Combination of prior distributions elicited from expert opinions previous to Bayesian inference. Application to precision medicine.

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Background

- Precision medicine
- Few patients: how to reach a conclusion on treatment efficacy ?
- Eliciting experts opinions: bring *prior* information to add to the data using Bayesian inference
- Combining multiple experts opinions (distributions): synthesize information

How should distributions be combined?

Objective

- To compare existing approaches of distribution combination, and give recommendations

- Approaches to be compared:
    - Combination approaches based on averaging
    - Combination approaches based on modelling

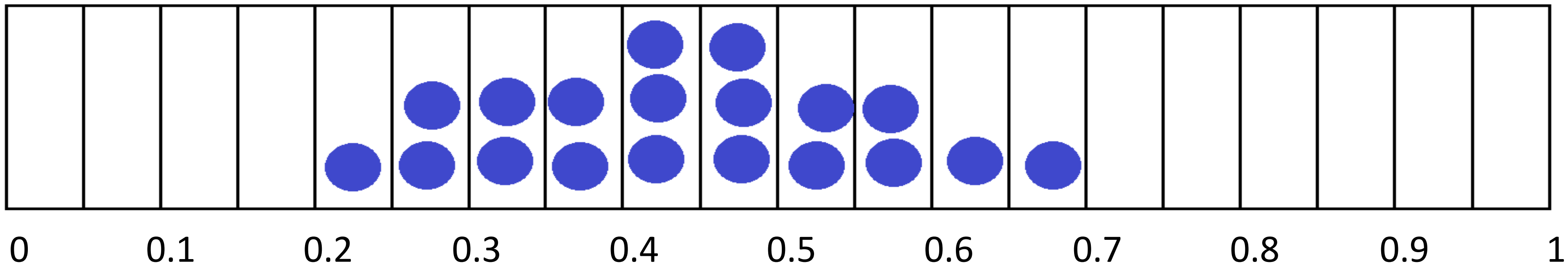
- Simulation: Impact of parameters on combined distribution

Methods

Clinical application context and elicitation

Two Ear-Nose-Throat surgeons and six oncologists interviewed about θ = proportion of patients without progression after 8 weeks of treatment (reference chemotherapy or anti-PD1 monoclonal antibody), for an ENT epidermoid carcinoma

- **Roulette method:** each expert put 19 coins on a grid to represent his/her opinion on θ plausible values



- **Empirical distribution** $\boldsymbol{F_j(\theta)}$= raw values
- **Beta distributions** $\boldsymbol{p_j(\theta)}$ fitted by minimization of the Cramer Von Mises distance

Combination approaches based on averaging

- **1st possibility: calculate the arithmetic mean $p(\theta)$** of individual distributions $p_j(\theta)$, with n as the number of experts:

$$p(\theta) = \sum_{j=1}^{n} \frac{1}{n} p_j(\theta)$$

(Arithm. mean)

- **2nd possibility: calculate the geometric mean, then normalize the combined distribution** (constant ν):

$$p(\theta) = \nu \prod_{j=1}^{n} p_j(\theta)^{\frac{1}{n}}$$

(Geom. mean)

Combination approaches based on modelling

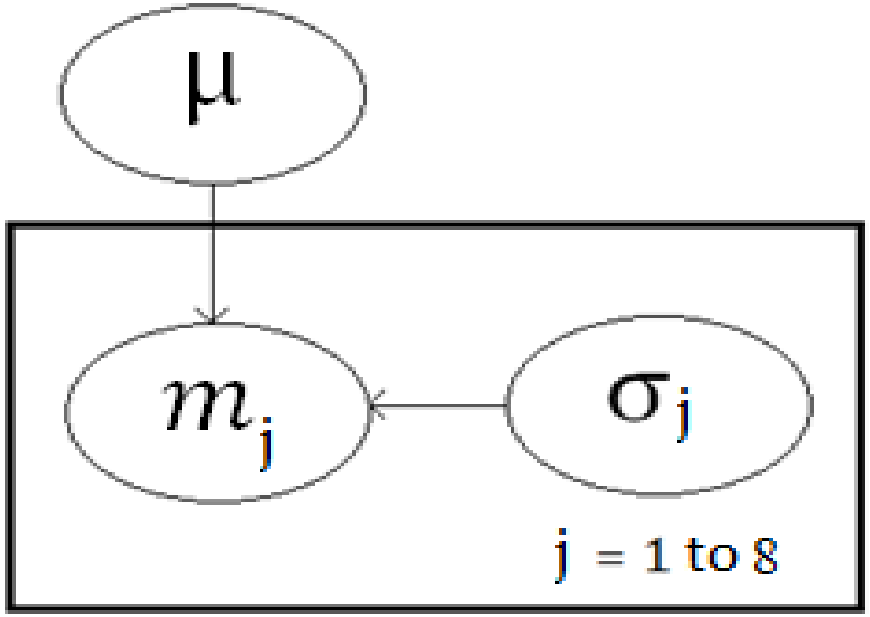
- Principle: Experts estimate the target parameter and uncertainty

$$F_j(\theta) \rightarrow \text{Logit}(\theta_j) \rightarrow \text{Fitting of } N(m_j, s_j)$$

m_j = estimate of the target parameter, and
s_j = uncertainty about it

- The summary parameters m_j and s_j are combined using different models
- Distributions for the model parameters obtained by Bayesian inference (using vague priors)

Model without variability between experts



- **Fixed effect model:** considers that the experts give their opinion on a single parameter, θ

variability between m_j values = measurement error

- Logical link:

$$\text{logit}(\theta) = \mu$$

σ_j estimated by s_j

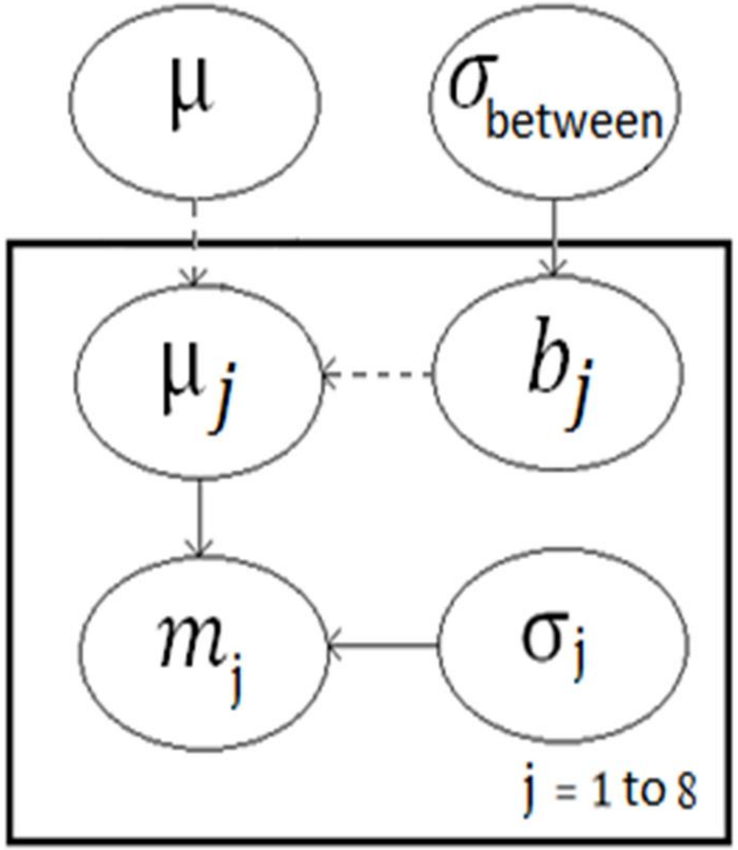
- Stochastic link:

$$m_j \sim N(\mu, \sigma_j)$$

- **Combined distribution**: Posterior Distribution of **μ** (after antilogit transformation)

(Fixed Mod.)

Model allowing for variability between experts



- **Mixed effect model:** considers that the experts give their opinion on a different parameter value, denoted θ_j

  - Logical link :

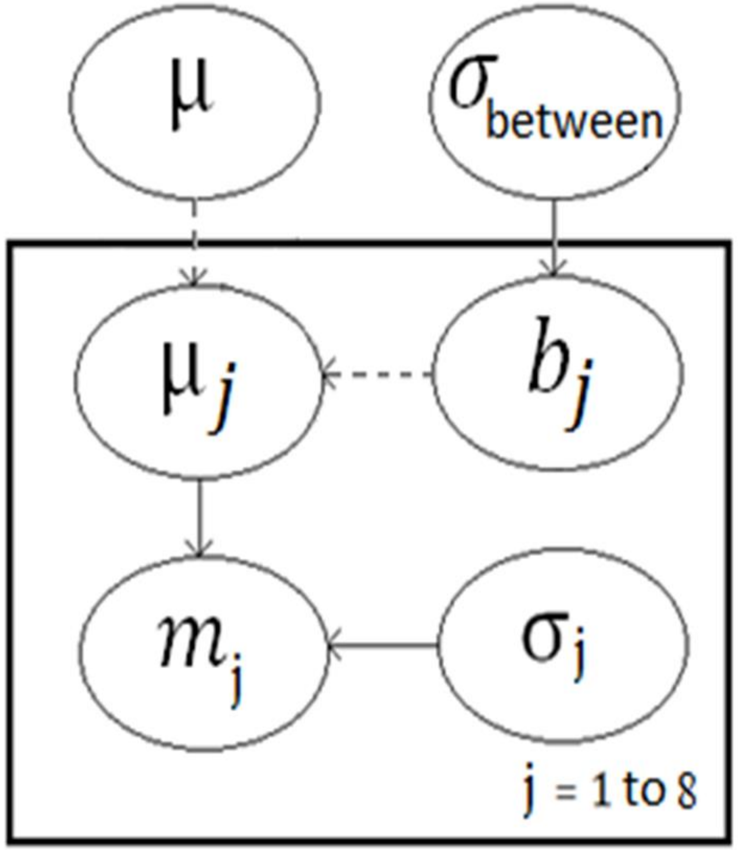
    $$\mathrm{logit}(\theta_j) = \mu + b_j = \mu_j$$

  - Stochastic links :

    $$m_j \sim N(\mu_j, \sigma_j)$$
    $$b_j \sim N(0, \sigma_{between})$$

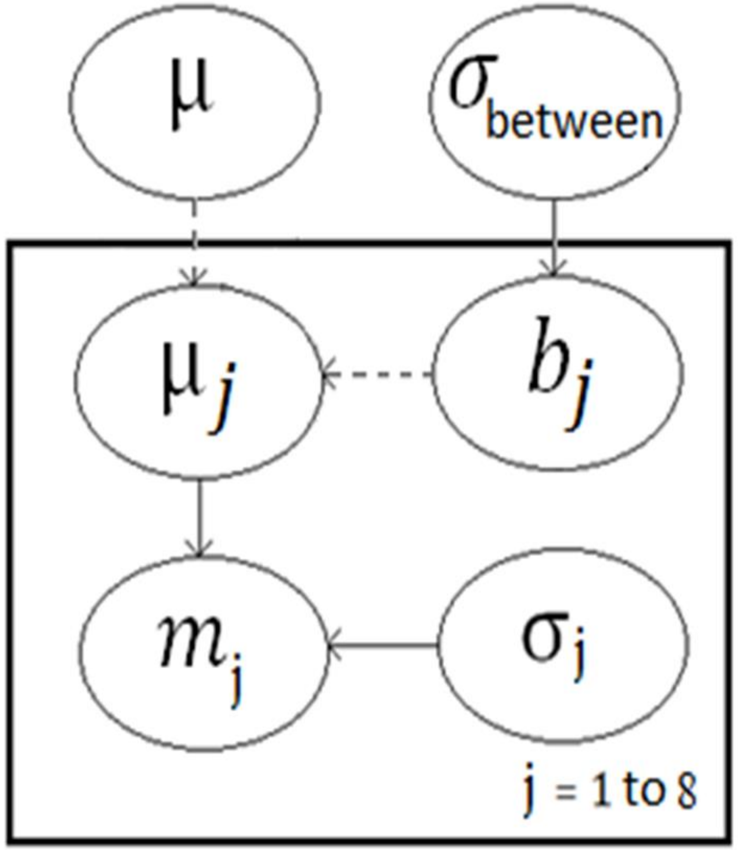
  σ_j estimated by s_j

Model allowing for variability between experts



How to integrate opinion variability between experts within the combined distribution?

Model allowing for variability between experts



Combined distribution - two possibilities (after antilogit transformation):

- **Distribution of μ**: model the uncertainty on the mean of the distribution of μ_j among experts

  (Mixed mod. μ)

- **Distribution of μ_j**: model the uncertainty around any individual value of μ_j, so a greater uncertainty due to inter-expert variability

  (Mixed mod. μ_j)

Simulations

- Four scenarios in which the following parameters varied:
  - **Number of experts n**
  - **Variability between their opinions** $\sigma_{between}$

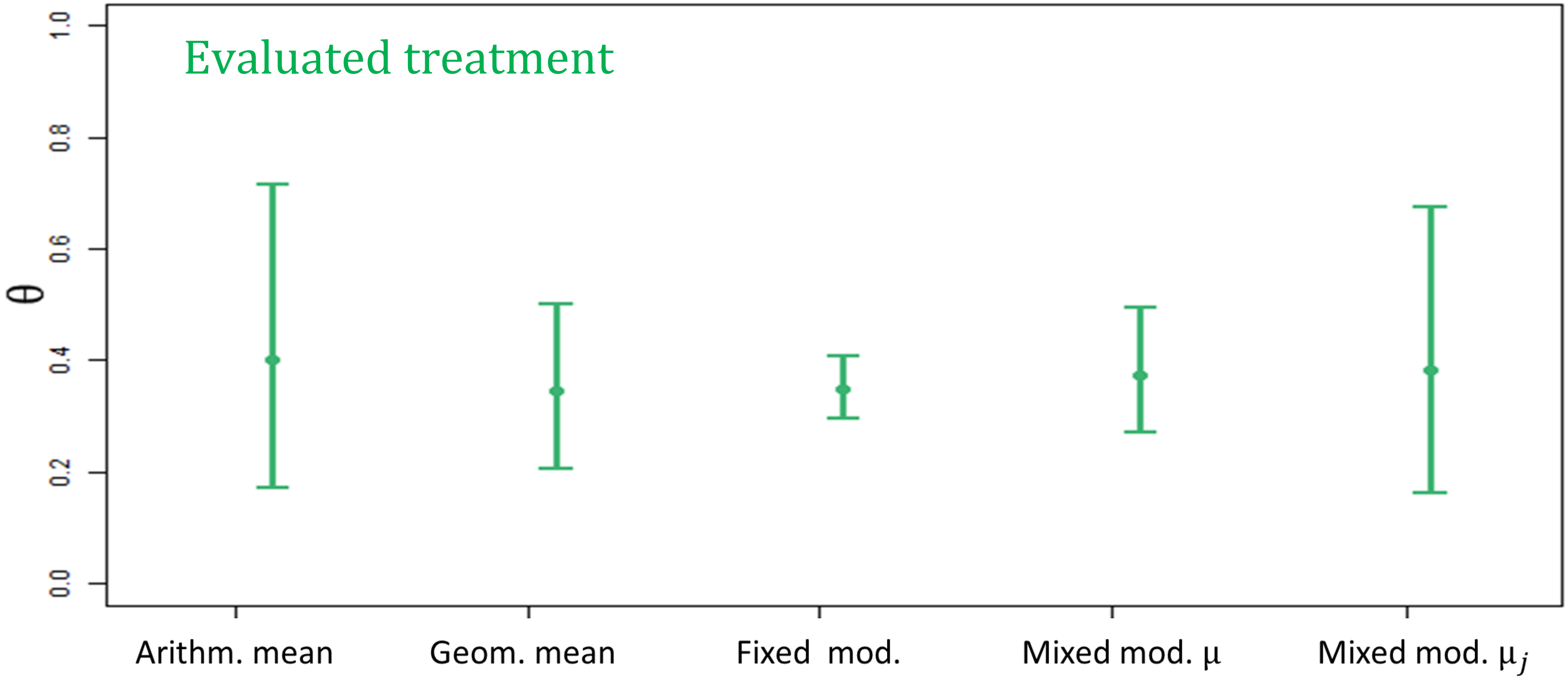
  Examination of their influence on combined distributions (all approaches)

- n expert distributions $\mathrm{N}(\mathrm{m_j}, \sigma_\mathrm{j})$
  - m_j generated from the model allowing for variability between experts (evaluated treatment)
  - σ_j fixed to the mean of s_j

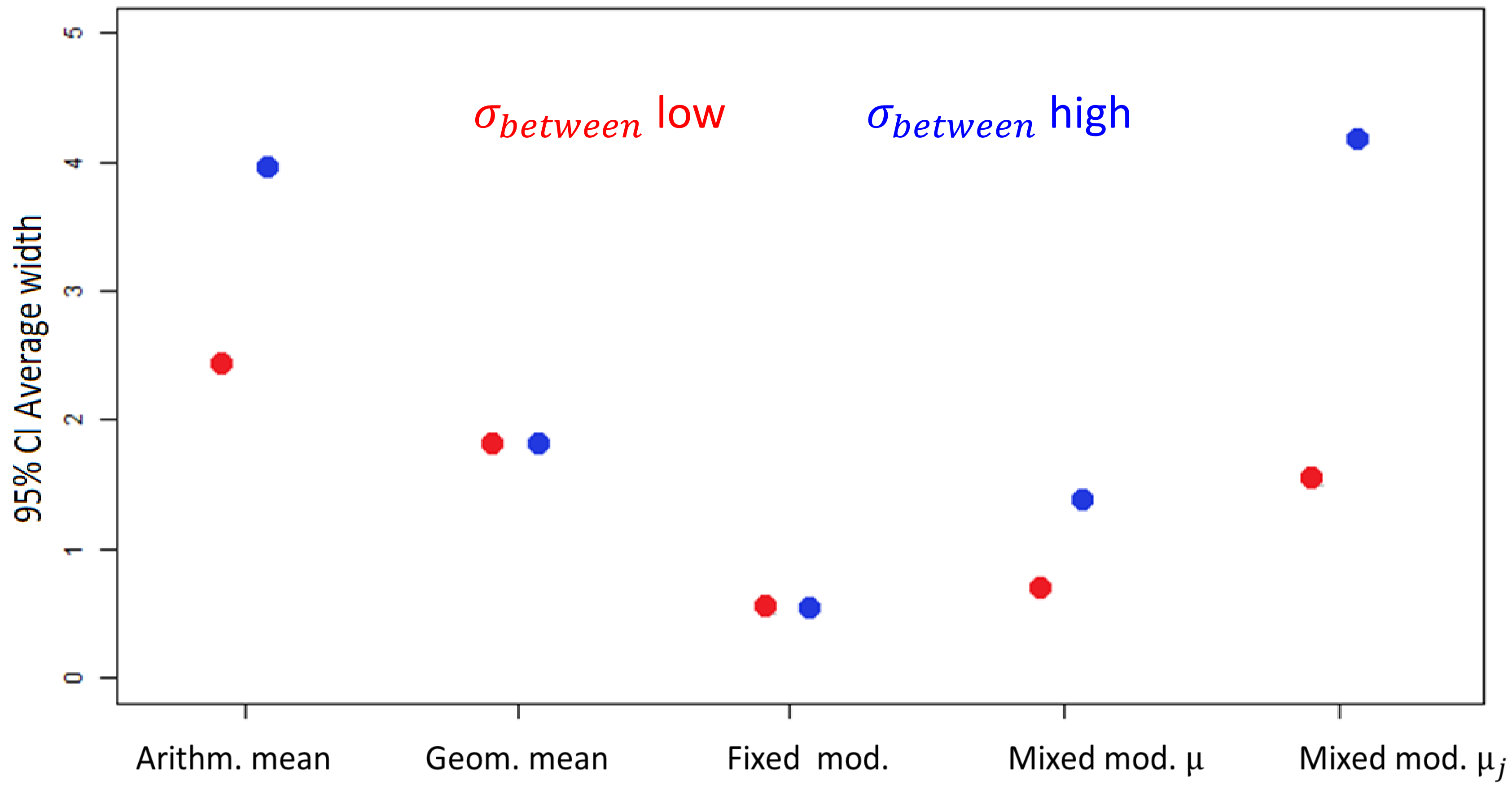
- Combined distributions compared in terms of **average width of 95% credibility intervals**

Results

Real experts data: 95% CI and means of the combined obtained distributions



Simulations: 95% CI average width for each approach/scenario



$\sigma_{between}$ increases:

CI width

Arithm. mean ↗

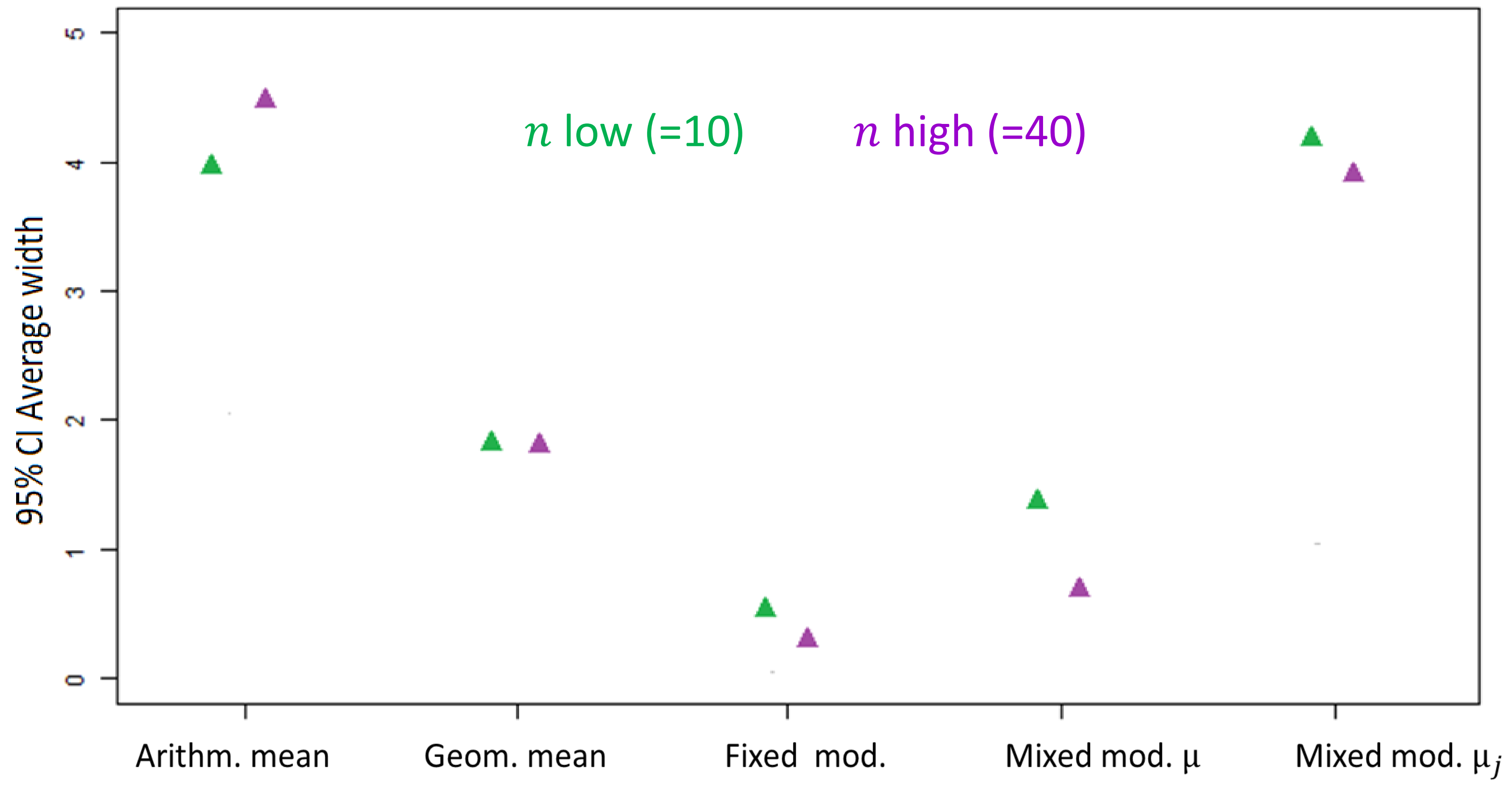
Geom. Mean =

Fixed mod. =

Mixed mod. μ ↗

Mixed mod. μ_j ↗

Simulations: 95% CI average width for each approach/scenario



n increases:

CI width

Arithm. mean ↗

Geom. Mean =

Fixed mod. ↘

Mixed mod. µ ↘

Mixed mod. μ_j ↘

Discussion

Arithmetic mean

- **Represents diversity** among expert opinions
- Combined distribution is **highly dispersed**
- Adding experts to a study **increases the CI width** **= Not expected**

Geometric mean

- **Forces consensus** between experts on θ value
- **Less dispersed** than with the arithmetic means
- **No effect of n and σ_{inter} = Not expected**

Fixed effect model

- **Least dispersed** combined distribution
- **Information provided by the experts is cumulative**
- **Possible to obtain the true value of θ** with a very large panel of experts (the dispersion tends to 0) **= Not expected**

Mixed effect model - distribution of μ

- **A bit more dispersed** than with fixed effect model

- **Possible to obtain the true value of θ** with a very large panel of experts (the dispersion tends to 0) **= Not expected**

Mixed effect model - distribution of μ_j

- **Dispersed** combined distribution
- **Integrates directly variability between experts** in the combined distributions
- n increases: **CI width decreases, but reaches the value of $\boldsymbol{\sigma_{between}}$** instead of 0

Conclusion

This work clarifies the interpretation of different combination approaches

Recommended approach: **Distribution of μ_j** obtained using a mixed model

- Take into account variability among expert opinions
- Information on the parameter value increases with the number of experts

Thank you