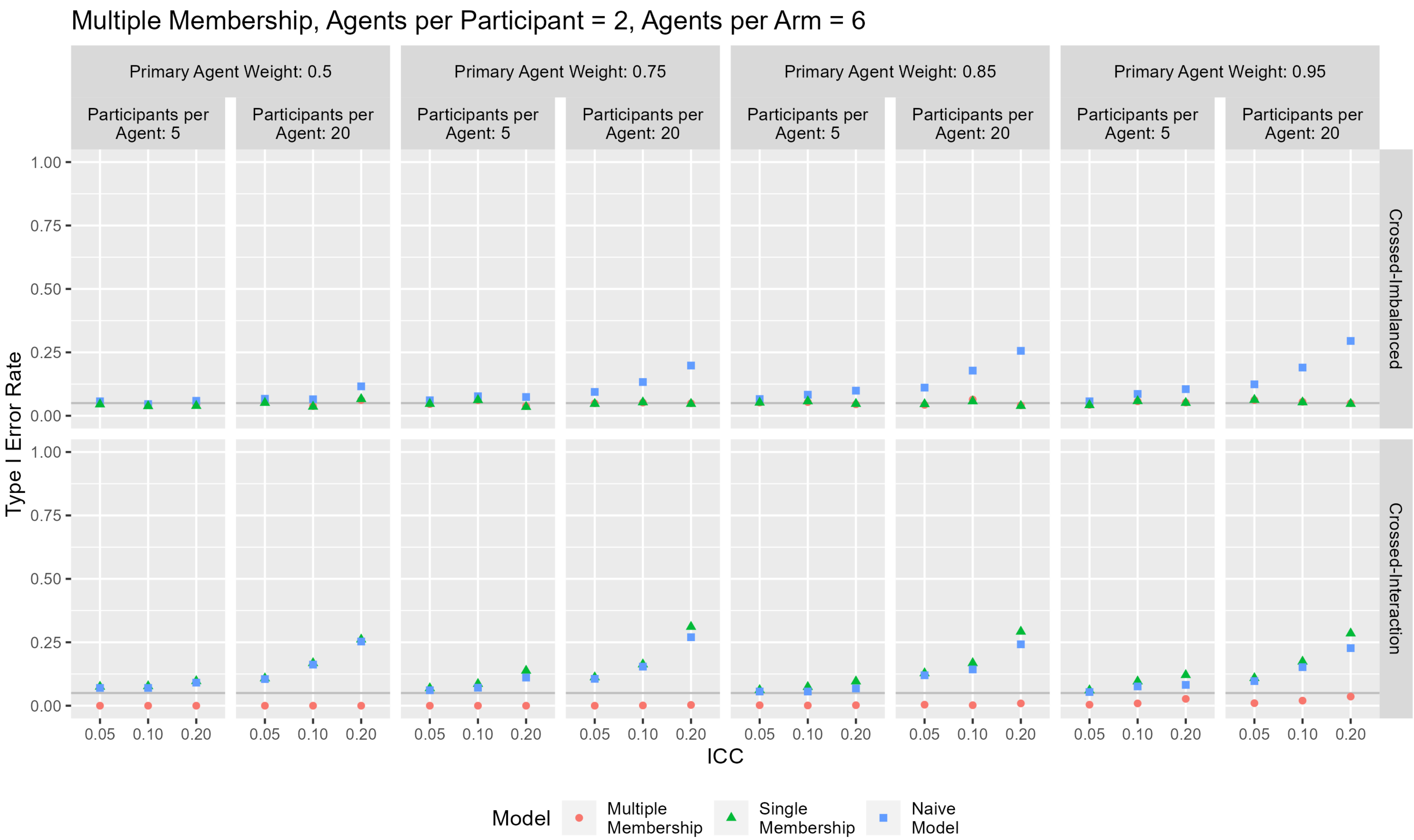
Results

- Type 1 error rate
  - Multiple Membership
  - Single Membership
  - Single Agent
  - Alternative Analyses
- Power


Multiple Membership, Agents per Participant = 2, Agents per Arm = 6
Primary Agent Weight: 0.5
Primary Agent Weight: 0.75
Primary Agent Weight: 0.85
Primary Agent Weight: 0.95
Participants per Agent: 5
Participants per Agent: 20
Fully Nested
Partially Nested
Type I Error Rate
1.00
0.75
0.50
0.25
0.00
0.05
0.10
0.20
ICC
Model
Multiple Membership
Single Membership
Naive Model



Multiple Membership, Agents per Participant = 2, Agents per Arm = 6
Primary Agent Weight: 0.5
Primary Agent Weight: 0.75
Primary Agent Weight: 0.85
Primary Agent Weight: 0.95
Participants per Agent: 5
Participants per Agent: 20
Crossed-Random Effects
Crossed-Fixed Effects
Type I Error Rate
1.00
0.75
0.50
0.25
0.00
0.05
0.10
0.20
ICC
Model
Multiple Membership
Single Membership
Naive Model



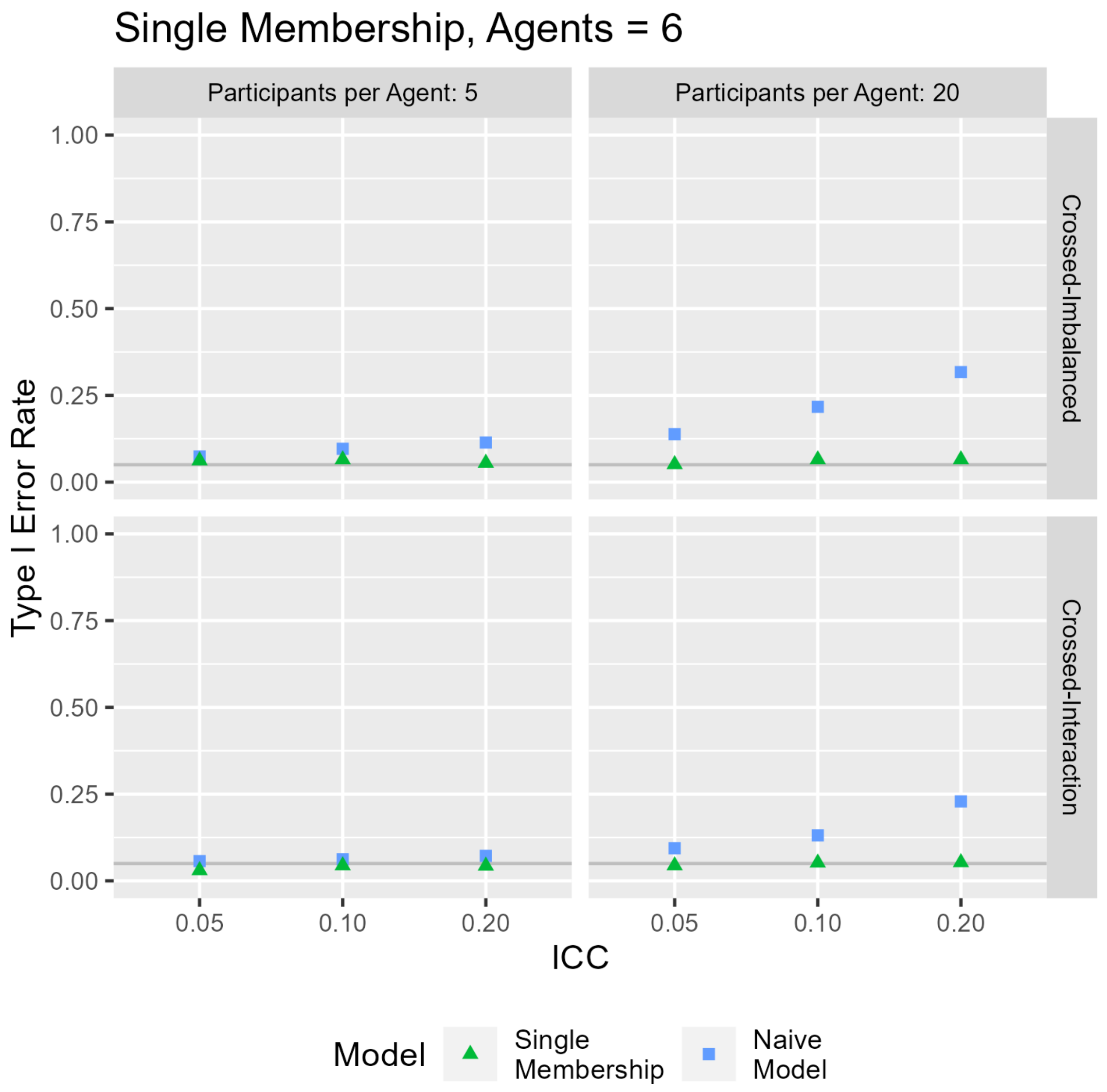
Multiple Membership, Agents per Participant = 2, Agents per Arm = 6
Primary Agent Weight: 0.5
Primary Agent Weight: 0.75
Primary Agent Weight: 0.85
Primary Agent Weight: 0.95
Participants per Agent: 5
Participants per Agent: 20
Crossed-Imbalanced
Crossed-Interaction
Type I Error Rate
1.00
0.75
0.50
0.25
0.00
0.05
0.10
0.20
ICC
Model
Multiple Membership
Single Membership
Naive Model

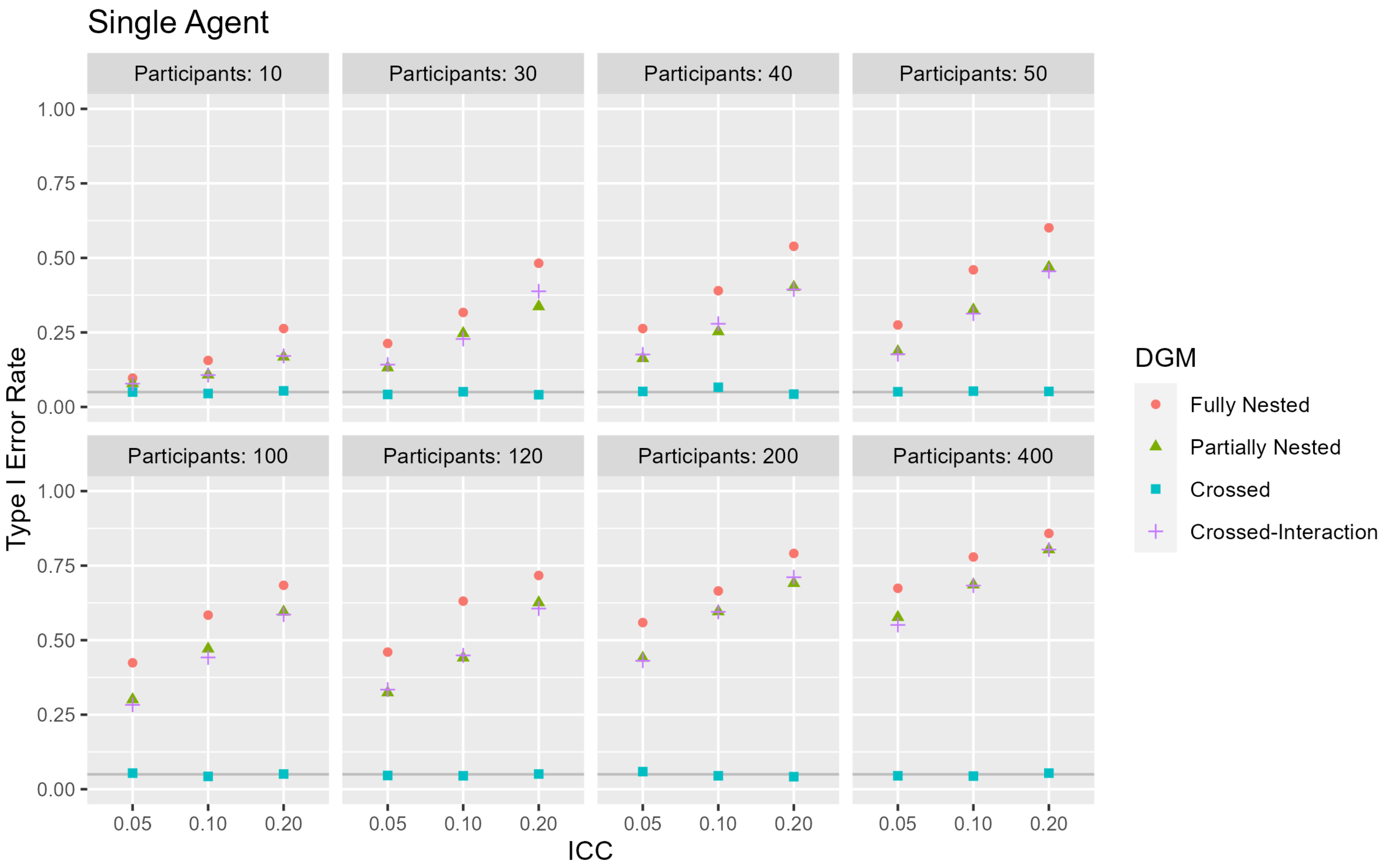
Complex Clustering Simulation Study – Type 1 Error

- For Multiple Membership data…
  - The Naive Model had an inflated type 1 error rate under almost all conditions in either the Nested structures or in a Crossed-Imbalanced structure.
  - The Single Membership model had an inflated type 1 error rate under many conditions in the Nested structures.
  - The Multiple Membership model had the nominal type 1 error rate in all Nested and Crossed structures, conditional on the correct specification of weights.
  - All three models had the nominal type 1 error rate in a balanced Crossed structure, with either random or fixed effects for agents, even with the incorrect specification of weights in the Multiple Membership model.

Single Membership, Agents per Arm = 6
Participants per Agent: 5
Participants per Agent: 20
Fully Nested
PartiallyNested
Type I Error Rate
1.00
0.75
0.50
0.25
0.00
0.05
0.10
0.20
ICC
Model
Single Membership
Naive Model

Single Membership, Agents = 6
Participants per Agent: 5
Participants per Agent: 20
Crossed-Random Effects
Crossed-Fixed Effects
Type I Error Rate
1.00
0.75
0.50
0.25
0.00
0.05
0.10
0.20
ICC
Model
Single Membership
Naive Model

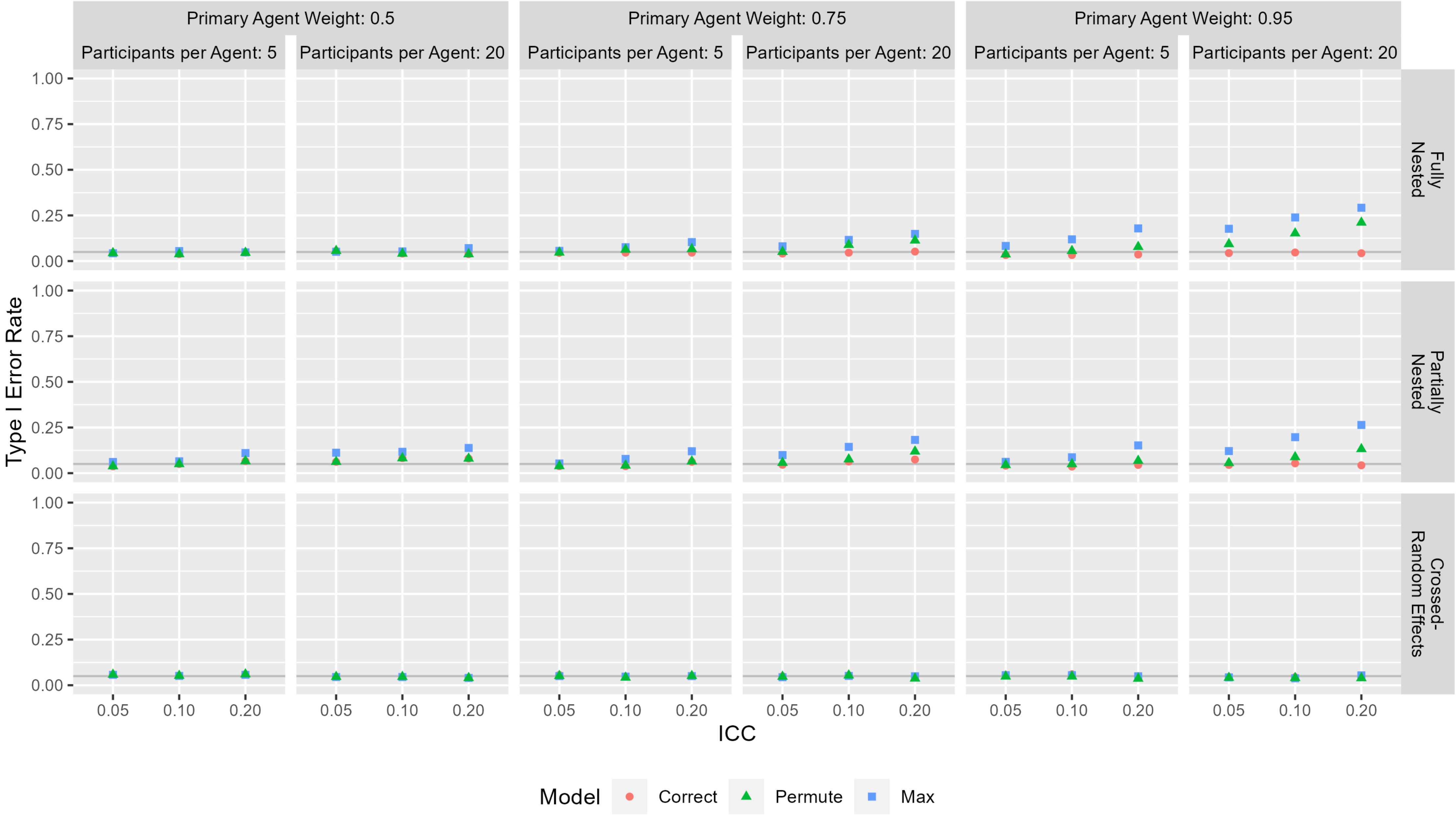

Single Membership, Agents = 6
Participants per Agent: 5
Participants per Agent: 20
Crossed-Imbalanced
Crossed-Interaction
Type I Error Rate
1.00
0.75
0.50
0.25
0.00
0.05
0.10
0.20
ICC
Model
Single Membership
Naive Model


Single Agent
Participants: 10
Participants: 30
Participants: 40
Participants: 50
Participants: 100
Participants: 120
Participants: 200
Participants: 400
Type I Error Rate
1.00
0.75
0.50
0.25
0.00
0.05
0.10
0.20
ICC
DGM
Fully Nested
Partially Nested
Crossed
Crossed-Interaction

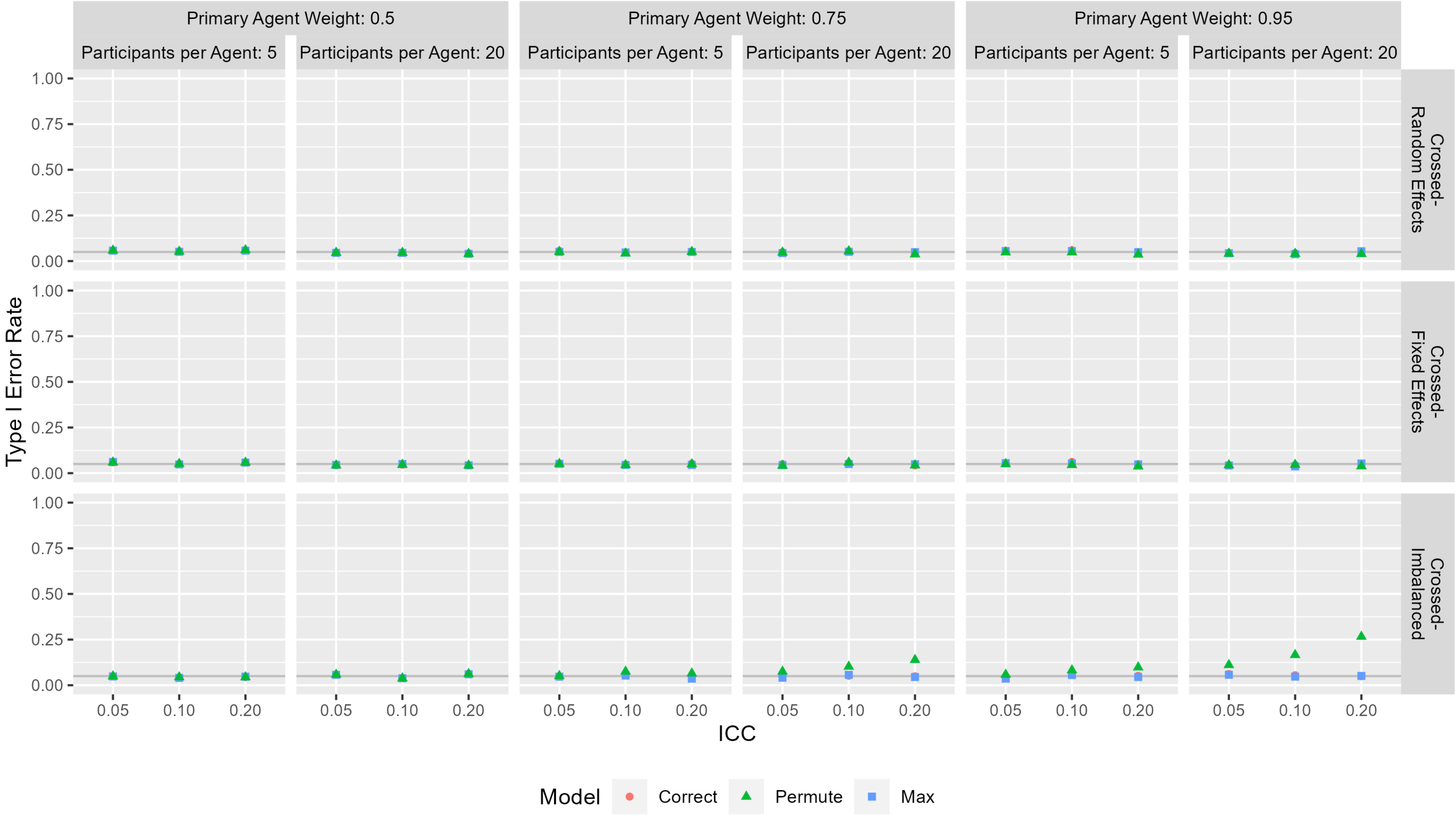
Complex Clustering Simulation Study – Type 1 Error

- For Single Membership data…
  - The Naive Model had an inflated type 1 error rate under almost all conditions in either the nested structures or in an unbalanced crossed structure.
  - The Single Membership model had the nominal type 1 error rate in all nested and crossed structures.
  - Both models had the nominal type 1 error rate in a balanced crossed structure with either random or fixed effects for agents.
- For Single Agent data…
  - The Naive Model had an inflated type 1 error rate in the nested structures.
  - The Naive Model had a nominal type 1 error rate only in a balanced crossed structure.

Alternative Analyses, Agents per Participant = 2, Agents per Arm = 6

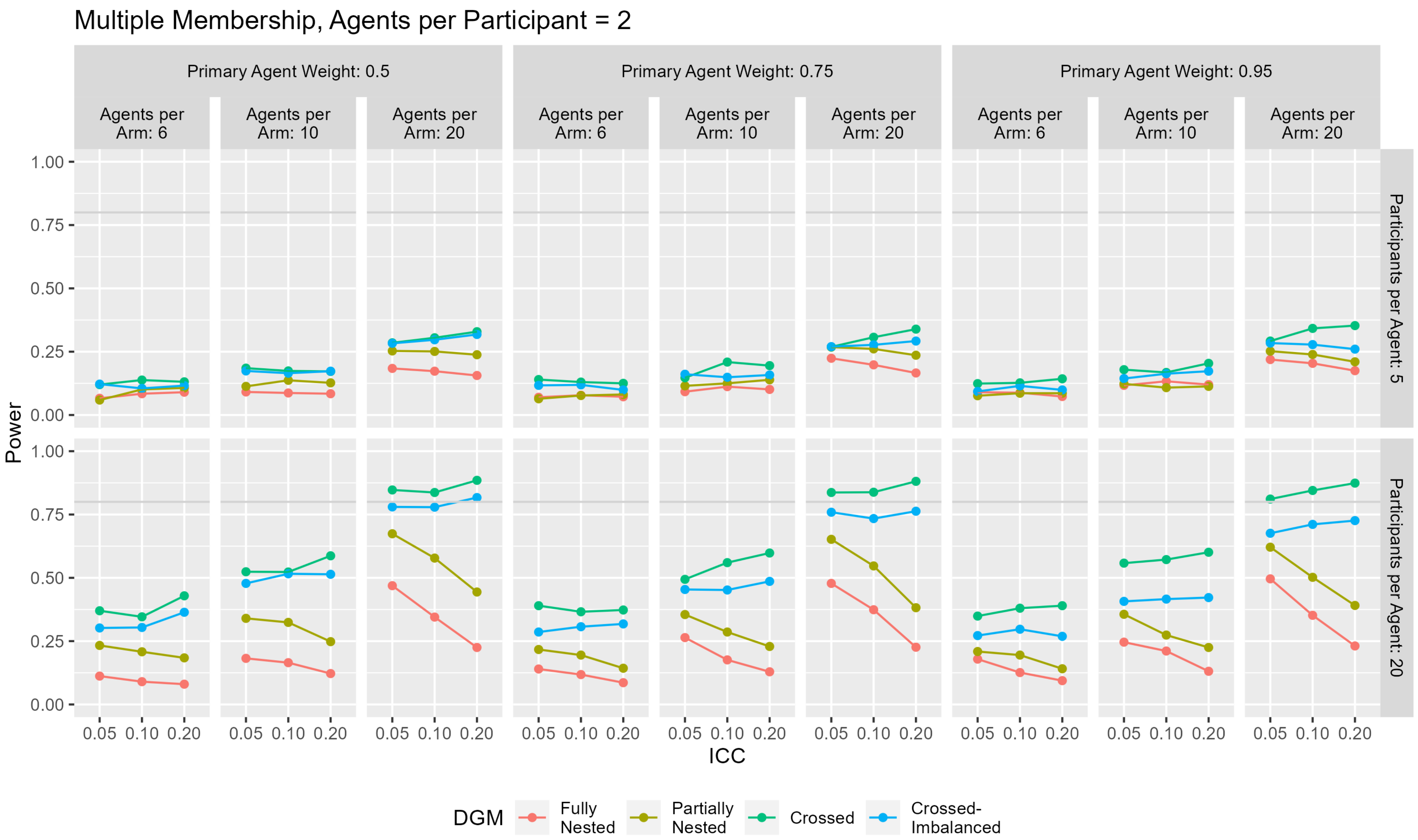


Alternative Analyses, Agents per Participant = 2, Agents = 6



Complex Clustering Simulation Study – Type 1 Error

- For Alternative Analyses…
  - For Fully Nested and Partially Nested data, inflated type 1 error rates were observed for Permuted and Max analyses.
    - This was more pronounced when the number of participants per agent was large and primary agent weight was closer to 1.
  - For Crossed data, type 1 error rates were maintained whether agents were modeled with random or fixed effects.
  - For Crossed-Imbalanced data, inflated type 1 error rates were observed with permuted agent weights.



Multiple Membership, Agents per Participant = 2
Primary Agent Weight: 0.5
Primary Agent Weight: 0.75
Primary Agent Weight: 0.95
Agents per Arm: 6
Agents per Arm: 10
Agents per Arm: 20
Participants per Agent: 5
Participants per Agent: 20
Power
1.00
0.75
0.50
0.25
0.00
ICC
0.05 0.10 0.20
DGM
Fully Nested
Partially Nested
Crossed
Crossed-Imbalanced

Complex Clustering Simulation Study – Type 1 Error

- For Power analyses…
  - For Multiple Membership data…
    - Power for the Multiple Membership model was largest when ICC was low, the number of agents per arm or in total was large, and the number of participants was large; the number of agents per participant had little effect.
    - Power for the Multiple Membership model was better in the Partially Nested design than in the Fully Nested design.
    - Power for the Multiple Membership model was similar in the balanced and unbalanced Crossed designs and much better than in the nested designs..
  - Results were similar for Single Membership data.
  - For Single Agent data, it only made sense to look at power for balanced Crossed settings.
    - Power increased in a manner similar to Crossed Multiple Membership.

Conclusions

- Crossed designs protect the type 1 error rate, allow flexibility in analytic models, and provide good power with sufficient sample size.
  - The risk is contamination, so consider that carefully.
- For Nested designs, the analytic model should be matched to the expected structure of the data (Multiple Membership vs. Single Membership) and Naive Models should not be used.
- Power in small studies is quite poor; a power analysis with realistic and data-based estimates is essential.
- Limitations:
  - Binary and count outcomes
  - Variation in the number of participants per agent

Multiple Membership Software and Resources

- SAS
  - PROC GLIMMIX EFFECT statement (Vazquez Arreola, 2017)
- R
  - `lme4`: https://bbolker.github.io/mixedmodels-misc/notes/multimember.html
  - `lmerMultiMember`: https://jvparidon.github.io/lmerMultiMember
  - `brms`: Bayesian Regression Models using Stan
- Stata
  - `mixed` with `_all` in random effects equation
- University of Bristol Centre for Multilevel Modeling
  - LEMMA: Learning Environment for Multilevel Methods and Applications (Leckie, 2013).

- Vazquez Arreola E. Analyzing multiple membership hierarchical data using PROC GLIMMIX. In: Western Users of SAS Software Educational Forum; Conference; 2017.
- Leckie G. Multiple membership multilevel models. Published online 2013. http://www.bristol.ac.uk/cmm/learning/course.html

NIH Resources

- Pragmatic and Group-Randomized Trials in Public Health and Medicine
  - https://prevention.nih.gov/grt
  - 7-part online course on GRTs and IRGTs
- Mind the Gap Webinars
  - https://prevention.nih.gov/education-training/methods-mind-gap
    - An Introduction to Cross-classified, Multiple Membership, and Dynamic Group Multilevel Models (Donald Hedeker, October 20, 2022)
    - Design and Analytic Methods for Group-Based Interventions. (David Murray, June 29, 2021)
    - Design and Analysis of IRGTs in Public Health (Sherri Pals, April 24, 2018)
- Research Methods Resources Website
  - https://researchmethodsresources.nih.gov/
  - Background material, key references, and a sample size calculator for IRGs.

Questions?

Statistical Models – Nested

$$Y_{ik} = \beta_0 + \beta_1 X_k + \sum_{j=1}^{J_k} w_{ijk} f_{jk} + e_{ik} \qquad (1)$$

- Y_{ik}: Continuous outcome for participant i of arm k.
- X_k: Intervention group indicator.
- $\beta_0,\ \beta_1$: Fixed effects for y-intercept and intervention effect.
- J_k: number of agents in arm k, with $k = 1$ defined as the control arm.
- w_{ijk}: weight for agent j interacting with participant i of arm k, $\sum_{j=1}^{J_k} w_{ijk} = 1$.
- $f_{jk} \sim N(0, \sigma^2_{f,k})$ and $e_{ik} \sim N(0, \sigma^2_{e,k})$
- Multiple Membership: at least two $w_{ijk} > 0$ and $J_k > 1$.
- Single Membership: one $w_{ijk} = 1$ and $J_k > 1$.
- Single Agent: one $w_{ijk} = 1$ and $J_k = 1$.
- Partially Nested: agent random effects in control arm, f_{j1}, are omitted.

Statistical Models – Crossed

$$Y_{ik} = \beta_0 + \beta_1 X_k + \sum_{j=1}^{J} w_{ijk} f_j + \sum_{j=1}^{J} w_{ijk}\, g_{jk} X_k + e_{ik} \qquad (2)$$

- J : number of agents in the study.
- w_{ijk} : proportion of treatment participant i of arm k receives from agent j, $\sum_{j=1}^{J} w_{ijk} = 1$.
- $\begin{pmatrix} f_j \\ g_{jk} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{bmatrix} \sigma_f^2 & \sigma_{fg} \\ \sigma_{fg} & \sigma_g^2 \end{bmatrix}\right)$ and $e_{ik} \sim N(0, \sigma_{e,k}^2)$.
- Multiple Membership: at least two $w_{ijk} > 0$ and $J > 1$.
- Single Membership: one $w_{ijk} = 1$ and $J > 1$.
- Single Agent: one $w_{ijk} = 1$ and $J = 1$.
- No interaction model: remove g_{jk}

ICCs for Nested and Crossed Models

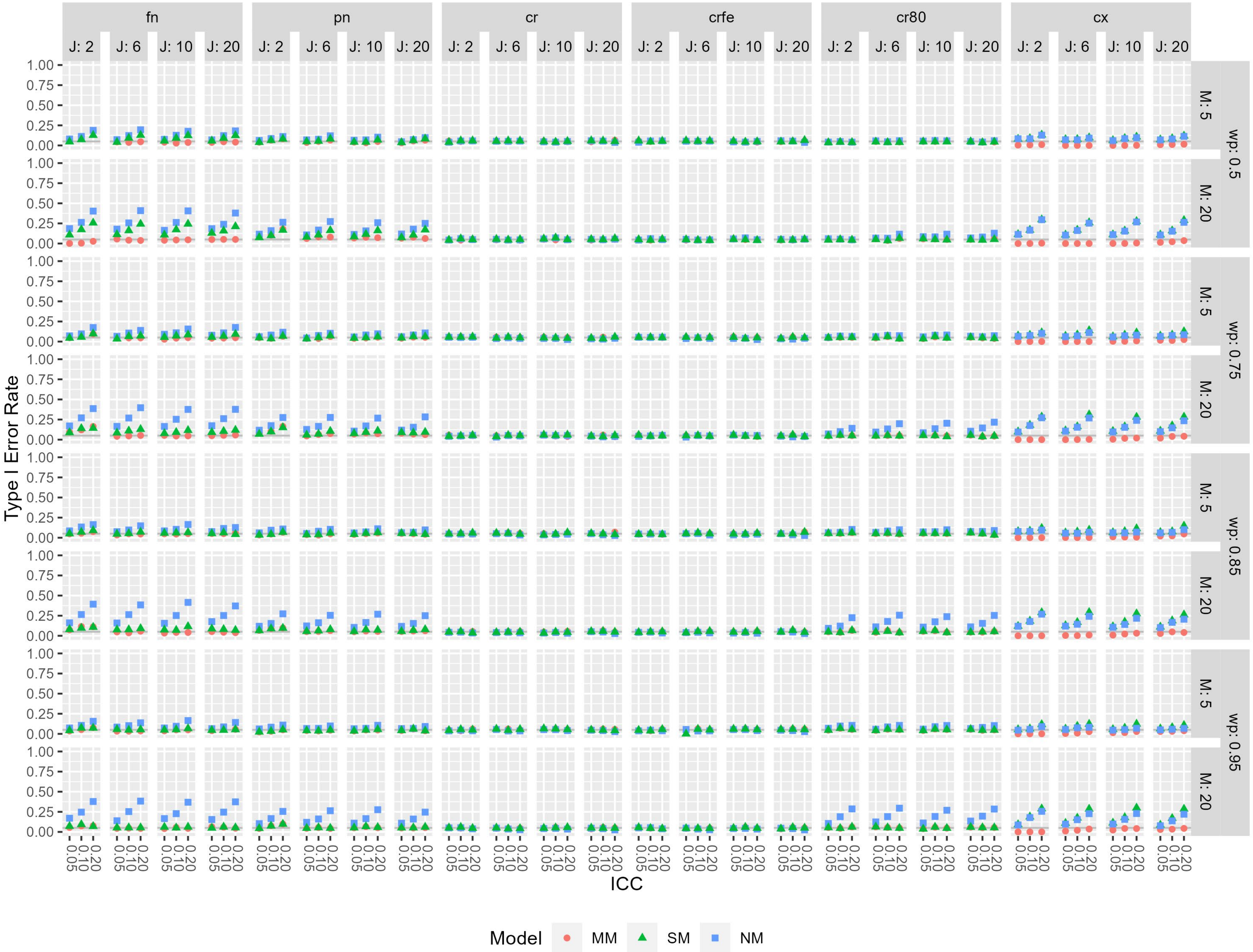
- Nested:

$$Corr(Y_{ik}, Y_{i'k}) = \frac{\sigma_{f,k}^2 \sum_{j=1}^{J_k} w_{ijk}\, w_{i'jk}}{\sqrt{\sigma_{f,k}^2 \sum_{j=1}^{J_k} \left(w_{ijk}\right)^2 + \sigma_{e,k}^2}\sqrt{\sigma_{f,k}^2 \sum_{j=1}^{J_k} \left(w_{i'jk}\right)^2 + \sigma_{e,k}^2}}$$

- Crossed:

$$Corr(Y_{i2}, Y_{i'2}) = \frac{\left(\sigma_f^2 + \sigma_g^2 + 2\sigma_{fg}\right) \sum_{j=1}^{J} w_{ij2}\, w_{i'j2}}{\sqrt{\left(\sigma_f^2 + \sigma_g^2 + 2\sigma_{fg}\right) \sum_{j=1}^{J} \left(w_{ij2}\right)^2 + \sigma_{e,2}^2}\sqrt{\left(\sigma_f^2 + \sigma_g^2 + 2\sigma_{fg}\right) \sum_{j=1}^{J} \left(w_{i'j2}\right)^2 + \sigma_{e,2}^2}}$$

Multiple Membership, A = 2



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Single Membership