A comprehensive evaluation of analytic models for individually randomized group treatment trials with complex clustering under nested and crossed designs

May 22, 2024

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Disclaimer

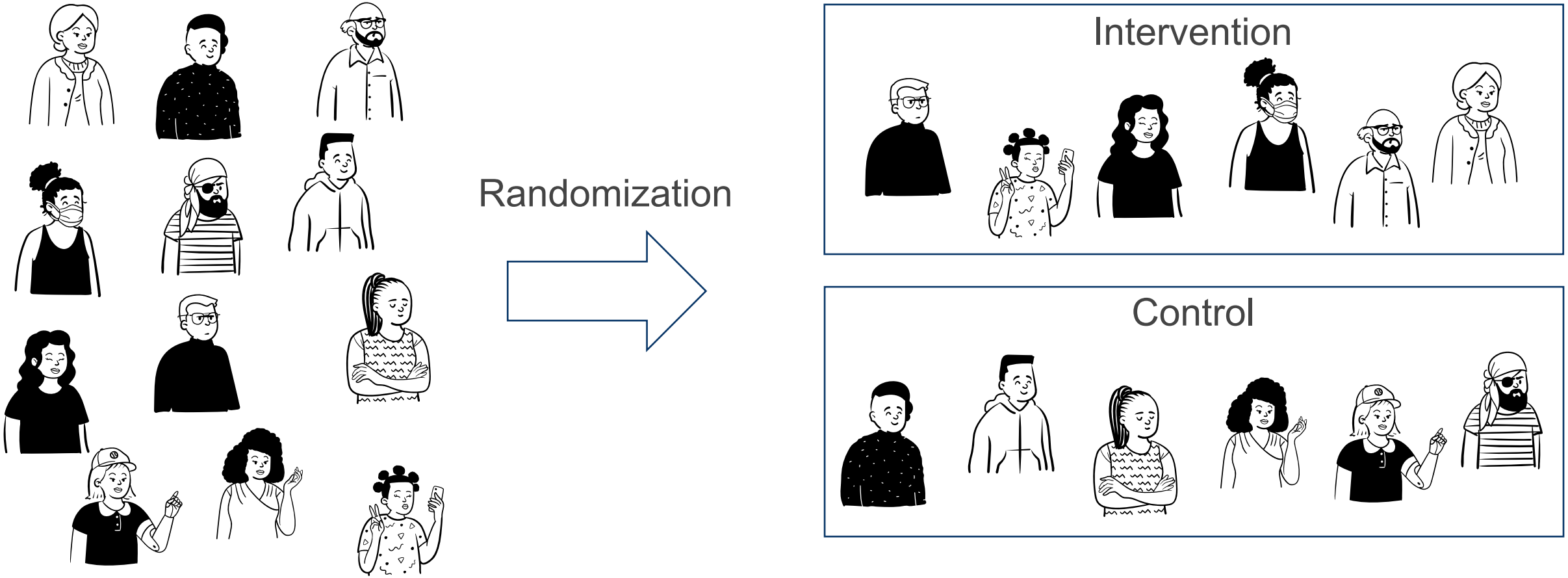
- The views expressed in this presentation are those of the speaker and do not necessarily reflect the position or policy of funding agencies or the U.S. government.

Today's Presentation

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

Individually Randomized Trials

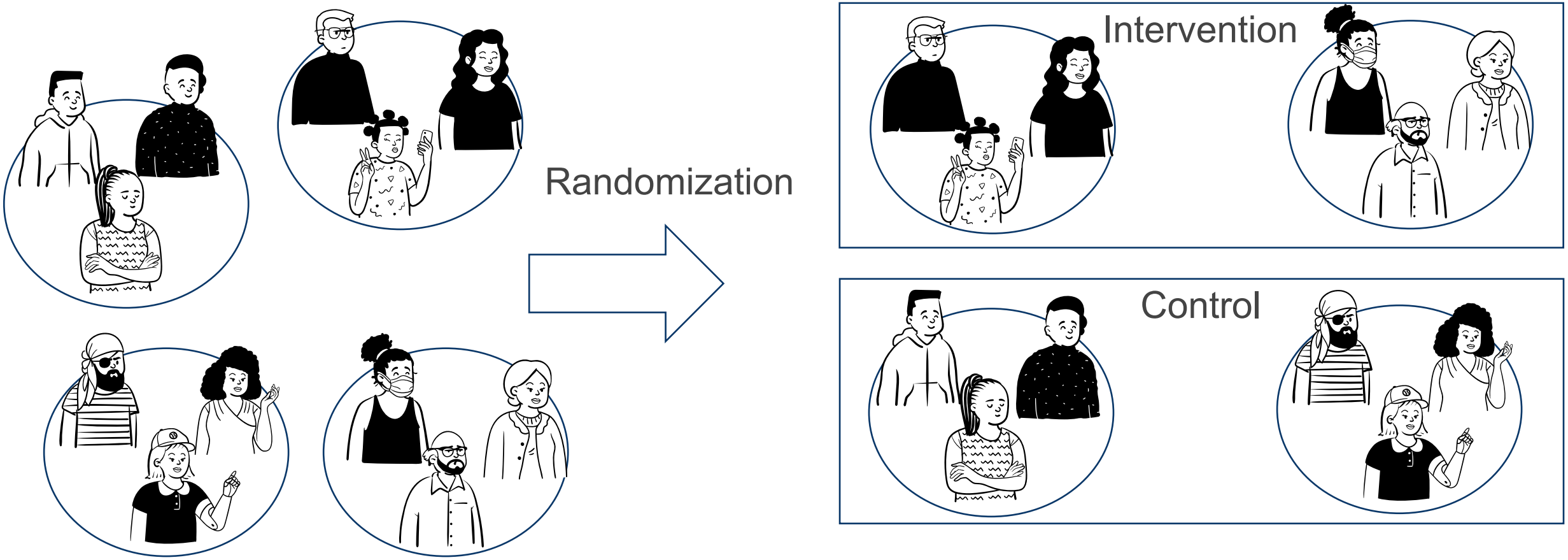
- Individuals are randomized to either control or intervention arms.



- Observations are independent before and after randomization.

Group- or Cluster-Randomized Trial (GRT)

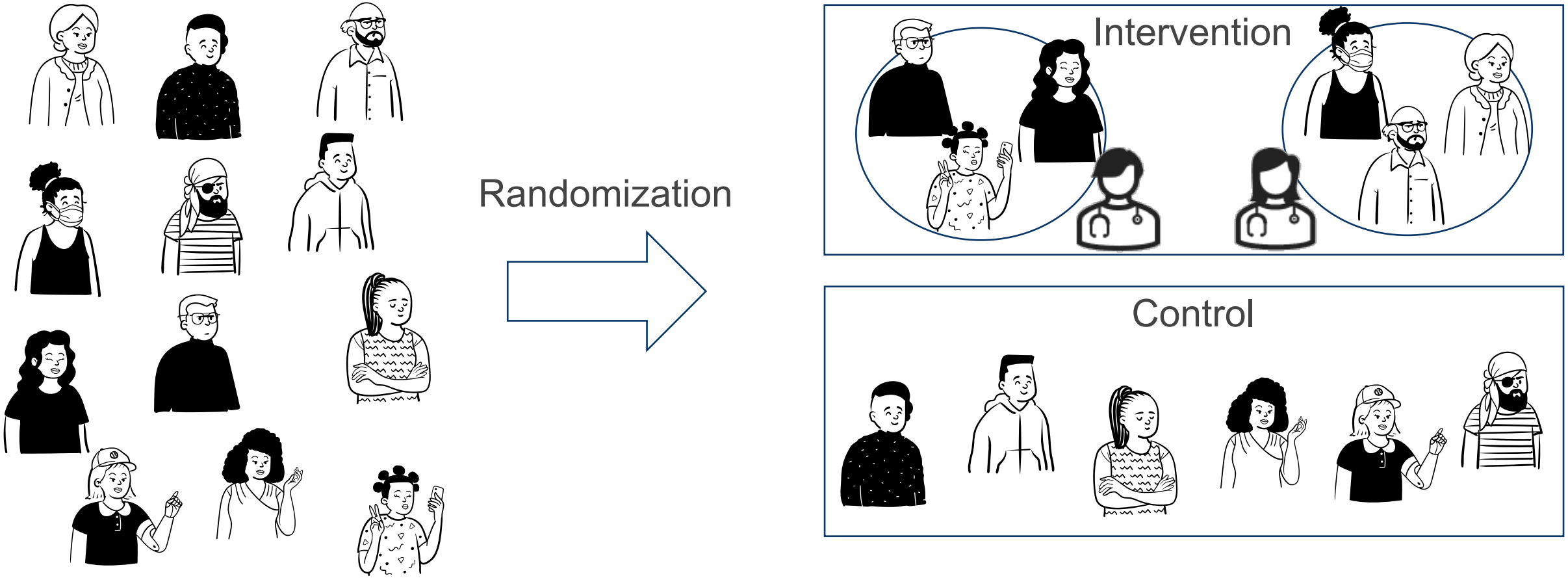
- Pre-existing groups are randomized to either control or intervention arms.



- 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 agents

Design and Analysis of IRGT Trials

- 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 a shared agent.
  - Examples: therapist, social worker, case manager, group facilitator/leader
- Failing to account for ICC is well understood to inflate type I error rates in the context of group- or cluster-randomized trials.
- Similar type I error rate inflation may be observed with IRGT trials.
- The potential impact of correlation is acknowledged less frequently in the context of IRGT trials.
- Methods are available for addressing some of these complex features in IRGT trials.

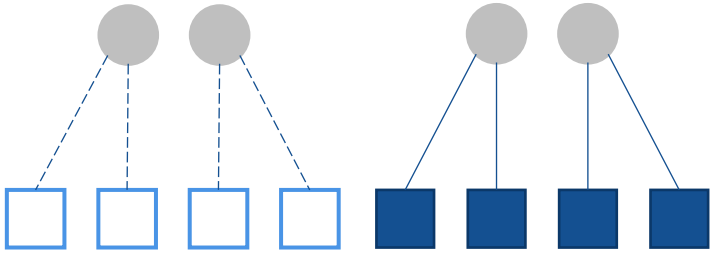
Questions about Complex Clustering in IRGT Trials

- The literature for IRGT trials has continued to assume:
  - Intervention agents operate only within the intervention arm.
  - Participants interact with a single agent.
  - There are several agents implementing the intervention.
- Questions about departures from these assumptions:
  - Does it matter if the multiple agents are nested within arm or if the same agents interact with participants in both arms?
  - What happens when participants interact with multiple agents?
  - 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?

Nesting Structures

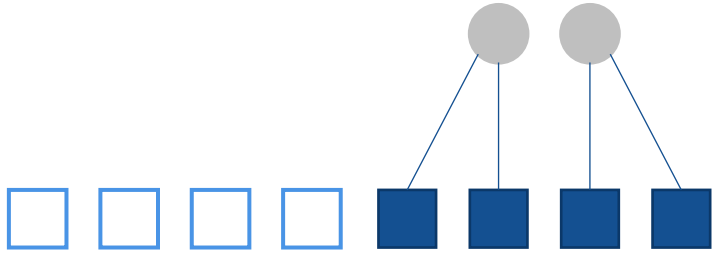
- Three data structures that are present in IRGT trials.

Fully Nested



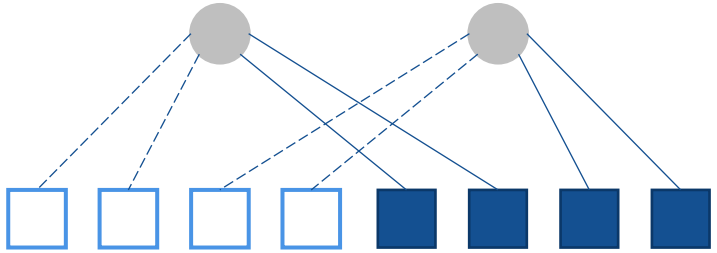
Agents are present in both arms, each agent only interacts with participants in a single arm.

Partially Nested



Agents are present in one arm only.

Crossed

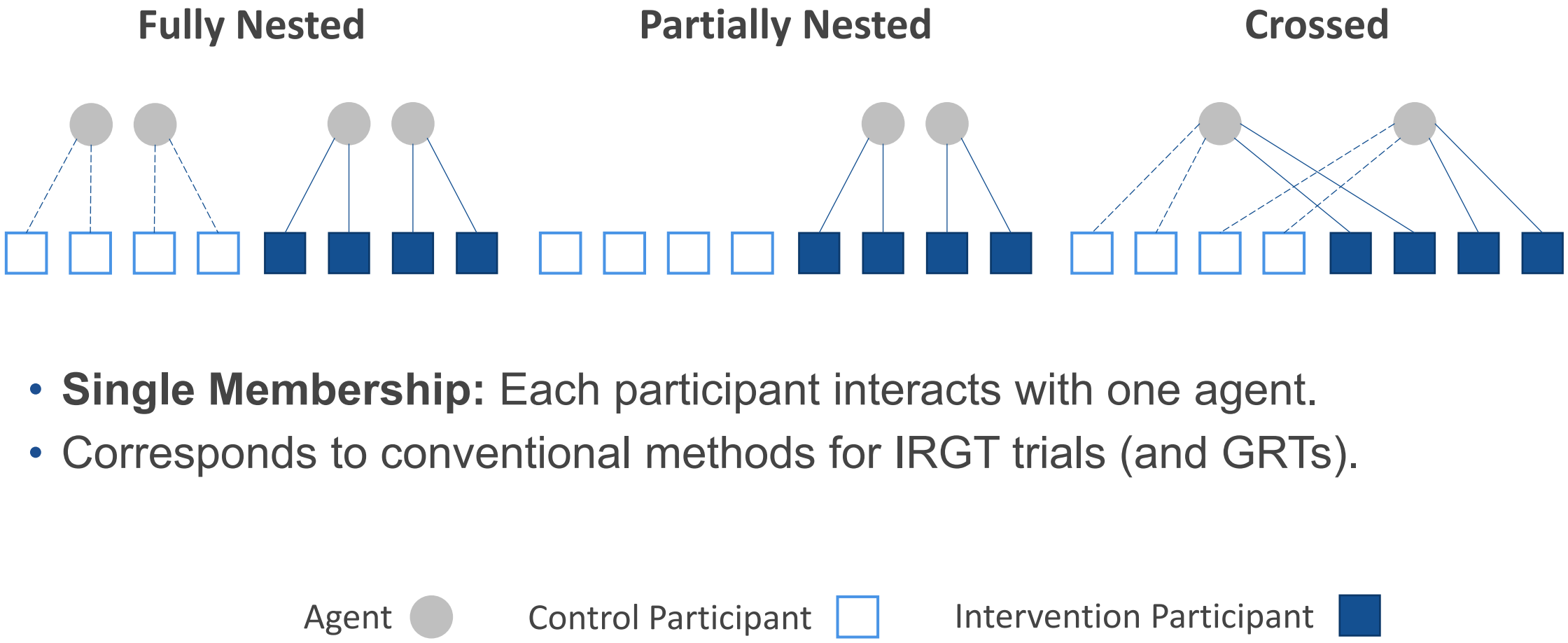


Same agents interact with participants in both arms.

Agent Control Participant Intervention Participant

Membership Structures

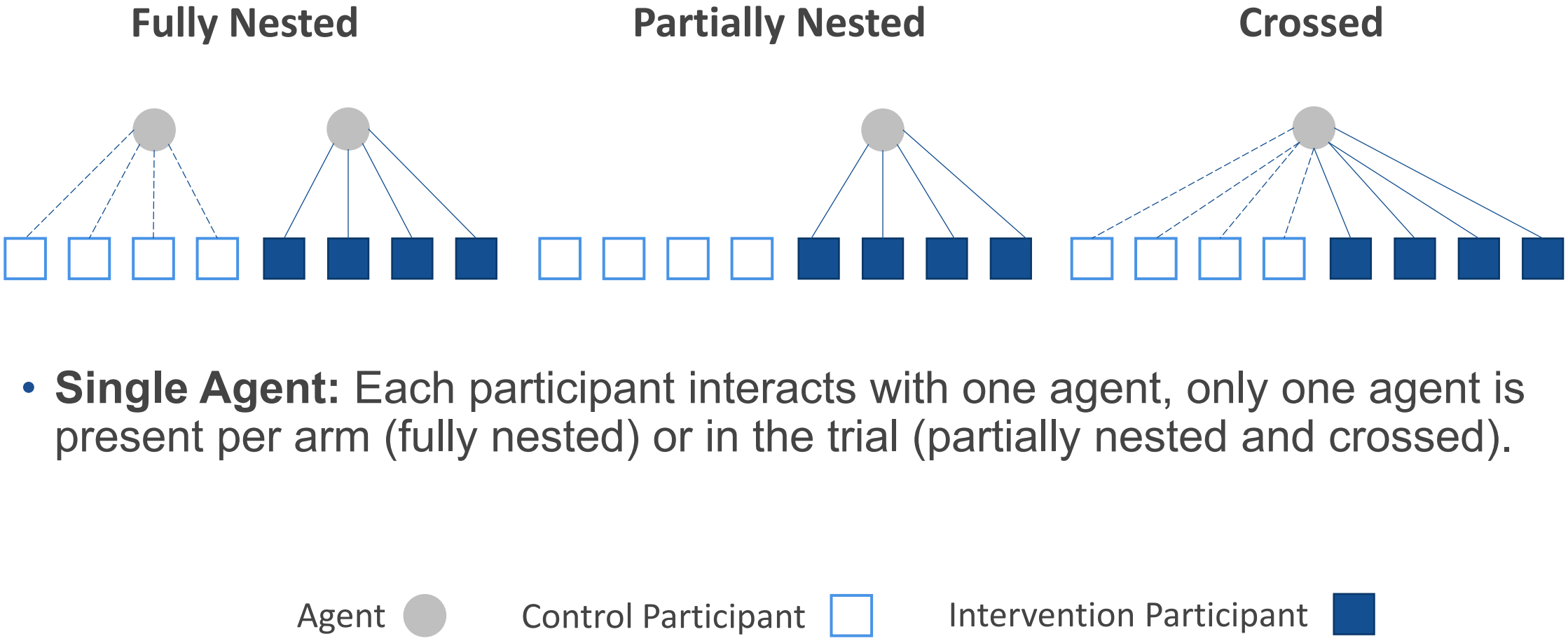
- Participants may interact with one or more agent.



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

Membership Structures

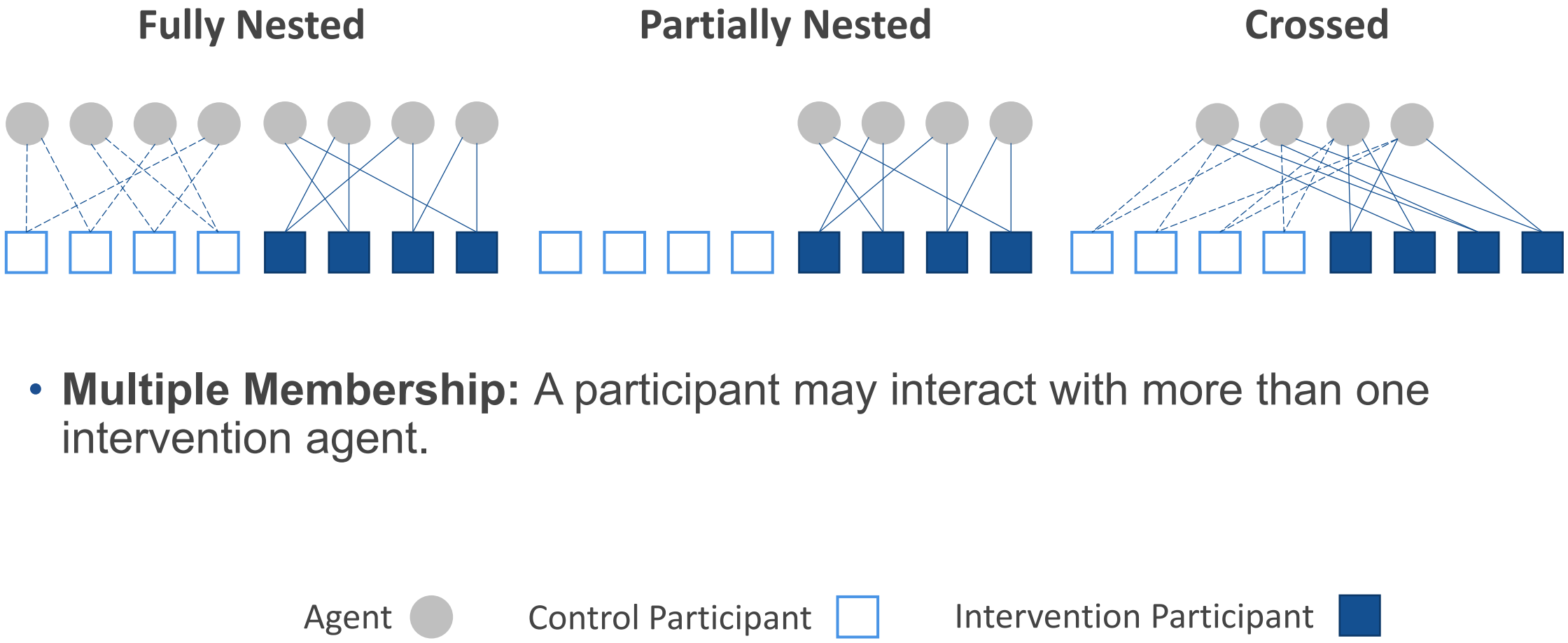
- Participants may interact with one or more agent.



- **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).

Membership Structures

- Participants may interact with one or more agent.



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

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.
  - Empirical Weights: Weights are determined empirically by assessing several different possibilities and choosing the best set based on some criterion.

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.
- Continuous outcome
- Two arms, post-test only
- 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.
- ICCs 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: 0.75, 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
- 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
    - Agent weights were assumed to be known (i.e. exogenous)
  - Single Membership model using a random effect for the primary agent
  - Naive Model ignoring agent effects altogether
- 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

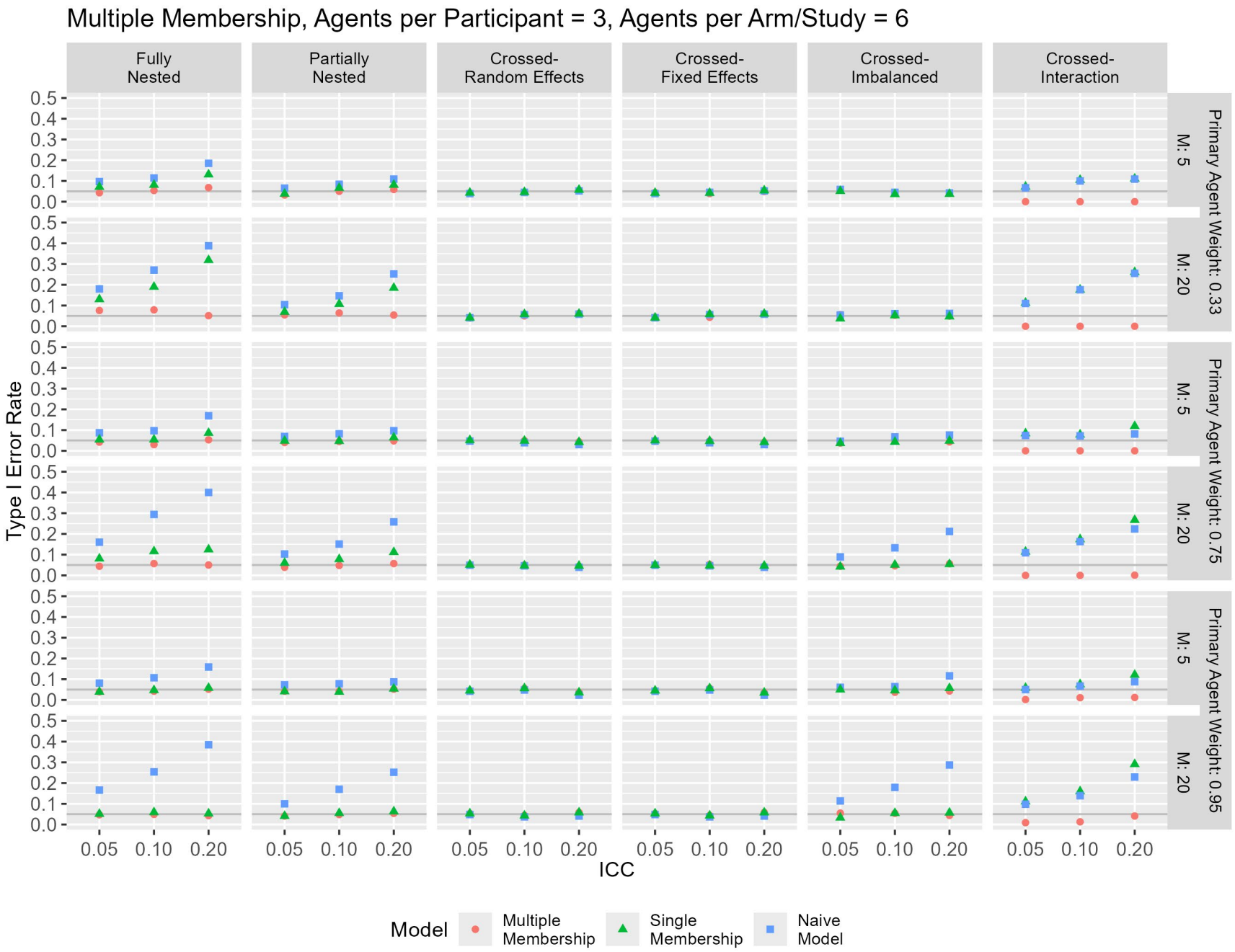
Complex Clustering Simulation Study - Methods

- Additional analytic models:
  - For Crossed 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

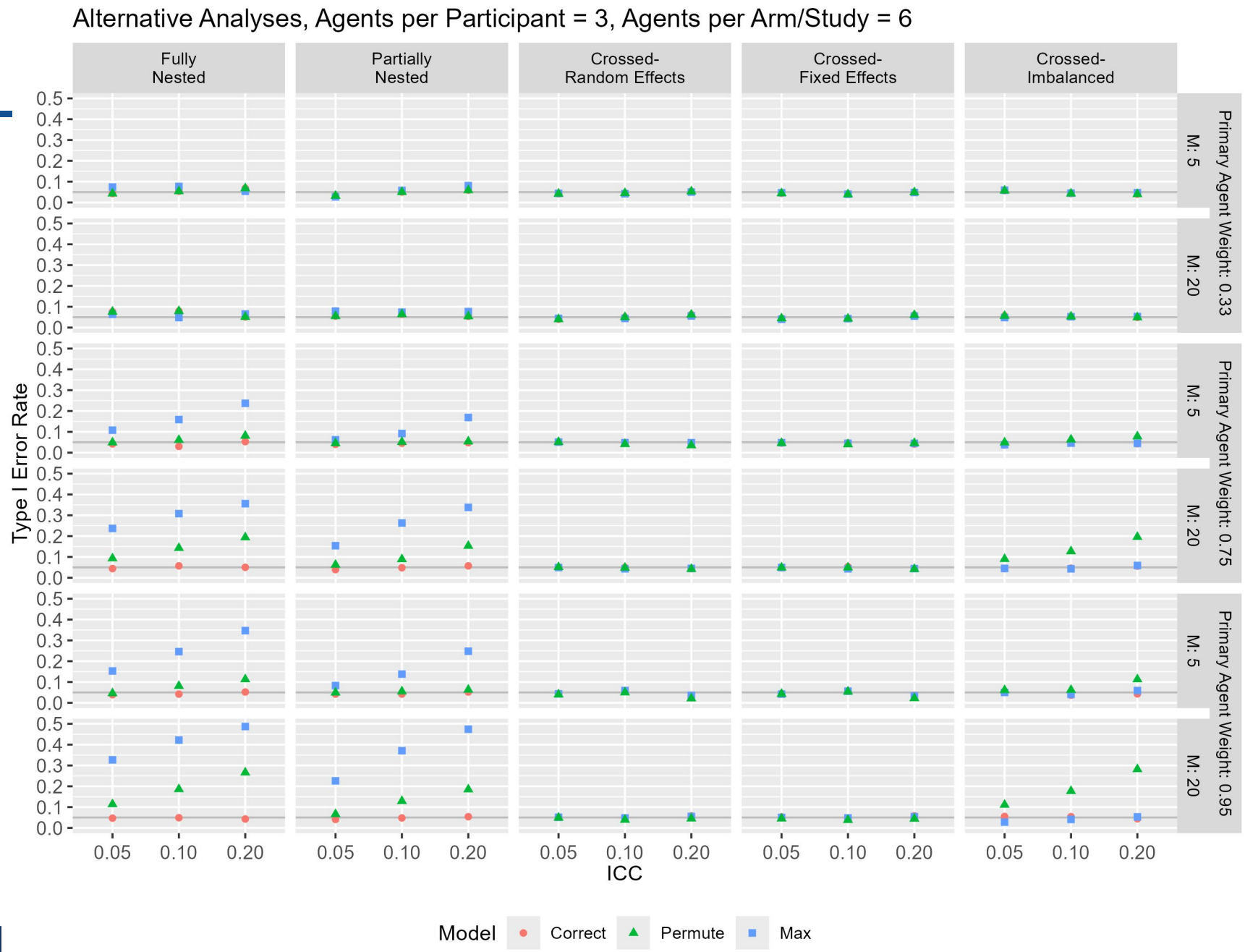
Results

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

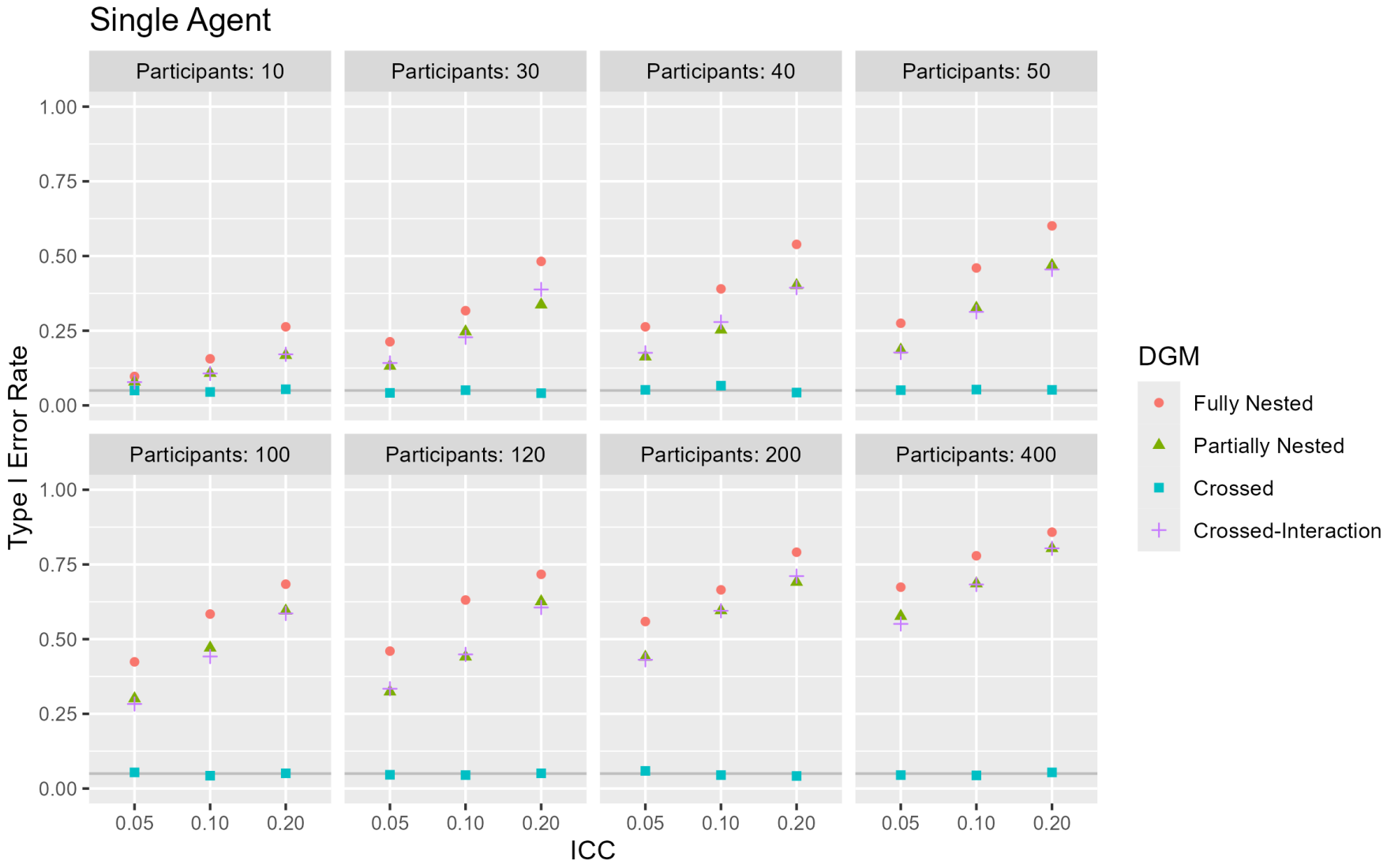
Multiple Membership



Multiple Membership – Alternative Analyses

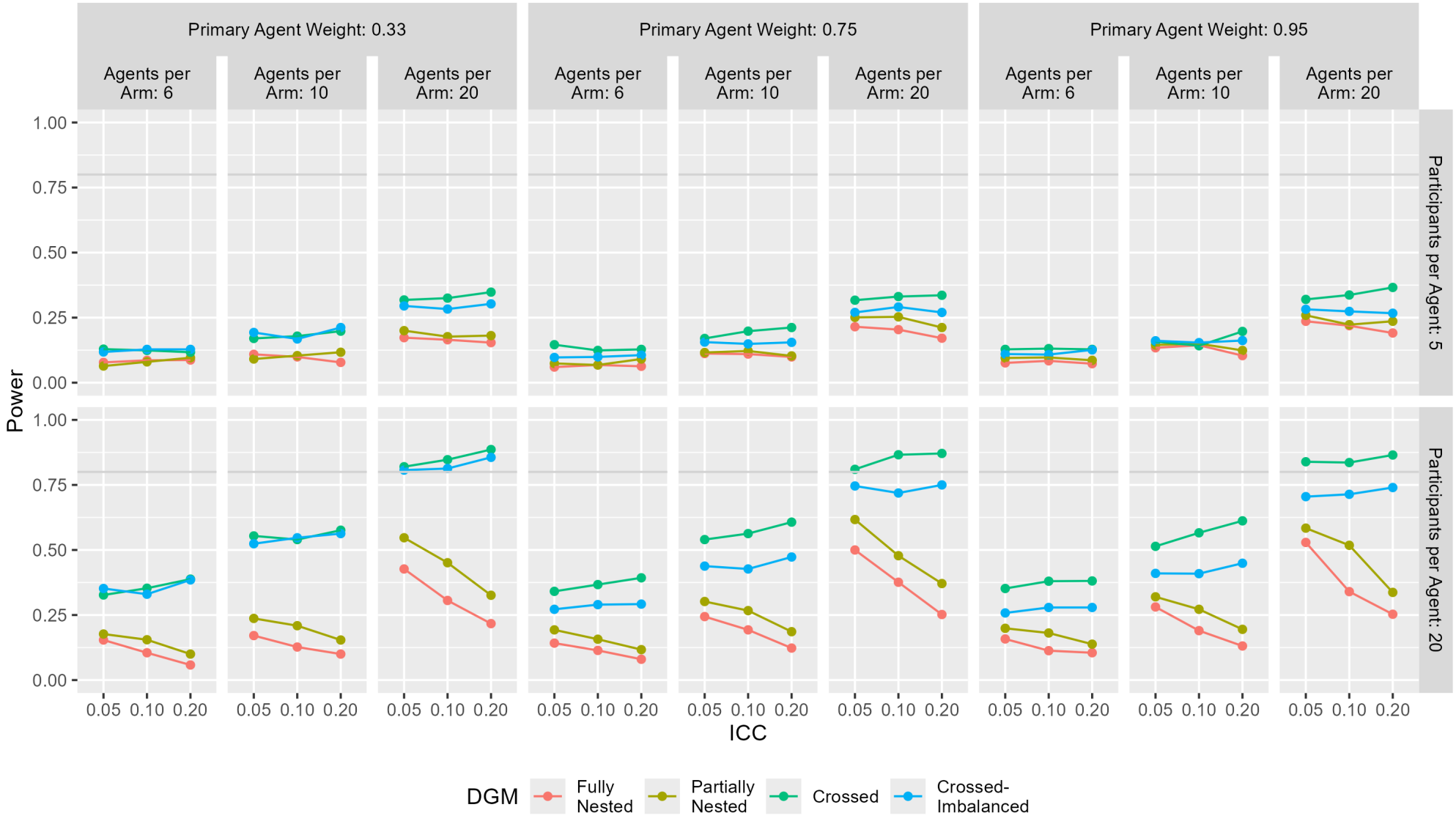


Type I Error Rate – Single Agent



Power – weak effect size

Multiple Membership, Agents per Participant = 3



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
- MLwiN
- 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.

Selected References

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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.
- β_0, β_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, $\sum_{j=1}^{J_k} w_{ijk} = 1$.
- $f_{jk} \sim N(0, \sigma_{f,k}^2)$ and $e_{ik} \sim N(0, \sigma_{e,k}^2)$
- 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-Interaction

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

- 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 $e_i \sim N(0, \sigma_e^2)$.
- 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}