01-A-BHM-Casestudy-ORR-Larotrectinib

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# Description

Reproduce Bayesian hierarchical model for Larotrectinib ORR data from ERG analysis, NICE STA Committee papers (ID1299).

In addition:

* Fit fixed effects (FE) meta-analysis (MA) model.
* Fit random effects (RE) meta-analysis (MA) with alternative prior 1: Half-normal(sigma = 1).
* Fit random effects (RE) meta-analysis (MA) with alternative prior 2: Half-normal(sigma = 0.5).
* Fit RE MA models to subset of data where only tissues with at least one event and one non-event retained.
* Fit RE MA models to subset of data where only tissues with sample size >= 5 are retained.

The half-normal HN(sigma) is defined as: HN(sigma) = abs(N(Mean = 0, Var = sigma^2))

# Reproduce ERG meta-analysis of ORR data

Read in response rate data extracted from ERG report in NICE Committee papers.

**Table** ORR data included in BHM by ERG

|  |  |  |  |
| --- | --- | --- | --- |
| Tumour type | n | x | orr |
| Soft tissue sarcoma | 20 | 16 | 0.8 |
| Salivary gland | 17 | 15 | 0.88 |
| Infantile fibrosarcoma | 13 | 12 | 0.92 |
| Thyroid | 10 | 7 | 0.7 |
| Lung | 7 | 5 | 0.71 |
| Melanoma | 7 | 3 | 0.43 |
| Colon | 6 | 2 | 0.33 |
| GIST | 5 | 5 | 1 |
| Bone sarcoma | 2 | 1 | 0.5 |
| Cholangiocarcinoma | 2 | 0 | 0 |
| Appendix | 1 | 0 | 0 |
| Breast | 1 | 0 | 0 |
| Congenital mesoblastic nephroma | 1 | 1 | 1 |
| Pancreas | 1 | 0 | 0 |

Total sample size matches ERG analysis: 93.

Global parameters for BHM.

djags <- list(ns = nrow(dorr\_erg),  
 r = dorr\_erg$x,  
 n = dorr\_erg$n)  
  
n\_chains <- 3  
n\_iter <- 15000  
n\_burnin <- 2000  
n\_thin <- 1  
  
pars\_fe <- c("mu", "p.pop", "p", "theta", "theta.new", "p.new")

Priors selected by ERG, see Section 4.6 (ERG report page 66 (which is page 490 in Committee papers pdf)).

**Note:** there are two inconsistencies in the ERG report page 66 regarding prior distributions:

1. “The prior distribution for p was centred around a probability of 0.3 (a log-odds of -1.3863)”. -> logit(0.3) = -0.847 -> inv.logit(-1.3863) ~= 0.2 (which sounds low) I select p=0.3.
2. They sey they have selected a uniform prior U(0,5) for the random effects variance as suggested by Cunanan (2019). But the recommendation from Cunanan is to put this prior on the heterogeneity sd, not on the var. I will put the U(0,5) on the sd. This leads to the same results as and in particular to the same predictive distribution of a new effect as presented by the ERG. Therefore, I believe the ERG did, in their modelling, put the prior on the sd, while the text contains a slight error.

Fit the random effects MA model used by the ERG.

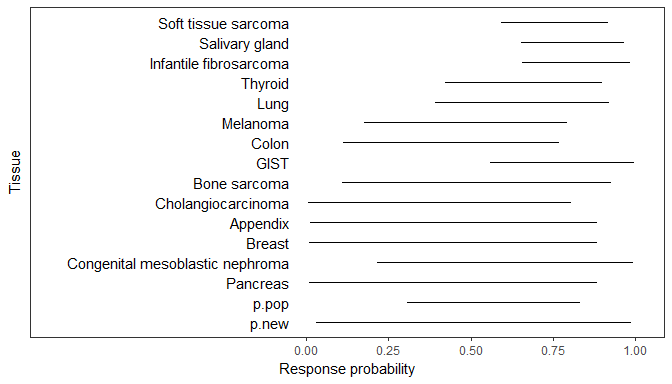
## module glm loaded

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 14  
## Unobserved stochastic nodes: 17  
## Total graph size: 70  
##   
## Initializing model

**Results: reproducing the ERG analysis**

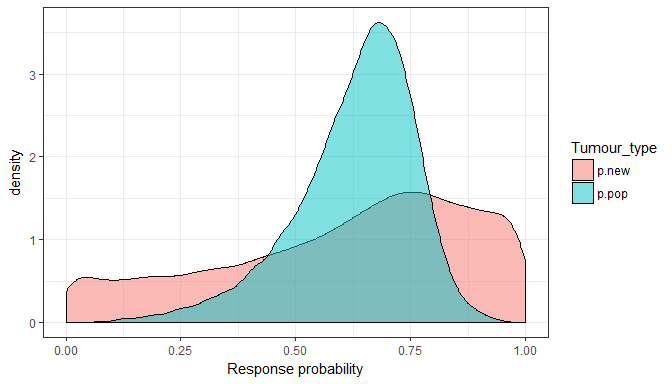
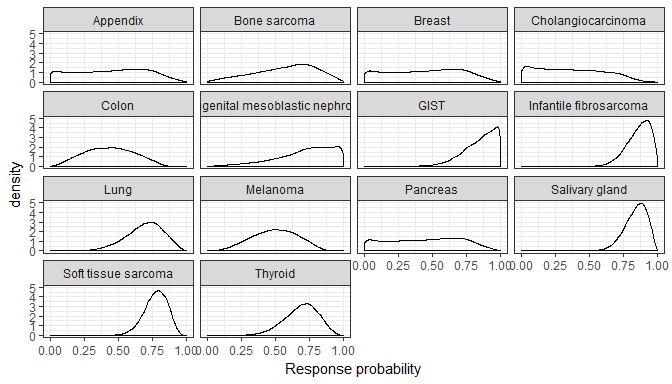
**Table** Reproducing ERG analysis: Study specific estimates

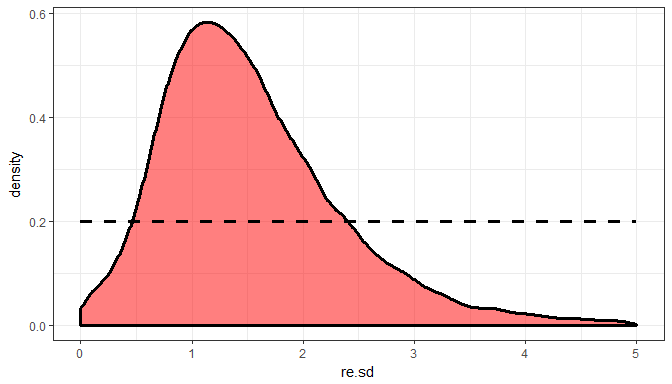
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.78 | 0.59 | 0.92 |
| Salivary gland | 0.85 | 0.65 | 0.96 |
| Infantile fibrosarcoma | 0.87 | 0.66 | 0.98 |
| Thyroid | 0.7 | 0.42 | 0.9 |
| Lung | 0.71 | 0.39 | 0.92 |
| Melanoma | 0.5 | 0.18 | 0.79 |
| Colon | 0.44 | 0.11 | 0.77 |
| GIST | 0.87 | 0.56 | 1 |
| Bone sarcoma | 0.6 | 0.11 | 0.93 |
| Cholangiocarcinoma | 0.35 | 0.0077 | 0.8 |
| Appendix | 0.46 | 0.012 | 0.88 |
| Breast | 0.46 | 0.011 | 0.88 |
| Congenital mesoblastic nephroma | 0.76 | 0.22 | 0.99 |
| Pancreas | 0.46 | 0.011 | 0.88 |
| p.pop | 0.65 | 0.31 | 0.83 |
| p.new | 0.66 | 0.031 | 0.99 |

**Figure** Reproducing ERG analysis: Forest plot 

**Table** Reproducing ERG analysis: Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.998 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 0.999 |
| Thyroid | 1 | 1 | 0.998 | 0.926 |
| Lung | 1 | 0.999 | 0.994 | 0.907 |
| Melanoma | 0.997 | 0.963 | 0.871 | 0.503 |
| Colon | 0.981 | 0.9 | 0.754 | 0.376 |
| GIST | 1 | 1 | 1 | 0.989 |
| Bone sarcoma | 0.979 | 0.932 | 0.864 | 0.653 |
| Cholangiocarcinoma | 0.824 | 0.687 | 0.558 | 0.312 |
| Appendix | 0.875 | 0.777 | 0.677 | 0.456 |
| Breast | 0.873 | 0.773 | 0.671 | 0.453 |
| Congenital mesoblastic nephroma | 0.995 | 0.979 | 0.951 | 0.842 |
| Pancreas | 0.873 | 0.775 | 0.672 | 0.453 |
| p.pop | 0.999 | 0.993 | 0.977 | 0.844 |
| p.new | 0.939 | 0.886 | 0.828 | 0.678 |

**Figure** Reproducing ERG analysis: Density estimates of response probability per tissue 

**Figure** Reproducing ERG analysis: Prior and posterior of random effect standard deviation 

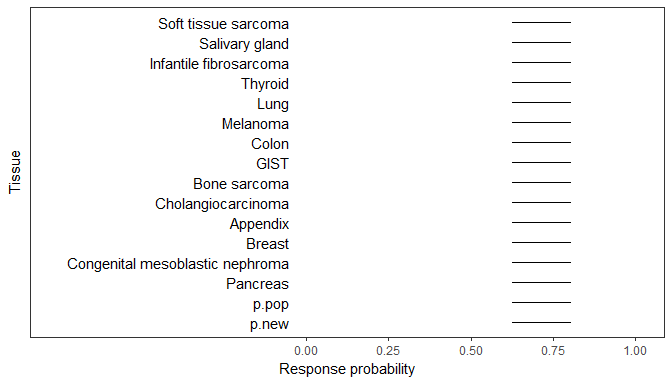
# For comparison: corresponding fixed effect model

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 14  
## Unobserved stochastic nodes: 1  
## Total graph size: 33  
##   
## Initializing model

**Results: FE model**

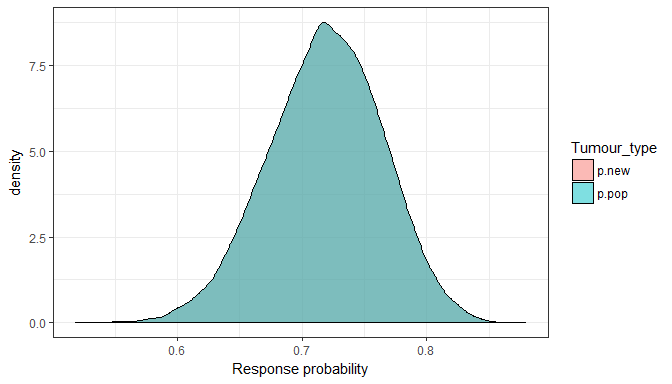
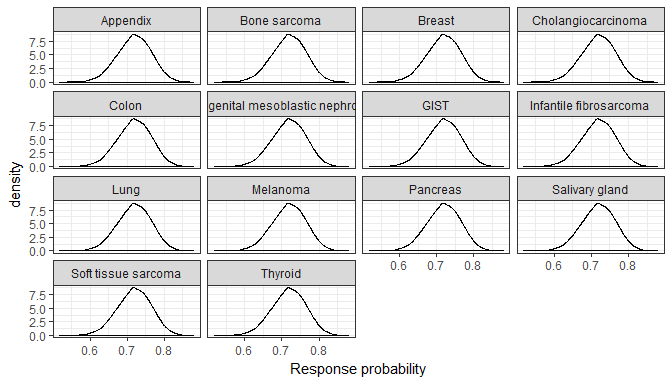
**Table** FE model estimates

|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.72 | 0.63 | 0.8 |
| Salivary gland | 0.72 | 0.63 | 0.8 |
| Infantile fibrosarcoma | 0.72 | 0.63 | 0.8 |
| Thyroid | 0.72 | 0.63 | 0.8 |
| Lung | 0.72 | 0.63 | 0.8 |
| Melanoma | 0.72 | 0.63 | 0.8 |
| Colon | 0.72 | 0.63 | 0.8 |
| GIST | 0.72 | 0.63 | 0.8 |
| Bone sarcoma | 0.72 | 0.63 | 0.8 |
| Cholangiocarcinoma | 0.72 | 0.63 | 0.8 |
| Appendix | 0.72 | 0.63 | 0.8 |
| Breast | 0.72 | 0.63 | 0.8 |
| Congenital mesoblastic nephroma | 0.72 | 0.63 | 0.8 |
| Pancreas | 0.72 | 0.63 | 0.8 |
| p.pop | 0.72 | 0.63 | 0.8 |
| p.new | 0.72 | 0.63 | 0.8 |

**Figure** FE model: Forest plot 

**Table** FE model: Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 1 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 1 |
| Thyroid | 1 | 1 | 1 | 1 |
| Lung | 1 | 1 | 1 | 1 |
| Melanoma | 1 | 1 | 1 | 1 |
| Colon | 1 | 1 | 1 | 1 |
| GIST | 1 | 1 | 1 | 1 |
| Bone sarcoma | 1 | 1 | 1 | 1 |
| Cholangiocarcinoma | 1 | 1 | 1 | 1 |
| Appendix | 1 | 1 | 1 | 1 |
| Breast | 1 | 1 | 1 | 1 |
| Congenital mesoblastic nephroma | 1 | 1 | 1 | 1 |
| Pancreas | 1 | 1 | 1 | 1 |
| p.pop | 1 | 1 | 1 | 1 |
| p.new | 1 | 1 | 1 | 1 |

**Figure** FE model: Density estimates of response probability per tissue 

# Alternative prior 1: HN(sigma = 1)

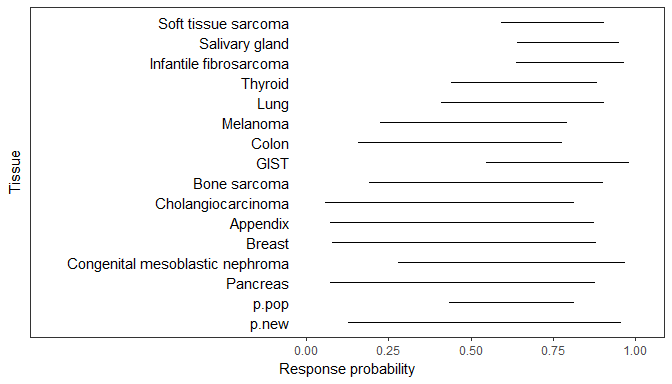
Use the same priors for the population mean mu, but instead of the U(0,5) for RE SD, use a half-normal(sigma = 1).

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 14  
## Unobserved stochastic nodes: 17  
## Total graph size: 71  
##   
## Initializing model

**Results: Alternative RE prior 1: HN(sigma = 1)**

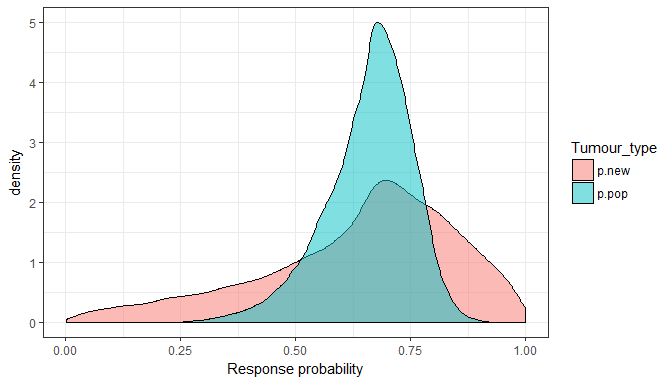
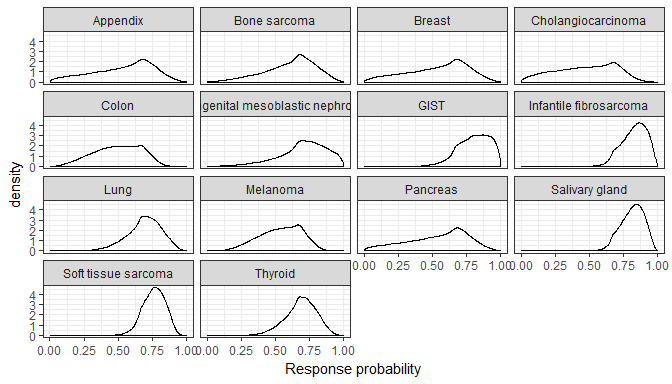
**Table** Alternative RE prior 1: HN(sigma = 1): response estimates

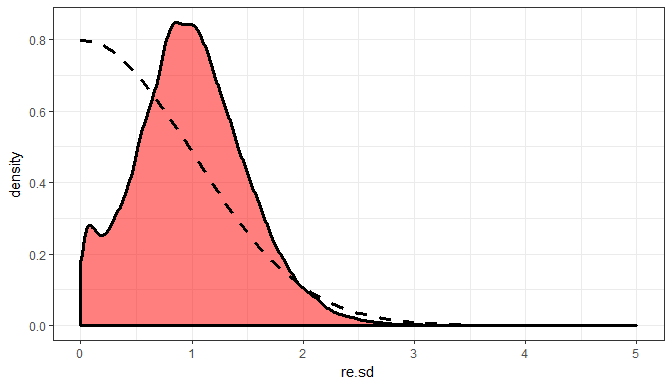
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.77 | 0.59 | 0.9 |
| Salivary gland | 0.82 | 0.64 | 0.95 |
| Infantile fibrosarcoma | 0.84 | 0.64 | 0.97 |
| Thyroid | 0.7 | 0.44 | 0.88 |
| Lung | 0.7 | 0.41 | 0.9 |
| Melanoma | 0.55 | 0.22 | 0.79 |
| Colon | 0.51 | 0.16 | 0.78 |
| GIST | 0.81 | 0.55 | 0.98 |
| Bone sarcoma | 0.64 | 0.19 | 0.9 |
| Cholangiocarcinoma | 0.49 | 0.057 | 0.81 |
| Appendix | 0.58 | 0.073 | 0.88 |
| Breast | 0.58 | 0.079 | 0.88 |
| Congenital mesoblastic nephroma | 0.72 | 0.28 | 0.97 |
| Pancreas | 0.58 | 0.073 | 0.88 |
| p.pop | 0.67 | 0.43 | 0.81 |
| p.new | 0.68 | 0.13 | 0.95 |

**Figure** Alternative RE prior 1: HN(sigma = 1): Forest plot 

**Table** Alternative RE prior 1: HN(sigma = 1): Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.997 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 0.999 |
| Thyroid | 1 | 1 | 0.999 | 0.938 |
| Lung | 1 | 1 | 0.997 | 0.92 |
| Melanoma | 0.999 | 0.984 | 0.924 | 0.614 |
| Colon | 0.994 | 0.951 | 0.854 | 0.513 |
| GIST | 1 | 1 | 1 | 0.988 |
| Bone sarcoma | 0.994 | 0.973 | 0.928 | 0.746 |
| Cholangiocarcinoma | 0.948 | 0.86 | 0.753 | 0.484 |
| Appendix | 0.963 | 0.903 | 0.829 | 0.613 |
| Breast | 0.964 | 0.903 | 0.826 | 0.613 |
| Congenital mesoblastic nephroma | 0.997 | 0.99 | 0.97 | 0.869 |
| Pancreas | 0.962 | 0.903 | 0.827 | 0.612 |
| p.pop | 1 | 1 | 0.998 | 0.934 |
| p.new | 0.982 | 0.953 | 0.909 | 0.767 |

**Figure** Alternative RE prior 1: HN(sigma = 1): Density estimates of response probability per tissue 

**Figure** Alternative RE prior 1: HN(sigma = 1): Prior and posterior of random effect standard deviation 

# Alternative prior 2: HN(sigma = 0.5)

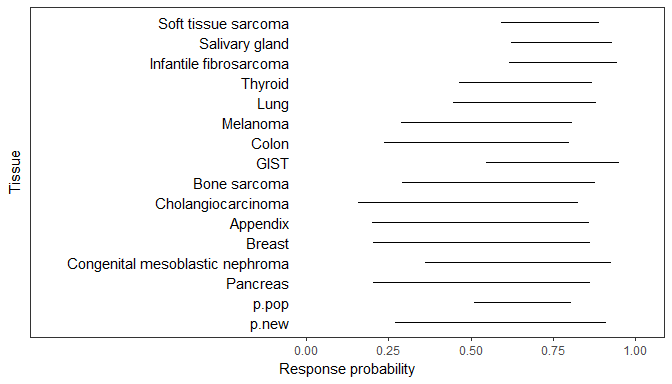
Use the same priors for the population mean mu, but instead of the U(0,5) for RE SD, use a half-normal(sigma = 0.5).

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 14  
## Unobserved stochastic nodes: 17  
## Total graph size: 71  
##   
## Initializing model

**Results: Alternative RE prior 2: HN(sigma = 0.5)**

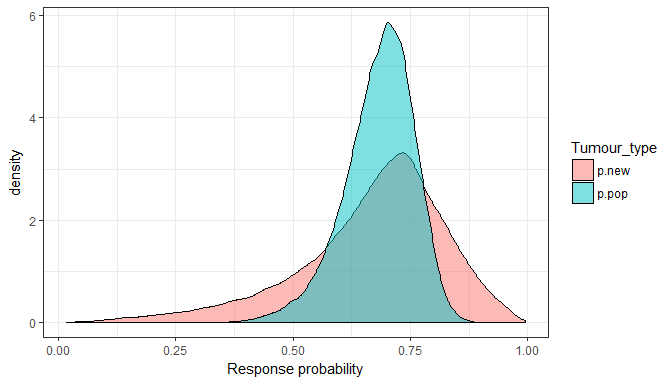
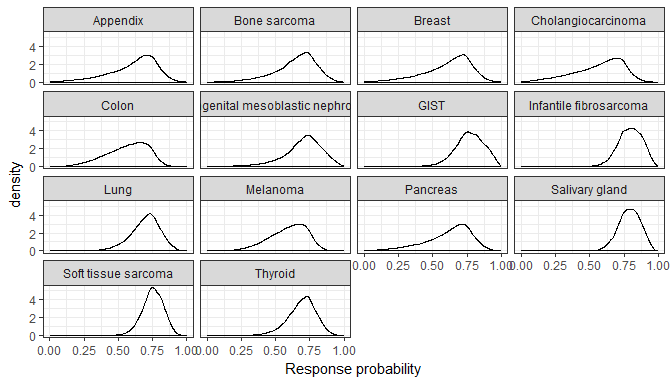
**Table** Alternative RE prior 2: HN(sigma = 0.5): response estimates

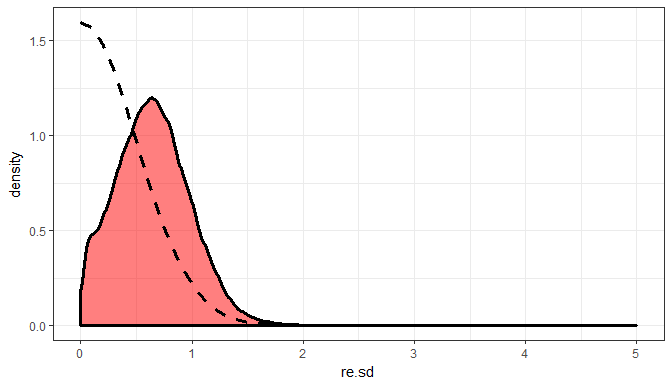
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.75 | 0.59 | 0.89 |
| Salivary gland | 0.79 | 0.62 | 0.93 |
| Infantile fibrosarcoma | 0.8 | 0.62 | 0.94 |
| Thyroid | 0.7 | 0.46 | 0.87 |
| Lung | 0.71 | 0.45 | 0.88 |
| Melanoma | 0.61 | 0.29 | 0.81 |
| Colon | 0.59 | 0.24 | 0.8 |
| GIST | 0.77 | 0.55 | 0.95 |
| Bone sarcoma | 0.67 | 0.29 | 0.88 |
| Cholangiocarcinoma | 0.6 | 0.16 | 0.83 |
| Appendix | 0.65 | 0.2 | 0.86 |
| Breast | 0.65 | 0.2 | 0.86 |
| Congenital mesoblastic nephroma | 0.72 | 0.36 | 0.93 |
| Pancreas | 0.65 | 0.2 | 0.86 |
| p.pop | 0.69 | 0.51 | 0.81 |
| p.new | 0.7 | 0.27 | 0.91 |

**Figure** Alternative RE prior 2: HN(sigma = 0.5): Forest plot 

**Table** Alternative RE prior 2: HN(sigma = 0.5): Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.998 |
| Salivary gland | 1 | 1 | 1 | 0.999 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 0.999 |
| Thyroid | 1 | 1 | 0.999 | 0.957 |
| Lung | 1 | 1 | 0.998 | 0.947 |
| Melanoma | 1 | 0.995 | 0.971 | 0.755 |
| Colon | 0.999 | 0.987 | 0.942 | 0.687 |
| GIST | 1 | 1 | 1 | 0.988 |
| Bone sarcoma | 0.999 | 0.994 | 0.972 | 0.844 |
| Cholangiocarcinoma | 0.99 | 0.96 | 0.904 | 0.688 |
| Appendix | 0.994 | 0.976 | 0.94 | 0.773 |
| Breast | 0.995 | 0.976 | 0.939 | 0.773 |
| Congenital mesoblastic nephroma | 1 | 0.996 | 0.987 | 0.913 |
| Pancreas | 0.994 | 0.976 | 0.94 | 0.777 |
| p.pop | 1 | 1 | 1 | 0.979 |
| p.new | 0.998 | 0.988 | 0.968 | 0.863 |

**Figure** Alternative RE prior 2: HN(sigma = 0.5): Density estimates of response probability per tissue 

**Figure** Alternative RE prior 2: HN(sigma = 0.5): Prior and posterior of random effect standard deviation 

# At least one event/non-event (but with ERG prior)

ERG model applied to a reduced data set: contains only tissue types with at least 1 event and 1 non-event. This means the analysis data set is the following.

**Table** ORR data (reduced set)

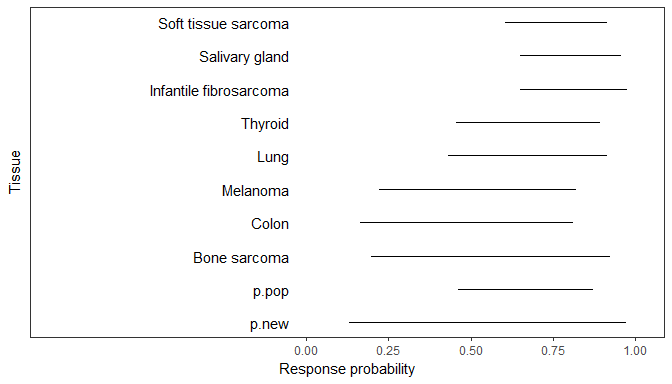
|  |  |  |  |
| --- | --- | --- | --- |
| Tumour type | n | x | orr |
| Soft tissue sarcoma | 20 | 16 | 0.8 |
| Salivary gland | 17 | 15 | 0.88 |
| Infantile fibrosarcoma | 13 | 12 | 0.92 |
| Thyroid | 10 | 7 | 0.7 |
| Lung | 7 | 5 | 0.71 |
| Melanoma | 7 | 3 | 0.43 |
| Colon | 6 | 2 | 0.33 |
| Bone sarcoma | 2 | 1 | 0.5 |

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 8  
## Unobserved stochastic nodes: 11  
## Total graph size: 46  
##   
## Initializing model

**Results: Reduced data set**

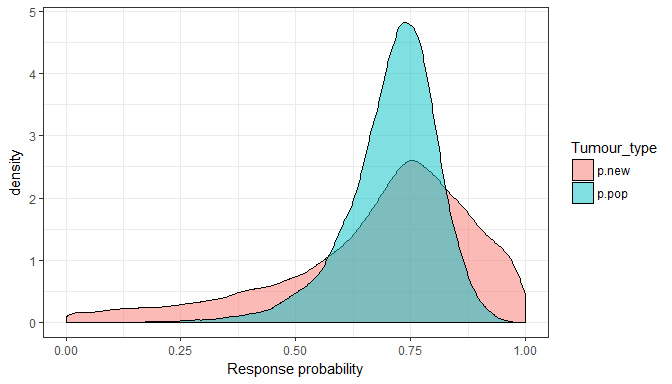
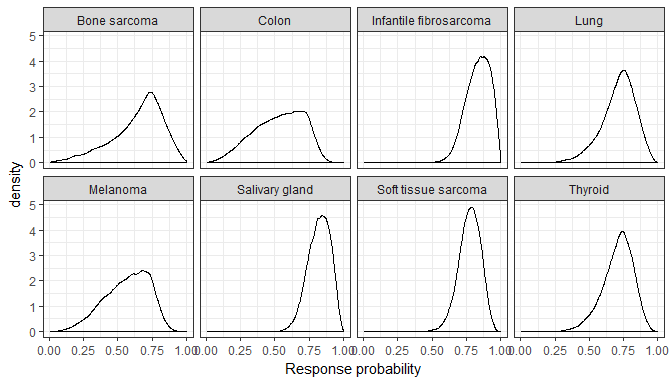
**Table** Reduced data set: response estimates

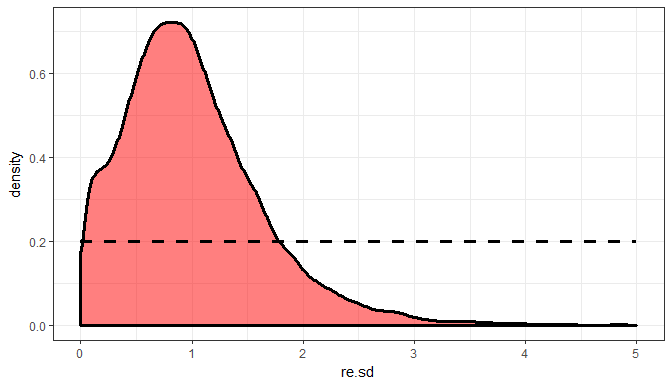
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.78 | 0.6 | 0.91 |
| Salivary gland | 0.83 | 0.65 | 0.96 |
| Infantile fibrosarcoma | 0.84 | 0.65 | 0.97 |
| Thyroid | 0.72 | 0.46 | 0.89 |
| Lung | 0.73 | 0.43 | 0.91 |
| Melanoma | 0.59 | 0.22 | 0.82 |
| Colon | 0.55 | 0.16 | 0.81 |
| Bone sarcoma | 0.69 | 0.2 | 0.92 |
| p.pop | 0.72 | 0.46 | 0.87 |
| p.new | 0.73 | 0.13 | 0.97 |

**Figure** Reduced data set: Forest plot 

**Table** Reduced data set: Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.998 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 0.999 |
| Thyroid | 1 | 1 | 0.999 | 0.952 |
| Lung | 1 | 1 | 0.997 | 0.94 |
| Melanoma | 0.999 | 0.983 | 0.936 | 0.675 |
| Colon | 0.993 | 0.958 | 0.877 | 0.584 |
| Bone sarcoma | 0.994 | 0.975 | 0.942 | 0.797 |
| p.pop | 1 | 0.999 | 0.996 | 0.961 |
| p.new | 0.981 | 0.959 | 0.93 | 0.825 |

**Figure** Reduced data set: Density estimates of response probability per tissue 

**Figure** Reduced data set: Prior and posterior of random effect standard deviation 

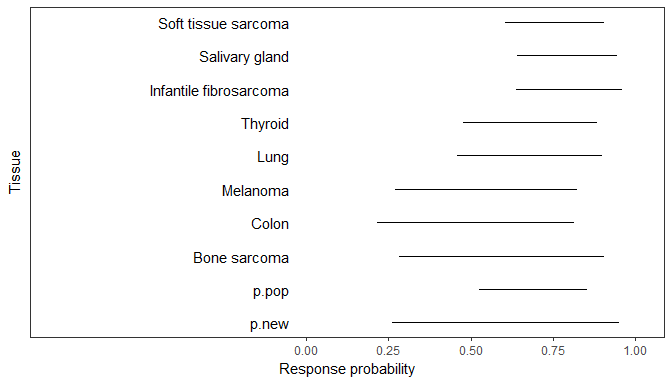
# At least one event/non-event and with alternative prior 1: HN(sigma = 1)

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 8  
## Unobserved stochastic nodes: 11  
## Total graph size: 47  
##   
## Initializing model

**Results: Reduced data set and Alternative RE prior 1: HN(sigma = 1)**

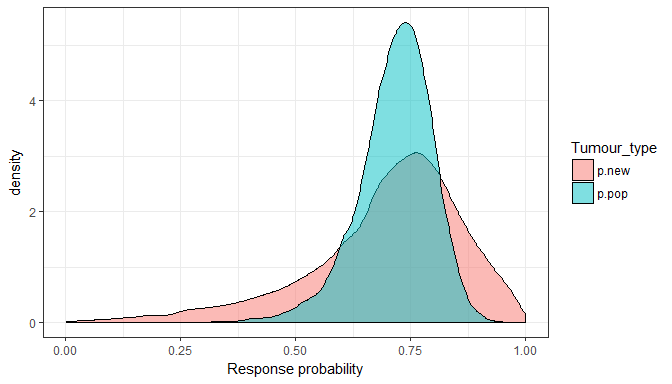
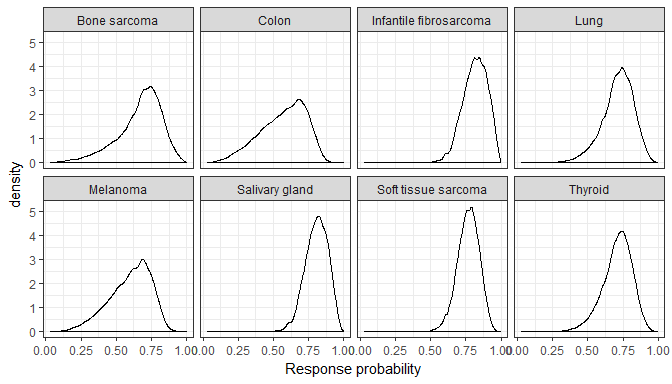
**Table** Reduced data set and Alternative RE prior 1: HN(sigma = 1): response estimates

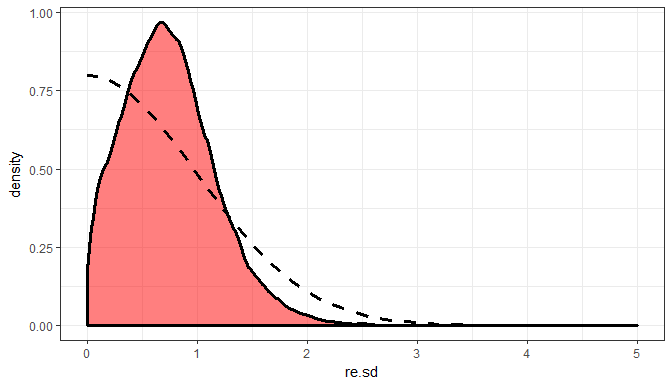
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.77 | 0.6 | 0.9 |
| Salivary gland | 0.81 | 0.64 | 0.94 |
| Infantile fibrosarcoma | 0.82 | 0.64 | 0.96 |
| Thyroid | 0.72 | 0.48 | 0.88 |
| Lung | 0.73 | 0.46 | 0.9 |
| Melanoma | 0.62 | 0.27 | 0.82 |
| Colon | 0.59 | 0.22 | 0.82 |
| Bone sarcoma | 0.7 | 0.28 | 0.9 |
| p.pop | 0.72 | 0.52 | 0.85 |
| p.new | 0.73 | 0.26 | 0.95 |

**Figure** Reduced data set and Alternative RE prior 1: HN(sigma = 1): Forest plot 

**Table** Reduced data set and Alternative RE prior 1: HN(sigma = 1): Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.999 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 0.999 |
| Thyroid | 1 | 1 | 1 | 0.964 |
| Lung | 1 | 1 | 0.999 | 0.955 |
| Melanoma | 1 | 0.992 | 0.962 | 0.756 |
| Colon | 0.998 | 0.981 | 0.931 | 0.682 |
| Bone sarcoma | 0.999 | 0.99 | 0.971 | 0.854 |
| p.pop | 1 | 1 | 0.999 | 0.984 |
| p.new | 0.996 | 0.985 | 0.966 | 0.877 |

**Figure** Reduced data set and Alternative RE prior 1: HN(sigma = 1): Density estimates of response probability per tissue 

**Figure** Reduced data set and Alternative RE prior 1: HN(sigma = 1): Prior and posterior of random effect standard deviation 

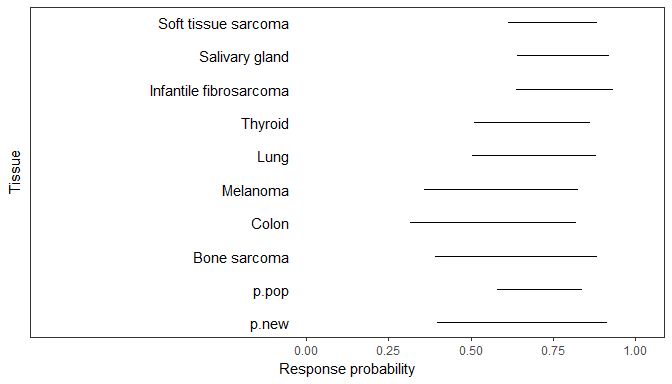
# At least one event/non-event and with alternative prior 2: HN(sigma = 0.5)

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 8  
## Unobserved stochastic nodes: 11  
## Total graph size: 47  
##   
## Initializing model

**Results: Reduced data set and Alternative RE prior 2: HN(sigma = 0.5)**

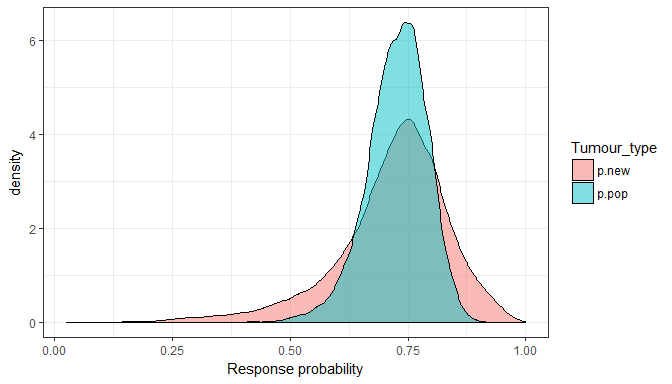
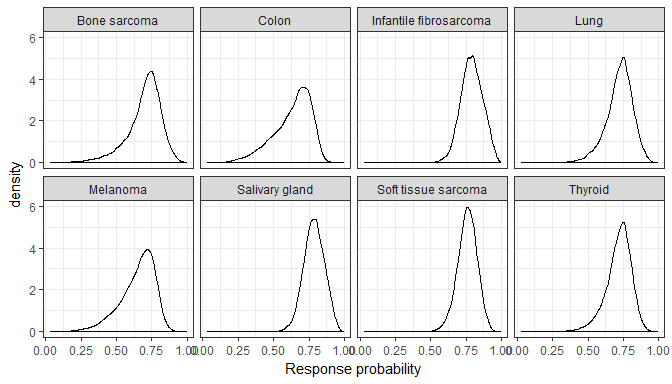
**Table** Reduced data set and Alternative RE prior 2: HN(sigma = 0.5): response estimates

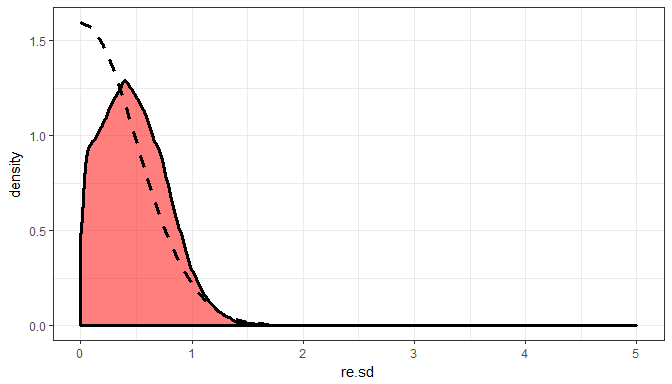
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.76 | 0.61 | 0.88 |
| Salivary gland | 0.79 | 0.64 | 0.92 |
| Infantile fibrosarcoma | 0.79 | 0.64 | 0.93 |
| Thyroid | 0.73 | 0.51 | 0.86 |
| Lung | 0.73 | 0.51 | 0.88 |
| Melanoma | 0.67 | 0.36 | 0.83 |
| Colon | 0.66 | 0.32 | 0.82 |
| Bone sarcoma | 0.72 | 0.39 | 0.88 |
| p.pop | 0.73 | 0.58 | 0.84 |
| p.new | 0.73 | 0.4 | 0.91 |

**Figure** Reduced data set and Alternative RE prior 2: HN(sigma = 0.5): Forest plot 

**Table** Reduced data set and Alternative RE prior 2: HN(sigma = 0.5): Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.999 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 0.999 |
| Thyroid | 1 | 1 | 1 | 0.979 |
| Lung | 1 | 1 | 1 | 0.978 |
| Melanoma | 1 | 0.998 | 0.989 | 0.877 |
| Colon | 1 | 0.997 | 0.98 | 0.832 |
| Bone sarcoma | 1 | 0.998 | 0.991 | 0.929 |
| p.pop | 1 | 1 | 1 | 0.996 |
| p.new | 1 | 0.998 | 0.991 | 0.94 |

**Figure** Reduced data set and Alternative RE prior 2: HN(sigma = 0.5): Density estimates of response probability per tissue 

**Figure** Reduced data set and Alternative RE prior 2: HN(sigma = 0.5): Prior and posterior of random effect standard deviation 

# Minimal size of 5 (but with ERG prior)

ERG model applied to a reduced data set: contains only tissue types with at least five observations. This means the analysis data set is the following.

**Table** ORR data (reduced to tissues with size >= 5)

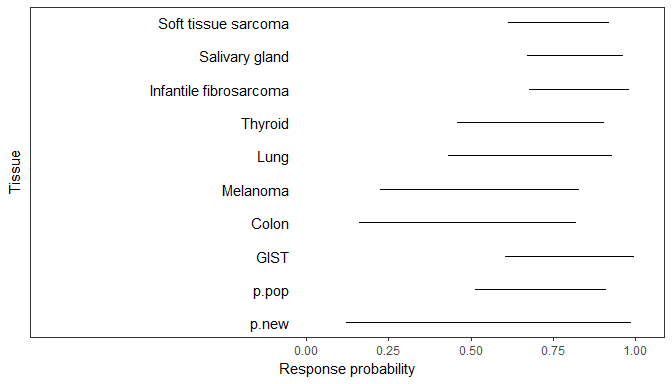
|  |  |  |  |
| --- | --- | --- | --- |
| Tumour type | n | x | orr |
| Soft tissue sarcoma | 20 | 16 | 0.8 |
| Salivary gland | 17 | 15 | 0.88 |
| Infantile fibrosarcoma | 13 | 12 | 0.92 |
| Thyroid | 10 | 7 | 0.7 |
| Lung | 7 | 5 | 0.71 |
| Melanoma | 7 | 3 | 0.43 |
| Colon | 6 | 2 | 0.33 |
| GIST | 5 | 5 | 1 |

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 8  
## Unobserved stochastic nodes: 11  
## Total graph size: 46  
##   
## Initializing model

**Results: subset (n>=5)**

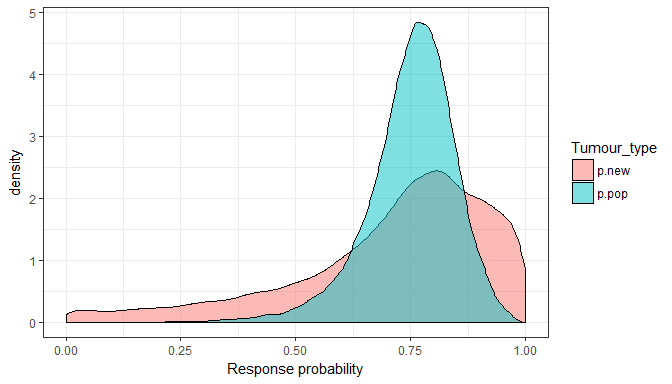
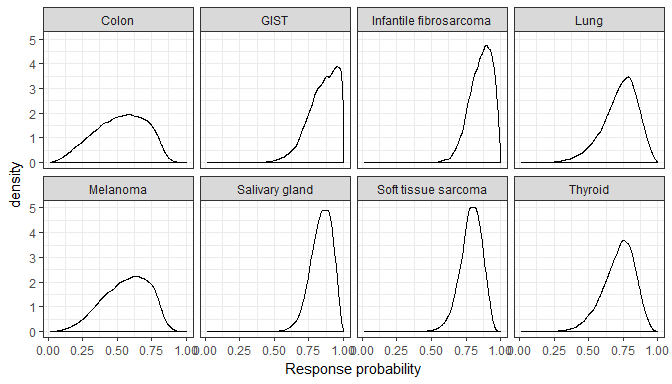
**Table** subset (n>=5): response estimates

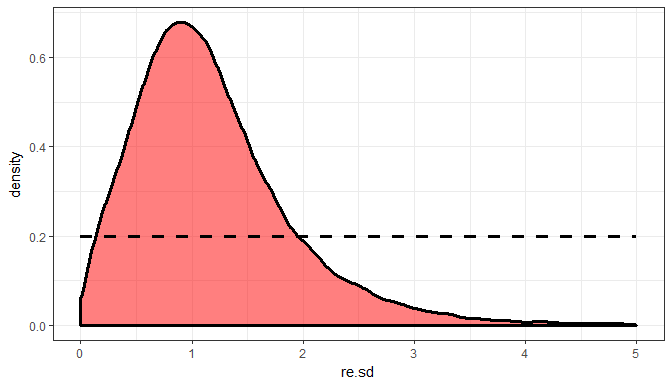
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.79 | 0.61 | 0.92 |
| Salivary gland | 0.85 | 0.67 | 0.96 |
| Infantile fibrosarcoma | 0.87 | 0.68 | 0.98 |
| Thyroid | 0.73 | 0.46 | 0.9 |
| Lung | 0.74 | 0.43 | 0.93 |
| Melanoma | 0.58 | 0.22 | 0.83 |
| Colon | 0.54 | 0.16 | 0.82 |
| GIST | 0.87 | 0.6 | 0.99 |
| p.pop | 0.76 | 0.51 | 0.91 |
| p.new | 0.76 | 0.12 | 0.99 |

**Figure** subset (n>=5): Forest plot 

**Table** subset (n>=5): Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.998 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 1 |
| Thyroid | 1 | 1 | 0.999 | 0.953 |
| Lung | 1 | 0.999 | 0.997 | 0.943 |
| Melanoma | 0.999 | 0.983 | 0.933 | 0.663 |
| Colon | 0.993 | 0.954 | 0.868 | 0.566 |
| GIST | 1 | 1 | 1 | 0.995 |
| p.pop | 1 | 0.999 | 0.998 | 0.979 |
| p.new | 0.979 | 0.958 | 0.93 | 0.838 |

**Figure** subset (n>=5): Density estimates of response probability per tissue 

**Figure** subset (n>=5): Prior and posterior of random effect standard deviation 

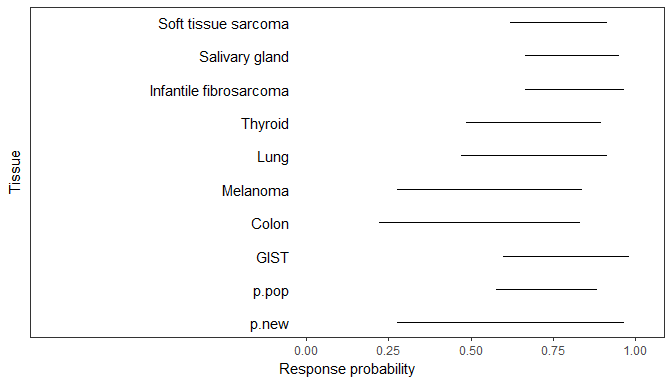
# Minimal size of 5 and with alternative prior 1: HN(sigma = 1)

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 8  
## Unobserved stochastic nodes: 11  
## Total graph size: 47  
##   
## Initializing model

**Results: subset (n>=5) and Alternative RE prior 1: HN(sigma = 1)**

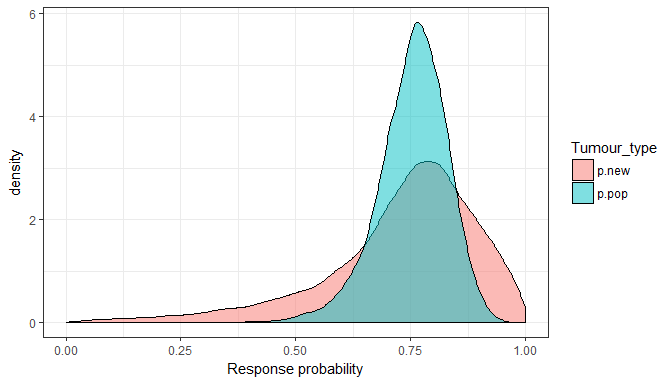
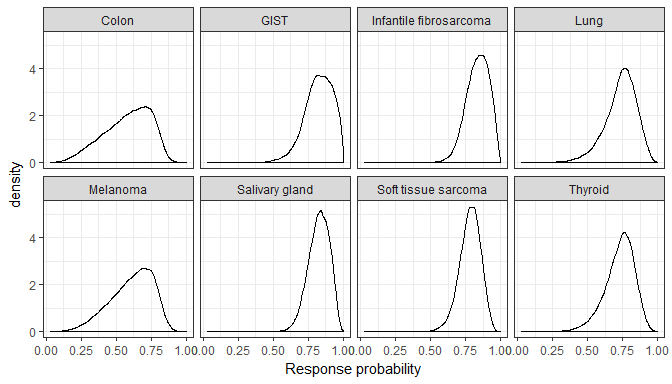
**Table** subset (n>=5) and Alternative RE prior 1: HN(sigma = 1): response estimates

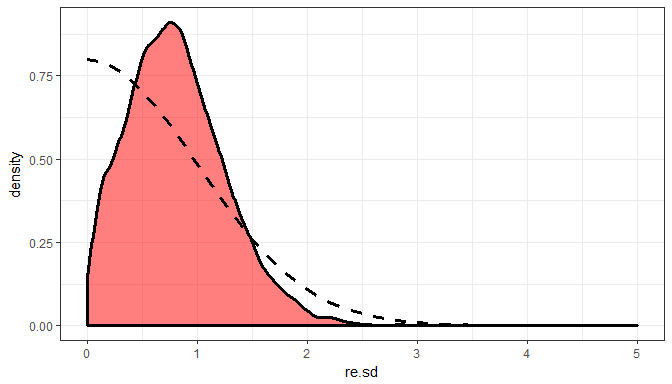
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.79 | 0.62 | 0.91 |
| Salivary gland | 0.83 | 0.67 | 0.95 |
| Infantile fibrosarcoma | 0.84 | 0.66 | 0.97 |
| Thyroid | 0.74 | 0.49 | 0.9 |
| Lung | 0.75 | 0.47 | 0.91 |
| Melanoma | 0.63 | 0.28 | 0.84 |
| Colon | 0.6 | 0.22 | 0.83 |
| GIST | 0.83 | 0.6 | 0.98 |
| p.pop | 0.76 | 0.58 | 0.88 |
| p.new | 0.76 | 0.28 | 0.97 |

**Figure** subset (n>=5) and Alternative RE prior 1: HN(sigma = 1): Forest plot 

**Table** subset (n>=5) and Alternative RE prior 1: HN(sigma = 1): Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.999 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 1 |
| Thyroid | 1 | 1 | 1 | 0.97 |
| Lung | 1 | 1 | 0.999 | 0.964 |
| Melanoma | 0.999 | 0.993 | 0.966 | 0.767 |
| Colon | 0.998 | 0.982 | 0.932 | 0.694 |
| GIST | 1 | 1 | 1 | 0.995 |
| p.pop | 1 | 1 | 1 | 0.994 |
| p.new | 0.995 | 0.986 | 0.971 | 0.899 |

**Figure** subset (n>=5) and Alternative RE prior 1: HN(sigma = 1): Density estimates of response probability per tissue 

**Figure** subset (n>=5) and Alternative RE prior 1: HN(sigma = 1): Prior and posterior of random effect standard deviation 

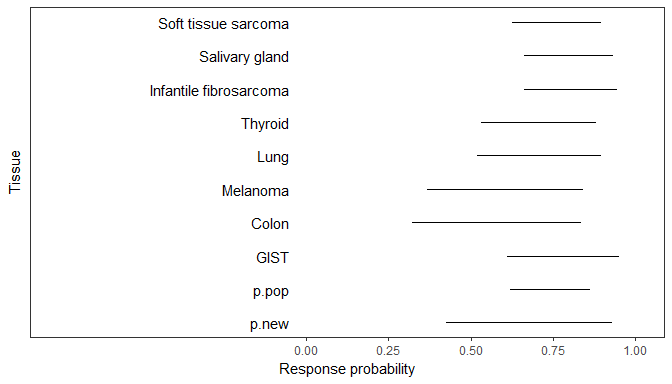
# Minimal size of 5 and with alternative prior 2: HN(sigma = 0.5)

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 8  
## Unobserved stochastic nodes: 11  
## Total graph size: 47  
##   
## Initializing model

**Results: subset (n>=5) and Alternative RE prior 2: HN(sigma = 0.5)**

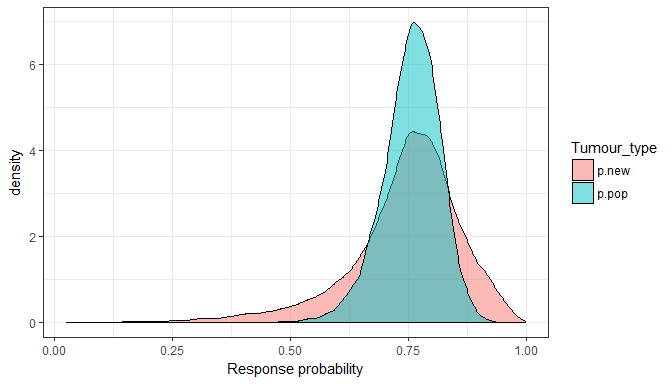
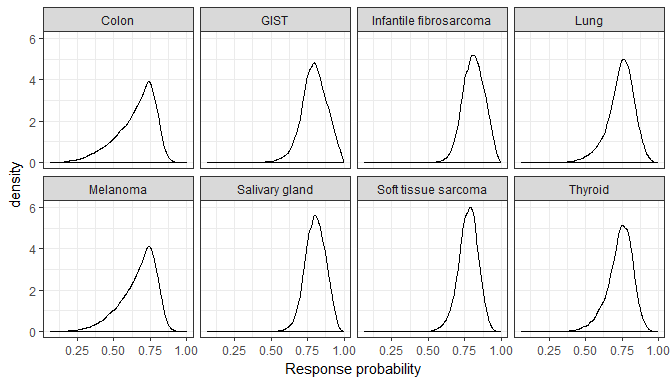
**Table** subset (n>=5) and Alternative RE prior 2: HN(sigma = 0.5): response estimates

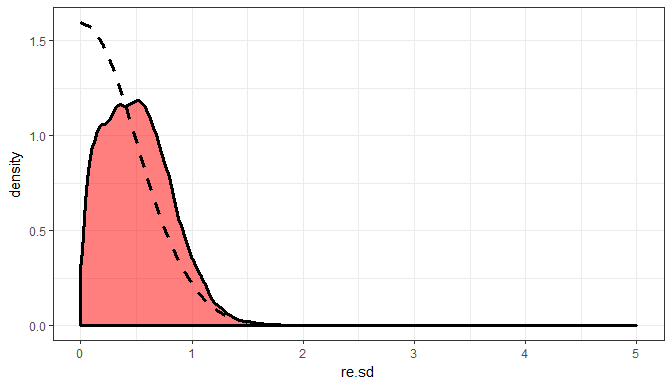
|  |  |  |  |
| --- | --- | --- | --- |
| node | est | ci\_lo | ci\_up |
| Soft tissue sarcoma | 0.78 | 0.63 | 0.9 |
| Salivary gland | 0.8 | 0.66 | 0.93 |
| Infantile fibrosarcoma | 0.81 | 0.66 | 0.94 |
| Thyroid | 0.75 | 0.53 | 0.88 |
| Lung | 0.75 | 0.52 | 0.89 |
| Melanoma | 0.69 | 0.37 | 0.84 |
| Colon | 0.68 | 0.32 | 0.83 |
| GIST | 0.8 | 0.61 | 0.95 |
| p.pop | 0.76 | 0.62 | 0.86 |
| p.new | 0.76 | 0.42 | 0.93 |

**Figure** subset (n>=5) and Alternative RE prior 2: HN(sigma = 0.5): Forest plot 

**Table** subset (n>=5) and Alternative RE prior 2: HN(sigma = 0.5): Threshold probabilities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| node | ProbAbove0.1 | ProbAbove0.2 | ProbAbove0.3 | ProbAbove0.5 |
| Soft tissue sarcoma | 1 | 1 | 1 | 0.999 |
| Salivary gland | 1 | 1 | 1 | 1 |
| Infantile fibrosarcoma | 1 | 1 | 1 | 0.999 |
| Thyroid | 1 | 1 | 1 | 0.985 |
| Lung | 1 | 1 | 0.999 | 0.982 |
| Melanoma | 1 | 0.999 | 0.991 | 0.89 |
| Colon | 1 | 0.996 | 0.981 | 0.852 |
| GIST | 1 | 1 | 1 | 0.997 |
| p.pop | 1 | 1 | 1 | 0.999 |
| p.new | 1 | 0.997 | 0.992 | 0.954 |

**Figure** subset (n>=5) and Alternative RE prior 2: HN(sigma = 0.5): Density estimates of response probability per tissue 

**Figure** subset (n>=5) and Alternative RE prior 2: HN(sigma = 0.5): Prior and posterior of random effect standard deviation 

# Compare posterior inferences across RE fits

**Table** Compare RE SD posterior summaries across models

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | 2.5% | 25% | 50% | 75% | 97.5% | IQR | CrIR |
| U(0,5) | 0.315 | 0.967 | 1.4 | 1.97 | 3.58 | 1 | 3.27 |
| HN(1) | 0.0677 | 0.658 | 0.972 | 1.3 | 2.04 | 0.645 | 1.97 |
| HN(0.5) | 0.0643 | 0.408 | 0.635 | 0.863 | 1.33 | 0.454 | 1.26 |
| Event/non-event and U(0,5) | 0.0756 | 0.564 | 0.917 | 1.34 | 2.57 | 0.774 | 2.49 |
| Event/non-event and HN(1) | 0.0701 | 0.437 | 0.709 | 0.999 | 1.7 | 0.562 | 1.63 |
| Event/non-event and HN(0.5) | 0.0275 | 0.252 | 0.454 | 0.677 | 1.11 | 0.426 | 1.08 |
| Min. size 5 and U(0,5) | 0.166 | 0.689 | 1.06 | 1.53 | 3 | 0.839 | 2.83 |
| Min. size 5 and HN(1) | 0.0893 | 0.485 | 0.772 | 1.08 | 1.8 | 0.6 | 1.71 |
| Min. size 5 and HN(0.5) | 0.0427 | 0.27 | 0.487 | 0.712 | 1.17 | 0.443 | 1.12 |

**Table** Compare p.new posterior summaries across models

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Model | 2.5% | 25% | 50% | 75% | 97.5% | IQR | CrIR |
| U(0,5) | 0.0309 | 0.415 | 0.659 | 0.821 | 0.986 | 0.406 | 0.955 |
| HN(1) | 0.127 | 0.517 | 0.678 | 0.792 | 0.955 | 0.275 | 0.828 |
| HN(0.5) | 0.269 | 0.59 | 0.696 | 0.774 | 0.912 | 0.185 | 0.643 |
| Event/non-event and U(0,5) | 0.13 | 0.584 | 0.727 | 0.828 | 0.972 | 0.244 | 0.842 |
| Event/non-event and HN(1) | 0.263 | 0.618 | 0.728 | 0.812 | 0.95 | 0.194 | 0.687 |
| Event/non-event and HN(0.5) | 0.399 | 0.66 | 0.734 | 0.795 | 0.912 | 0.135 | 0.513 |
| Min. size 5 and U(0,5) | 0.121 | 0.607 | 0.76 | 0.866 | 0.986 | 0.258 | 0.865 |
| Min. size 5 and HN(1) | 0.276 | 0.655 | 0.762 | 0.843 | 0.965 | 0.188 | 0.69 |
| Min. size 5 and HN(0.5) | 0.424 | 0.69 | 0.759 | 0.818 | 0.93 | 0.128 | 0.505 |

**Table** Compare threshold probabilities: Prob(p.new >= threshold)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | >=0.1 | >=0.2 | >=0.3 | >=0.4 | >=0.5 | >=0.6 | >=0.7 | >=0.8 | >=0.9 |
| U(0,5) | 0.939 | 0.886 | 0.828 | 0.761 | 0.678 | 0.575 | 0.441 | 0.283 | 0.139 |
| HN(1) | 0.982 | 0.953 | 0.909 | 0.849 | 0.767 | 0.647 | 0.448 | 0.233 | 0.0789 |
| HN(0.5) | 0.998 | 0.988 | 0.968 | 0.931 | 0.863 | 0.732 | 0.489 | 0.187 | 0.0344 |
| Event/non-event and U(0,5) | 0.981 | 0.959 | 0.93 | 0.886 | 0.825 | 0.73 | 0.565 | 0.314 | 0.117 |
| Event/non-event and HN(1) | 0.996 | 0.985 | 0.966 | 0.933 | 0.877 | 0.777 | 0.579 | 0.283 | 0.0775 |
| Event/non-event and HN(0.5) | 1 | 0.998 | 0.991 | 0.975 | 0.94 | 0.857 | 0.634 | 0.232 | 0.0347 |
| Min. size 5 and U(0,5) | 0.979 | 0.958 | 0.93 | 0.892 | 0.838 | 0.758 | 0.623 | 0.405 | 0.18 |
| Min. size 5 and HN(1) | 0.995 | 0.986 | 0.971 | 0.944 | 0.899 | 0.821 | 0.665 | 0.379 | 0.122 |
| Min. size 5 and HN(0.5) | 1 | 0.997 | 0.992 | 0.98 | 0.954 | 0.892 | 0.724 | 0.323 | 0.059 |

**Table** Compare threshold probabilities: Prob(p.new < threshold)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | <0.1 | <0.2 | <0.3 | <0.4 | <0.5 | <0.6 | <0.7 | <0.8 | <0.9 |
| U(0,5) | 0.0611 | 0.114 | 0.172 | 0.239 | 0.322 | 0.425 | 0.559 | 0.717 | 0.861 |
| HN(1) | 0.0176 | 0.0471 | 0.0912 | 0.151 | 0.233 | 0.353 | 0.552 | 0.767 | 0.921 |
| HN(0.5) | 0.00228 | 0.0123 | 0.032 | 0.0692 | 0.137 | 0.268 | 0.511 | 0.813 | 0.966 |
| Event/non-event and U(0,5) | 0.0185 | 0.0414 | 0.0703 | 0.114 | 0.175 | 0.27 | 0.435 | 0.686 | 0.883 |
| Event/non-event and HN(1) | 0.00433 | 0.015 | 0.0344 | 0.0669 | 0.123 | 0.223 | 0.421 | 0.717 | 0.923 |
| Event/non-event and HN(0.5) | 0.000333 | 0.00208 | 0.00941 | 0.0251 | 0.0597 | 0.143 | 0.366 | 0.768 | 0.965 |
| Min. size 5 and U(0,5) | 0.0213 | 0.0425 | 0.0701 | 0.108 | 0.162 | 0.242 | 0.377 | 0.595 | 0.82 |
| Min. size 5 and HN(1) | 0.00459 | 0.014 | 0.0293 | 0.0557 | 0.101 | 0.179 | 0.335 | 0.621 | 0.878 |
| Min. size 5 and HN(0.5) | 0.000487 | 0.00254 | 0.00751 | 0.02 | 0.0465 | 0.108 | 0.276 | 0.677 | 0.941 |

(**Table** Compare input data sets)

# Cumulative meta-analysis

## Background

Assess the impact of adding tissues with very low sample size. Intuitively, one would expect that as more and more tissue types become available, the data becomes more and more informative. However, by adding tissues with very small group size one may actually introduce more heterogeneity (as suggested by SA1 and SA2).

Illustrate this by doing a cumulative MA and studying the range of the predictive distribution.

Use the U(0, 5) prior from the ERG - the least informative prior from the case study - since the objective is to assess estimability of from the data. Therefore use “as little prior information as possible”.

## Data and “procedure”

Recall the ORR data used by the ERG.

## # A tibble: 14 x 4  
## `Tumour type` n x orr  
## <chr> <dbl> <dbl> <dbl>  
## 1 Soft tissue sarcoma 20 16 0.8   
## 2 Salivary gland 17 15 0.882  
## 3 Infantile fibrosarcoma 13 12 0.923  
## 4 Thyroid 10 7 0.7   
## 5 Lung 7 5 0.714  
## 6 Melanoma 7 3 0.429  
## 7 Colon 6 2 0.333  
## 8 GIST 5 5 1   
## 9 Bone sarcoma 2 1 0.5   
## 10 Cholangiocarcinoma 2 0 0   
## 11 Appendix 1 0 0   
## 12 Breast 1 0 0   
## 13 Congenital mesoblastic nephroma 1 1 1   
## 14 Pancreas 1 0 0

I will do a cumulative MA starting with the RE MA model fitted to the first 3 tissues (in the order given above), then to the first four, then five and so on.

## Run the cumulative MA

Global parameters for BHM.

n\_chains <- 3  
n\_iter <- 30000 # 15000 # double the iterations since for initial fits data limited  
n\_burnin <- 4000 # 2000  
n\_thin <- 2 # 1

## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 3  
## Unobserved stochastic nodes: 6  
## Total graph size: 26  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 4  
## Unobserved stochastic nodes: 7  
## Total graph size: 30  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 5  
## Unobserved stochastic nodes: 8  
## Total graph size: 34  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 6  
## Unobserved stochastic nodes: 9  
## Total graph size: 38  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 7  
## Unobserved stochastic nodes: 10  
## Total graph size: 42  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 8  
## Unobserved stochastic nodes: 11  
## Total graph size: 46  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 9  
## Unobserved stochastic nodes: 12  
## Total graph size: 50  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 10  
## Unobserved stochastic nodes: 13  
## Total graph size: 54  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 11  
## Unobserved stochastic nodes: 14  
## Total graph size: 58  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 12  
## Unobserved stochastic nodes: 15  
## Total graph size: 62  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 13  
## Unobserved stochastic nodes: 16  
## Total graph size: 66  
##   
## Initializing model  
##   
## Compiling model graph  
## Resolving undeclared variables  
## Allocating nodes  
## Graph information:  
## Observed stochastic nodes: 14  
## Unobserved stochastic nodes: 17  
## Total graph size: 70  
##   
## Initializing model

## Cumulative MA results

### Posterior summaries of rates (population and new tissue) and of RE SD

**Table** Cumulative MA results: posterior summaries p.new

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| n\_tissues | n\_tot | dn | dr | 2.5% | 25% | 50% | 75% | 97.5% | IQR | CrIR |
| 3 | 50 | 13 | 12 | 0.0649 | 0.761 | 0.86 | 0.925 | 0.997 | 0.163 | 0.932 |
| 4 | 60 | 10 | 7 | 0.178 | 0.753 | 0.834 | 0.896 | 0.99 | 0.143 | 0.813 |
| 5 | 67 | 7 | 5 | 0.312 | 0.748 | 0.821 | 0.876 | 0.977 | 0.128 | 0.665 |
| 6 | 74 | 7 | 3 | 0.191 | 0.674 | 0.778 | 0.857 | 0.979 | 0.183 | 0.788 |
| 7 | 80 | 6 | 2 | 0.127 | 0.583 | 0.736 | 0.839 | 0.979 | 0.255 | 0.852 |
| 8 | 85 | 5 | 5 | 0.12 | 0.615 | 0.763 | 0.868 | 0.987 | 0.253 | 0.867 |
| 9 | 87 | 2 | 1 | 0.144 | 0.615 | 0.754 | 0.852 | 0.981 | 0.237 | 0.837 |
| 10 | 89 | 2 | 0 | 0.0616 | 0.515 | 0.719 | 0.849 | 0.986 | 0.334 | 0.925 |
| 11 | 90 | 1 | 0 | 0.0448 | 0.475 | 0.696 | 0.836 | 0.985 | 0.361 | 0.941 |
| 12 | 91 | 1 | 0 | 0.0287 | 0.422 | 0.666 | 0.826 | 0.986 | 0.404 | 0.957 |
| 13 | 92 | 1 | 1 | 0.0414 | 0.454 | 0.684 | 0.833 | 0.985 | 0.379 | 0.944 |
| 14 | 93 | 1 | 0 | 0.0302 | 0.41 | 0.657 | 0.824 | 0.985 | 0.414 | 0.955 |

**Table** Cumulative MA results: posterior summaries p.pop

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| n\_tissues | n\_tot | dn | dr | 2.5% | 25% | 50% | 75% | 97.5% | IQR | CrIR |
| 3 | 50 | 13 | 12 | 0.375 | 0.796 | 0.86 | 0.907 | 0.973 | 0.111 | 0.597 |
| 4 | 60 | 10 | 7 | 0.516 | 0.78 | 0.833 | 0.877 | 0.951 | 0.0967 | 0.434 |
| 5 | 67 | 7 | 5 | 0.61 | 0.774 | 0.82 | 0.86 | 0.93 | 0.086 | 0.32 |
| 6 | 74 | 7 | 3 | 0.531 | 0.722 | 0.777 | 0.823 | 0.911 | 0.101 | 0.38 |
| 7 | 80 | 6 | 2 | 0.455 | 0.667 | 0.733 | 0.788 | 0.887 | 0.121 | 0.432 |
| 8 | 85 | 5 | 5 | 0.511 | 0.702 | 0.762 | 0.816 | 0.913 | 0.114 | 0.402 |
| 9 | 87 | 2 | 1 | 0.521 | 0.694 | 0.752 | 0.801 | 0.894 | 0.108 | 0.372 |
| 10 | 89 | 2 | 0 | 0.41 | 0.637 | 0.712 | 0.773 | 0.879 | 0.136 | 0.469 |
| 11 | 90 | 1 | 0 | 0.361 | 0.607 | 0.687 | 0.751 | 0.861 | 0.144 | 0.501 |
| 12 | 91 | 1 | 0 | 0.306 | 0.564 | 0.656 | 0.729 | 0.841 | 0.164 | 0.535 |
| 13 | 92 | 1 | 1 | 0.364 | 0.592 | 0.674 | 0.741 | 0.851 | 0.149 | 0.487 |
| 14 | 93 | 1 | 0 | 0.307 | 0.554 | 0.646 | 0.717 | 0.835 | 0.162 | 0.528 |

**Table** Cumulative MA results: posterior summaries re.sd

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| n\_tissues | n\_tot | dn | dr | mean | sd | IQR | CrIR |
| 3 | 50 | 13 | 12 | 1.2 | 1.1 | 1.3 | 4.2 |
| 4 | 60 | 10 | 7 | 0.92 | 0.9 | 0.97 | 3.5 |
| 5 | 67 | 7 | 5 | 0.7 | 0.67 | 0.7 | 2.5 |
| 6 | 74 | 7 | 3 | 0.91 | 0.71 | 0.82 | 2.7 |
| 7 | 80 | 6 | 2 | 1.1 | 0.69 | 0.81 | 2.7 |
| 8 | 85 | 5 | 5 | 1.2 | 0.74 | 0.86 | 2.9 |
| 9 | 87 | 2 | 1 | 1.1 | 0.67 | 0.8 | 2.6 |
| 10 | 89 | 2 | 0 | 1.4 | 0.77 | 0.9 | 3.1 |
| 11 | 90 | 1 | 0 | 1.4 | 0.79 | 0.95 | 3.2 |
| 12 | 91 | 1 | 0 | 1.6 | 0.82 | 1 | 3.3 |
| 13 | 92 | 1 | 1 | 1.5 | 0.78 | 0.94 | 3.2 |
| 14 | 93 | 1 | 0 | 1.6 | 0.8 | 0.96 | 3.2 |

Compare this with the U(0, 5) prior summaries: **Table** Summaries of U(0,5) prior

|  |  |  |  |
| --- | --- | --- | --- |
| mean | sd | IQR | CrIR |
| 2.5 | 1.44 | 2.5 | 4.75 |

### Shrinkage

Exchangeability is assumed on the logit scale, therefore also shrinkage of the estimates should be calculated on the logit scale. For tissues no. 8 and 10 - 14 this is not possible since the observed rates are 0 or 1 and the shrinkage and shrinkage factors are not properly defined. Therefore, I calculate the shrinkage for the first seven tissues and show how it evolves in the cumulative MA.

#### Shrinkage factors

I first use shrinkage factors to quantify shrinkage on a relative and therefore interpretable scale.

**Fully Bayesian version** Shrinkage factor:

For each round in the cumulative MA, for each of the first seven tissue types (when available), calculate the full posterior of and derive posterior summaries (take the mean and the median).

Shrinkage factor of 0 indicates no shrinkage to the population mean of the meta-analysis estimate for tissue (the BHM estimate stays at , the estimate when considering this tissue in isolation). A shrinkage factor of 1 indicates complete shrinkage meaning the tissue specific estimate from the BHM model collapses with the population estimate.

More shrinkage - larger values of omega - also mean more borrowing of information across tissues.

Note that for some tissues, the observed rate may be close to the population estimate leading to denominator values close to zero in the calculation of the shrinkage factor. For some tissues, these factors using plug-in estimates may, therefore, be numerically unstable and depend for example on whether the posterior mean or median is taken as point estimate.

Also, the population estimate still evolves quite a lot in the cumulative MA where with start with three tissues only. Therefore the normalization is not really a “normalization constant”, which makes interpretation not as straightforward as one may think.

**Approximation using plug-in estimates**

Shrinkage factor:

where the observed response rate in tissue on the logit scale; a point estimate of the true response rate in tissue (on the logit scale); and the corresponding population estimate.

Point estimates would typically be the posterior median or the posterior mean.

#### Absolute shrinkage

As seen, the shrinkage factors have two limitations:

* Numerical issues due to some tissues having observed estimate close to the population mean.
* Normalizing not with a constant.

Therefore, I also assess the abolute shrinkage, defined as the difference between the observed rate and tissue specific rate estimate (both on the logit scale) from the MA:

Again, larger values show more shrinkage, i.e. more borrowing of information. Lower values mean less borrowing of information across tissues.

This has the additional advantage that proper posterior summaries of can be obtained via plug-in estimates given the piecewise linear structure.

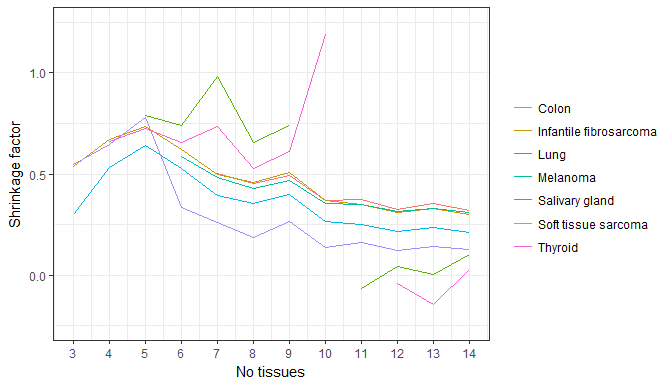
#### Results

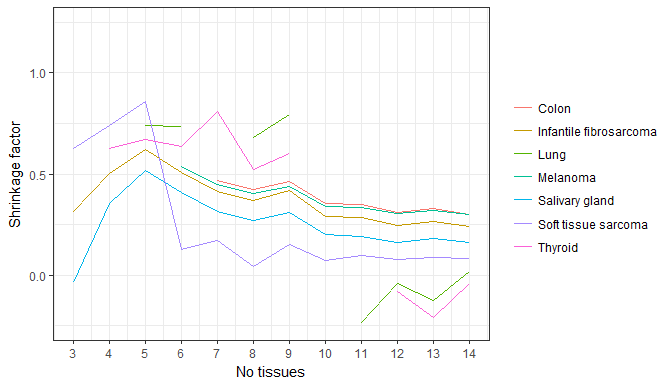
**Table** Shrinkage results across the cumulative MA

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| cma\_id | tissue\_id | n\_tissues | tissue | srkf\_med\_ij | srkf\_mean\_ij | srkf\_B\_med\_ij | srkf\_B\_mean\_ij | asrk\_med\_ij | asrk\_mean\_ij |
| 1 | 1 | 3 | Soft tissue sarcoma | 0.545 | 0.625 | 0.461 | -0.435 | 0.233 | 0.242 |
| 1 | 2 | 3 | Salivary gland | 0.301 | -0.0361 | 0.52 | 1.45 | 0.0603 | 0.00868 |
| 1 | 3 | 3 | Infantile fibrosarcoma | 0.535 | 0.315 | 0.631 | 0.933 | 0.359 | 0.224 |
| 2 | 1 | 4 | Soft tissue sarcoma | 0.648 | 0.742 | 0.569 | 2.98 | 0.142 | 0.158 |
| 2 | 2 | 4 | Salivary gland | 0.535 | 0.353 | 0.65 | 0.761 | 0.219 | 0.147 |
| 2 | 3 | 4 | Infantile fibrosarcoma | 0.67 | 0.505 | 0.759 | 0.595 | 0.589 | 0.448 |
| 2 | 4 | 4 | Thyroid | 0.659 | 0.624 | 0.728 | 0.815 | 0.5 | 0.469 |
| 3 | 1 | 5 | Soft tissue sarcoma | 0.778 | 0.858 | 0.653 | -0.379 | 0.1 | 0.113 |
| 3 | 2 | 5 | Salivary gland | 0.643 | 0.517 | 0.743 | 0.122 | 0.322 | 0.257 |
| 3 | 3 | 5 | Infantile fibrosarcoma | 0.735 | 0.623 | 0.816 | 0.494 | 0.713 | 0.602 |
| 3 | 4 | 5 | Thyroid | 0.728 | 0.671 | 0.792 | 2.97 | 0.486 | 0.45 |
| 3 | 5 | 5 | Lung | 0.792 | 0.741 | 0.846 | 5.24 | 0.474 | 0.446 |
| 4 | 1 | 6 | Soft tissue sarcoma | 0.335 | 0.127 | 0.441 | -1.1 | 0.0455 | 0.0185 |
| 4 | 2 | 6 | Salivary gland | 0.528 | 0.409 | 0.558 | 0.42 | 0.404 | 0.317 |
| 4 | 3 | 6 | Infantile fibrosarcoma | 0.623 | 0.506 | 0.647 | 0.57 | 0.77 | 0.63 |
| 4 | 4 | 6 | Thyroid | 0.657 | 0.637 | 0.639 | 3.11 | 0.265 | 0.251 |
| 4 | 5 | 6 | Lung | 0.741 | 0.736 | 0.712 | 0.85 | 0.248 | 0.239 |
| 4 | 6 | 6 | Melanoma | 0.589 | 0.535 | 0.611 | 0.526 | 0.905 | 0.818 |
| 5 | 1 | 7 | Soft tissue sarcoma | 0.259 | 0.17 | 0.292 | 0.29 | 0.0979 | 0.067 |
| 5 | 2 | 7 | Salivary gland | 0.392 | 0.313 | 0.394 | 1.61 | 0.395 | 0.321 |
| 5 | 3 | 7 | Infantile fibrosarcoma | 0.496 | 0.413 | 0.497 | 0.487 | 0.733 | 0.617 |
| 5 | 4 | 7 | Thyroid | 0.736 | 0.811 | 0.443 | -0.285 | 0.118 | 0.117 |
| 5 | 5 | 7 | Lung | 0.982 | 1.37 | 0.535 | 1.95 | 0.09 | 0.103 |
| 5 | 6 | 7 | Melanoma | 0.481 | 0.447 | 0.497 | 0.115 | 0.623 | 0.572 |
| 5 | 7 | 7 | Colon | 0.501 | 0.468 | 0.517 | 0.456 | 0.851 | 0.789 |
| 6 | 1 | 8 | Soft tissue sarcoma | 0.186 | 0.0442 | 0.27 | -6.77 | 0.0409 | 0.0094 |
| 6 | 2 | 8 | Salivary gland | 0.357 | 0.272 | 0.369 | -3.35 | 0.303 | 0.229 |
| 6 | 3 | 8 | Infantile fibrosarcoma | 0.458 | 0.369 | 0.467 | 1.56 | 0.604 | 0.484 |
| 6 | 4 | 8 | Thyroid | 0.528 | 0.522 | 0.426 | -0.0117 | 0.168 | 0.17 |
| 6 | 5 | 8 | Lung | 0.656 | 0.682 | 0.517 | -13.4 | 0.164 | 0.176 |
| 6 | 6 | 8 | Melanoma | 0.429 | 0.405 | 0.441 | 0.392 | 0.624 | 0.592 |
| 6 | 7 | 8 | Colon | 0.451 | 0.422 | 0.46 | 0.447 | 0.838 | 0.787 |
| 7 | 1 | 9 | Soft tissue sarcoma | 0.266 | 0.15 | 0.316 | 0.849 | 0.0734 | 0.0419 |
| 7 | 2 | 9 | Salivary gland | 0.399 | 0.31 | 0.409 | -0.735 | 0.361 | 0.281 |
| 7 | 3 | 9 | Infantile fibrosarcoma | 0.51 | 0.42 | 0.513 | 0.456 | 0.701 | 0.578 |
| 7 | 4 | 9 | Thyroid | 0.611 | 0.601 | 0.495 | 1.24 | 0.16 | 0.156 |
| 7 | 5 | 9 | Lung | 0.739 | 0.795 | 0.563 | -1.85 | 0.143 | 0.152 |
| 7 | 6 | 9 | Melanoma | 0.469 | 0.439 | 0.481 | 0.392 | 0.656 | 0.613 |
| 7 | 7 | 9 | Colon | 0.492 | 0.461 | 0.503 | 0.462 | 0.887 | 0.83 |
| 8 | 1 | 10 | Soft tissue sarcoma | 0.138 | 0.0709 | 0.167 | 0.129 | 0.0661 | 0.0357 |
| 8 | 2 | 10 | Salivary gland | 0.266 | 0.2 | 0.266 | 1.3 | 0.294 | 0.226 |
| 8 | 3 | 10 | Infantile fibrosarcoma | 0.367 | 0.292 | 0.363 | 0.297 | 0.58 | 0.468 |
| 8 | 4 | 10 | Thyroid | 1.19 | 2.43 | 0.301 | 4.4 | 0.0707 | 0.0859 |
| 8 | 5 | 10 | Lung | -6.46 | -2.42 | 0.354 | 0.94 | 0.0628 | 0.0817 |
| 8 | 6 | 10 | Melanoma | 0.355 | 0.34 | 0.366 | 0.447 | 0.424 | 0.398 |
| 8 | 7 | 10 | Colon | 0.37 | 0.355 | 0.38 | 0.386 | 0.592 | 0.559 |
| 9 | 1 | 11 | Soft tissue sarcoma | 0.161 | 0.0947 | 0.171 | 1.16 | 0.097 | 0.0606 |
| 9 | 2 | 11 | Salivary gland | 0.25 | 0.192 | 0.246 | 0.0808 | 0.308 | 0.243 |
| 9 | 3 | 11 | Infantile fibrosarcoma | 0.352 | 0.283 | 0.345 | 0.241 | 0.598 | 0.493 |
| 9 | 4 | 11 | Thyroid | -0.573 | -0.524 | 0.269 | -0.409 | 0.0361 | 0.0532 |
| 9 | 5 | 11 | Lung | -0.0641 | -0.235 | 0.31 | -0.959 | 0.00846 | 0.04 |
| 9 | 6 | 11 | Melanoma | 0.351 | 0.337 | 0.36 | 0.615 | 0.376 | 0.348 |
| 9 | 7 | 11 | Colon | 0.374 | 0.35 | 0.386 | 0.147 | 0.552 | 0.503 |
| 10 | 1 | 12 | Soft tissue sarcoma | 0.123 | 0.0775 | 0.129 | -6.13 | 0.091 | 0.0616 |
| 10 | 2 | 12 | Salivary gland | 0.214 | 0.162 | 0.207 | -0.273 | 0.293 | 0.23 |
| 10 | 3 | 12 | Infantile fibrosarcoma | 0.311 | 0.243 | 0.304 | 0.17 | 0.571 | 0.461 |
| 10 | 4 | 12 | Thyroid | -0.0424 | -0.082 | 0.195 | -0.33 | 0.00846 | 0.021 |
| 10 | 5 | 12 | Lung | 0.0405 | -0.0437 | 0.233 | -0.538 | 0.0109 | 0.0142 |
| 10 | 6 | 12 | Melanoma | 0.313 | 0.303 | 0.328 | 1.81 | 0.293 | 0.266 |
| 10 | 7 | 12 | Colon | 0.326 | 0.312 | 0.342 | -0.0713 | 0.437 | 0.4 |
| 11 | 1 | 13 | Soft tissue sarcoma | 0.143 | 0.0888 | 0.152 | -1.07 | 0.0944 | 0.0618 |
| 11 | 2 | 13 | Salivary gland | 0.237 | 0.181 | 0.234 | 0.18 | 0.305 | 0.24 |
| 11 | 3 | 13 | Infantile fibrosarcoma | 0.331 | 0.266 | 0.326 | 0.253 | 0.582 | 0.478 |
| 11 | 4 | 13 | Thyroid | -0.145 | -0.21 | 0.234 | -0.00754 | 0.0175 | 0.0331 |
| 11 | 5 | 13 | Lung | 0.00363 | -0.126 | 0.284 | 1.52 | 0.00069 | 0.0284 |
| 11 | 6 | 13 | Melanoma | 0.332 | 0.317 | 0.35 | 0.824 | 0.336 | 0.31 |
| 11 | 7 | 13 | Colon | 0.353 | 0.329 | 0.362 | 0.759 | 0.502 | 0.454 |
| 12 | 1 | 14 | Soft tissue sarcoma | 0.129 | 0.0824 | 0.133 | 0.156 | 0.101 | 0.0692 |
| 12 | 2 | 14 | Salivary gland | 0.209 | 0.161 | 0.203 | 0.192 | 0.296 | 0.236 |
| 12 | 3 | 14 | Infantile fibrosarcoma | 0.302 | 0.242 | 0.294 | 0.225 | 0.569 | 0.468 |
| 12 | 4 | 14 | Thyroid | 0.0284 | -0.0426 | 0.179 | -0.887 | 0.00699 | 0.0128 |
| 12 | 5 | 14 | Lung | 0.103 | 0.0178 | 0.225 | 1.39 | 0.0325 | 0.00657 |
| 12 | 6 | 14 | Melanoma | 0.31 | 0.301 | 0.319 | 0.406 | 0.275 | 0.251 |
| 12 | 7 | 14 | Colon | 0.321 | 0.301 | 0.336 | 0.572 | 0.415 | 0.373 |

##### Shrinkage factors (approximate with plug-in estimates)

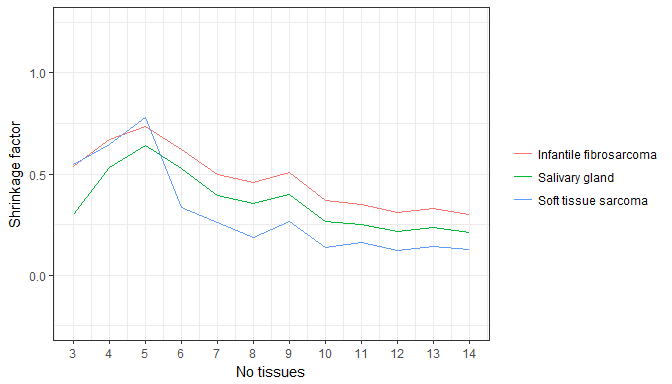
*First seven tissues*

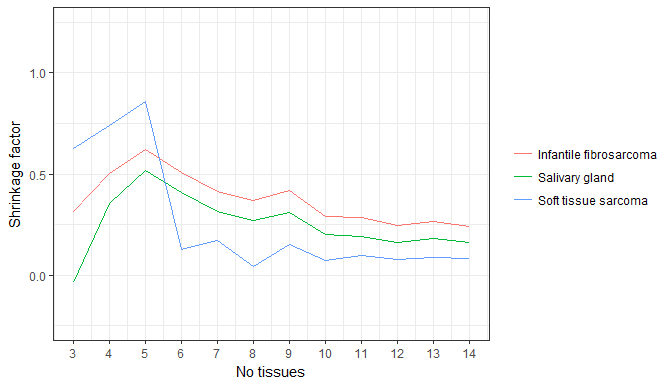
**Figure** Approximate shrinkage factors by tissue type (posterior median as plug-in estimate) 

**Figure** Approximate shrinkage factors by tissue type (posterior mean as plug-in estimate) 

Borrowing of information increases initially as more, relatively homogeneous tissues are added to the MA. After reaching a peak, borrowing decreases again. Despite adding more tissues, the mutual sharing of information goes down since the (estimated) heterogeneity increases when adding small, low information tissues.

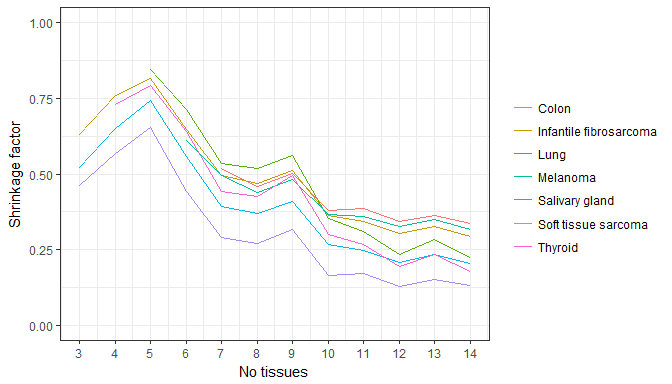
*First three tissues (which can be followed all along the cumulative MA)*

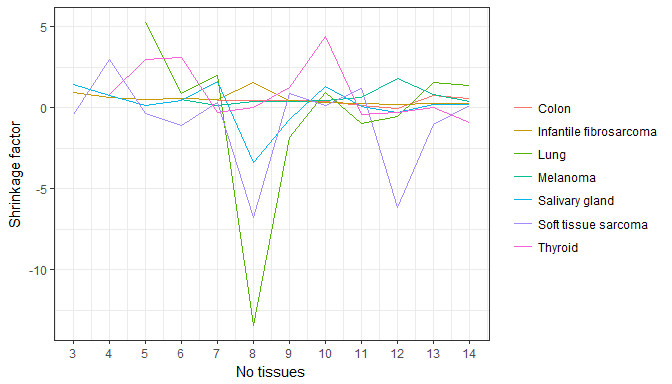
**Figure** Approximate shrinkage factors by tissue type (posterior median as plug-in estimate) 

**Figure** Approximate shrinkage factors by tissue type (posterior mean as plug-in estimate) 

##### Shrinkage factors (fully Bayesian)

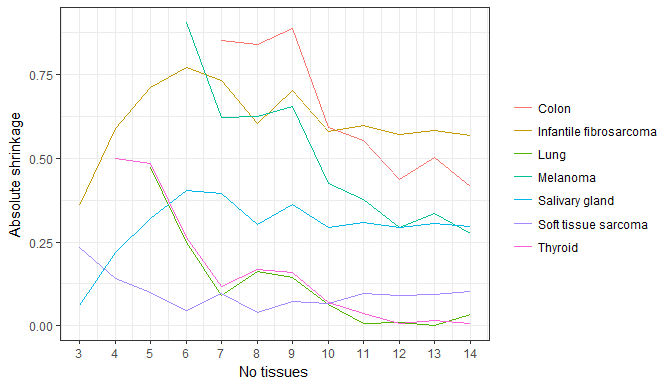
*First seven tissues*

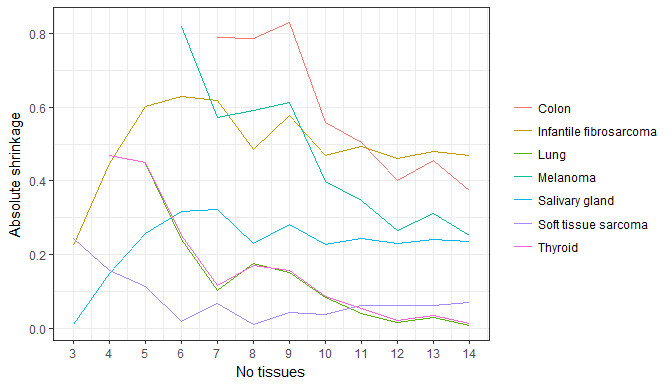
**Figure** Shrinkage factors by tissue type (posterior median)  Borrowing of information initially increases (larger shrinkage factor). But when adding the low information tissue types, borrowing of information across tissue types decreases again (shrinkage factor goes down).

**Figure** Approximate shrinkage factors by tissue type (posterior mean)  -> the ratio in the shrinkage factor makes the calculation somewhat numerically unstable; posterior means cannot be used reliably

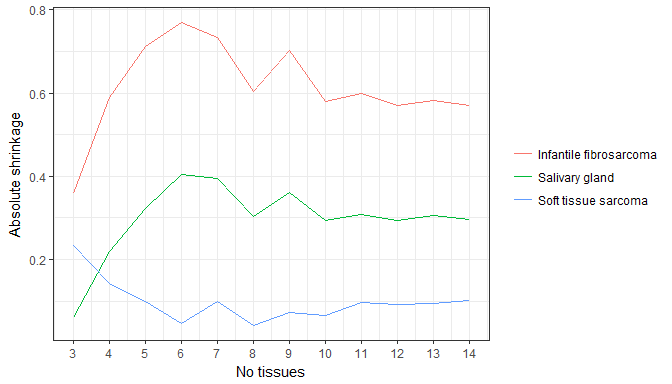
##### Absolute shrinkage

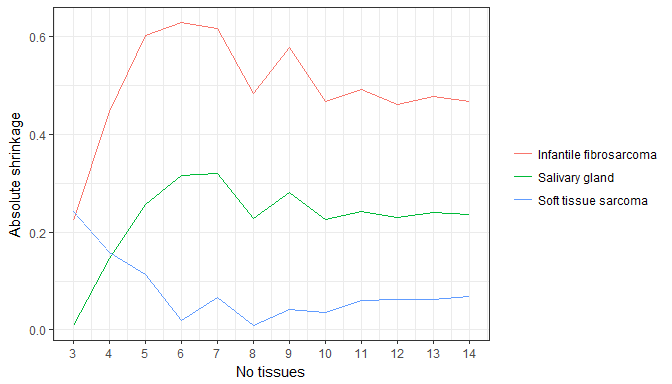
*First seven tissues*

**Figure** Absolute shrinkage (posterior medians) 

**Figure** Absolute shrinkage (posterior means) 

*First three tissues (which can be followed across the full cumulative MA)*

**Figure** Absolute shrinkage (posterior medians) 

**Figure** Absolute shrinkage (posterior means) 

# Session info

## [1] "C:/GIT/punta"

## R version 3.4.2 (2017-09-28)  
## Platform: x86\_64-w64-mingw32/x64 (64-bit)  
## Running under: Windows 10 x64 (build 17763)  
##   
## Matrix products: default  
##   
## locale:  
## [1] LC\_COLLATE=English\_United Kingdom.1252   
## [2] LC\_CTYPE=English\_United Kingdom.1252   
## [3] LC\_MONETARY=English\_United Kingdom.1252  
## [4] LC\_NUMERIC=C   
## [5] LC\_TIME=English\_United Kingdom.1252   
##   
## attached base packages:  
## [1] stats graphics grDevices utils datasets methods base   
##   
## other attached packages:  
## [1] ggplot2\_2.2.1 R2jags\_0.5-7 rjags\_4-6 coda\_0.19-3 reshape2\_1.4.2  
## [6] dplyr\_0.8.0.1 readxl\_1.3.1   
##   
## loaded via a namespace (and not attached):  
## [1] Rcpp\_1.0.1 cellranger\_1.1.0 pillar\_1.4.3 compiler\_3.4.2   
## [5] plyr\_1.8.4 tools\_3.4.2 zeallot\_0.1.0 boot\_1.3-24   
## [9] digest\_0.6.12 evaluate\_0.14 tibble\_2.1.1 gtable\_0.2.0   
## [13] lattice\_0.20-35 pkgconfig\_2.0.3 rlang\_0.3.4 cli\_2.0.2   
## [17] yaml\_2.2.0 parallel\_3.4.2 xfun\_0.12 stringr\_1.4.0   
## [21] knitr\_1.28 vctrs\_0.1.0 grid\_3.4.2 tidyselect\_0.2.5  
## [25] glue\_1.3.1 R6\_2.2.2 fansi\_0.4.0 rmarkdown\_2.1   
## [29] pander\_0.6.1 purrr\_0.3.2 magrittr\_1.5 backports\_1.1.1   
## [33] scales\_0.5.0 htmltools\_0.3.6 R2WinBUGS\_2.1-21 assertthat\_0.2.0  
## [37] abind\_1.4-5 colorspace\_1.3-2 labeling\_0.3 utf8\_1.1.4   
## [41] stringi\_1.4.3 lazyeval\_0.2.1 munsell\_0.4.3 crayon\_1.3.4