

Consensus clustering for Bayesian mixture models: Supplementary materials

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Abstract

1 Yeast data

The "Yeast data" consists of three *S. cerevisiae* datasets with gene products associated with a common set of 551 genes. The datasets are:

- microarray profiles of RNA expression from Granovskia et al. (2010). This a cell cycle dataset that comprises measurements taken at 41 time points (the **Timecourse** dataset).
- Chromatin immunoprecipitation followed by microarray hybridization (**ChIP-chip**) data from Harbison et al. (2004). This dataset has 117 features.
- Protein-protein interaction (**PPI**) data from BioGrid (Stark et al., 2006). This dataset has 603 features.

The datasets were reduced to 551 items by considering only the genes identified by Granovskia et al. (2010) as having periodic expression profiles with no missing data in the PPI and ChIP-chip data, following the same steps as the original MDI paper (Kirk et al., 2012). The datasets were modelled using a base measure of a Gaussian process in the Timecourse dataset and Multinomial distributions in the ChIP-chip and PPI datasets.

1.1 Bayesian analysis

10 chains were run for 36 hours, resulting in 676,000 iterations per chain, thinned to every thousandth sample, resulting in 676 samples per chain.

1.1.1 Convergence

These chains were investigated for

- within-chain stationarity using the Geweke convergence diagnostic (Geweke et al., 1991), and
- across-chain convergence using the potential scale reduction factor (\hat{R} , Gelman et al., 1992) and the Vats-Knudson extension (*stable* \hat{R} , Vats and Knudson, 2018).

The Geweke convergence diagnostic is a standard Z-score; it compares the sample mean of two sets of samples (in this case buckets of samples from the first half of the samples to the sample mean of the entire second half of samples). It is calculated under the assumption that the two parts of the chain are asymptotically independent and if this assumption holds than the scores are expected to be standard normally distributed presenting evidence for within chain stationarity.

\hat{R} is expected to approach 1.0 if the set of chains are converged. Low \hat{R} is not sufficient in itself to claim chain convergence, but values above 1.1 are clear evidence for a lack of convergence (Gelman et al., 2013). Vats and Knudson (2018) show that this threshold is significantly too high (1.01 being a better choice) and propose extensions to \hat{R} that enable a more formal rule for a threshold. It is their method as implemented in the R package `stableGR` (Knudson and Vats, 2020) that is the final check of convergence.

We focus upon stationarity of the continuous variables. This is as convergence of the allocation labels is difficult due to the label-switching problem. In MDI, the continuous variables consist of the concentration parameters of the Dirichlet distribution for the dataset-specific component weights and the ϕ_{ij} parameter associated with the correlation between the i^{th} and j^{th} datasets.

We plot the Geweke-statistic for each chain in figure 1 and the series of the ϕ parameters alone in figure 2, excluding the most poorly behaved chain (chain 9). Very few of the chains appear to be truly stationary, but some behave far worse than others. Based upon this we exclude chains 1, 2, 4, 6 and 9, restricting the analysis to the 5 better, if not ideally, behaved chains. Further evidence that even these chains are not converged can be seen in figure 3, where the values of \hat{R} do not drop below 1.25 for the ϕ parameters. Stable \hat{R} is also too high, with several million more samples recommended before convergence is expected.

Investigating the Posterior similarity matrices (PSMs) we can see that the Timecourse data appears to have only the mildest of disagreement between the PSMs from different chains. The lack of convergence between chains emerges in the ChIP-chip data and, to a far greater degree, in the PPI data.

1.2 Consensus clustering analysis

We investigate an ensemble of depth $R = 1001$ and width $S = 10000$. The consensus matrices for this ensemble was compared to those for the combinations of $R = (1, 101, 501, 1001, 5001, 10001)$, $S = (1, 100, 500, 1, 000)$ in the three datasets. We use a heuristic to decide if the ensemble is sufficiently deep and wide to stop growing. For a given depth r and width s , if there is no visible difference between the consensus matrices from the ensembles using $R = (ar, r)$,

Within chain convergence

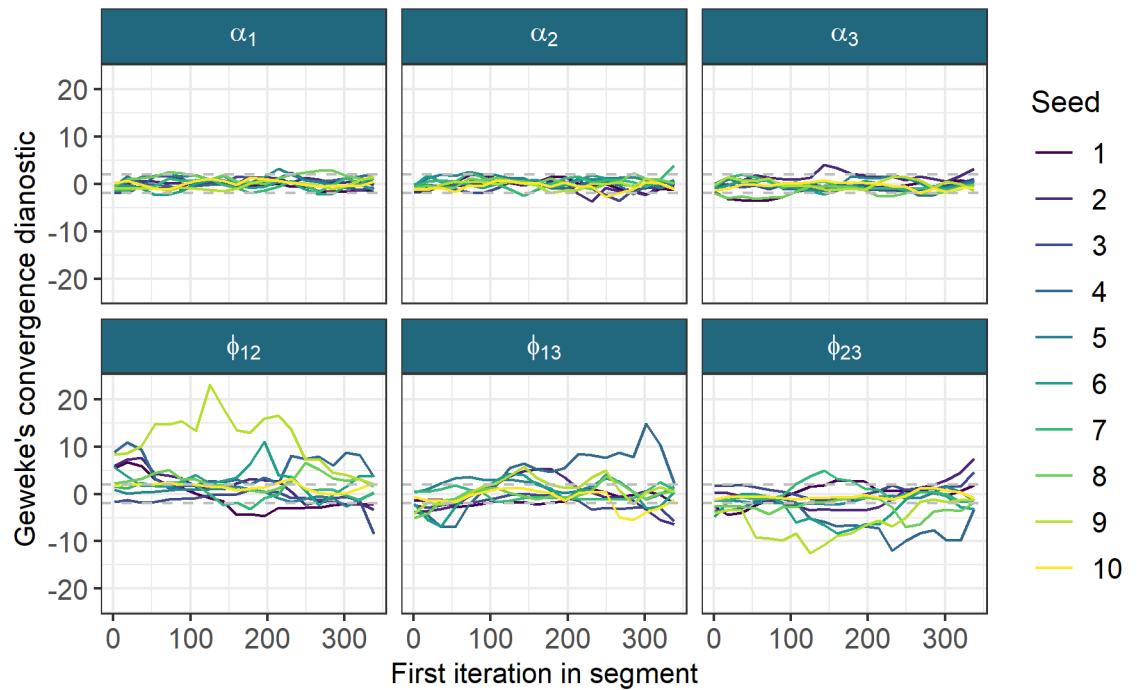


Figure 1: Chain 9 can be seen to have the most extreme behaviour in the distribution of the Geweke diagnostic for ϕ_{12}, ϕ_{13} and ϕ_{23} . We remove this chain from the analysis. We also see that in these same variables that the chains reveal poor behaviour and focus on these.

Within chain convergence

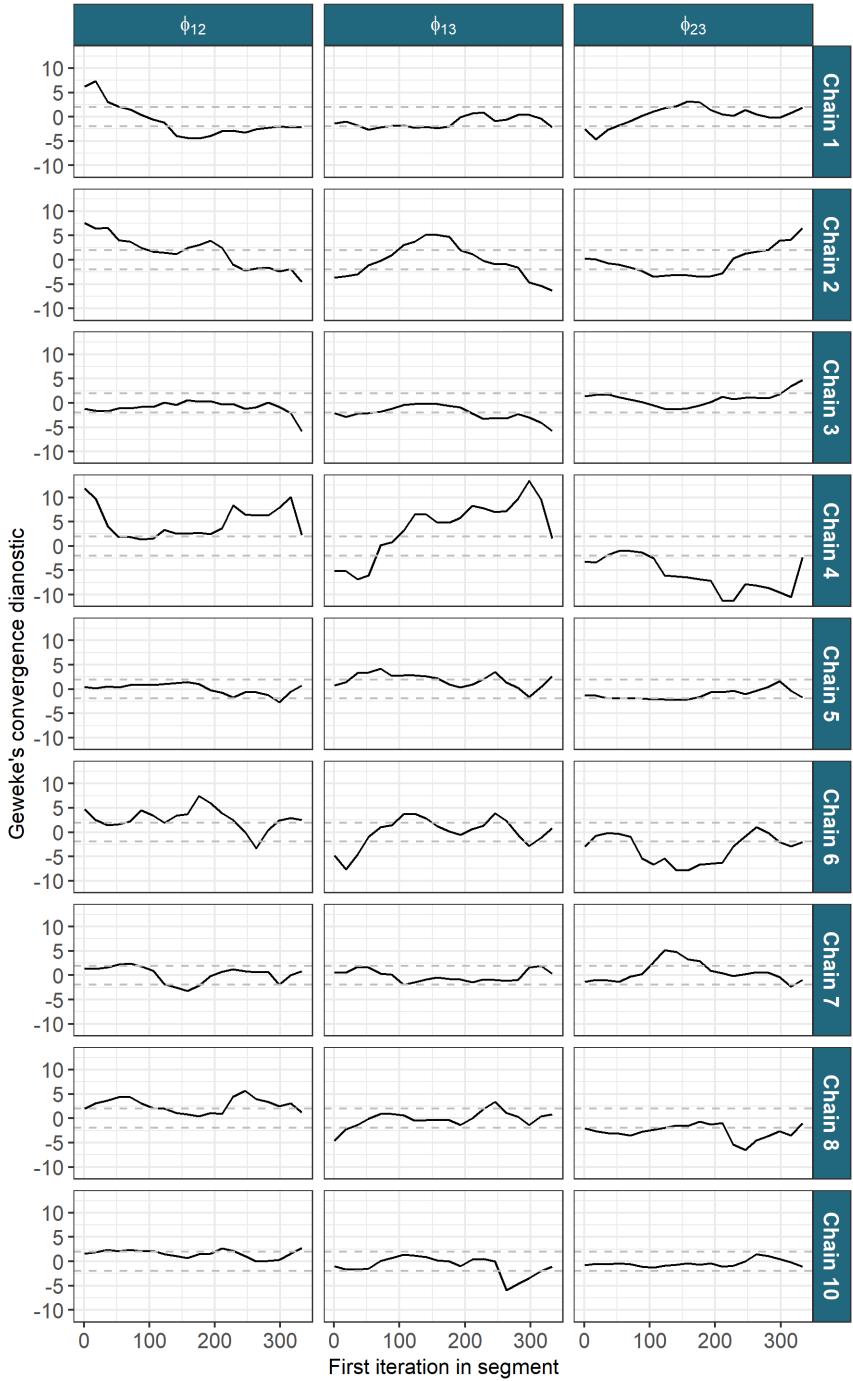


Figure 2: None of the chains appear to be standard normal in their distribution. Chain 4 behaves very strangely and is also dropped from the analysis. Of the remaining chains there is less clear distinctions, but chains 1, 2, and 6 appear most extreme and thus are dropped.

Gelman-R Rubin diagnostic plot

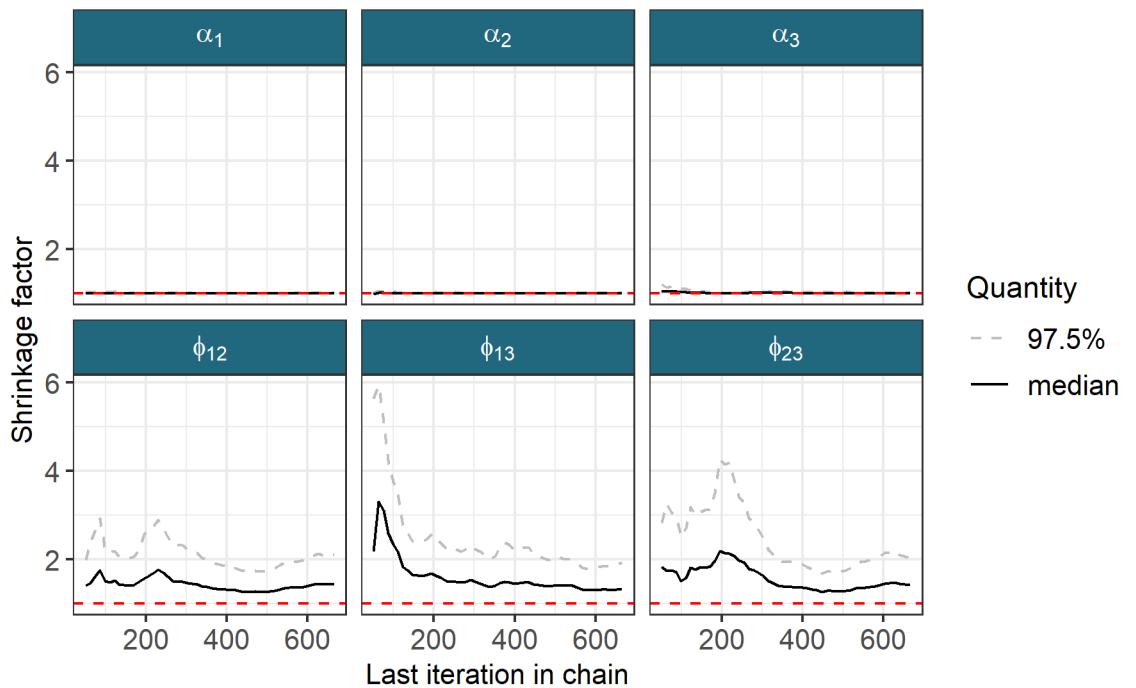


Figure 3: The chains still appear to be unconverged with \hat{R} remaining above 1.25 for the ϕ_{12}, ϕ_{13} and ϕ_{23} parameters. Stable \hat{R} is also too high with values of 1.049, 1.052 and 1.057.

Timecourse
Posterior similarity matrices

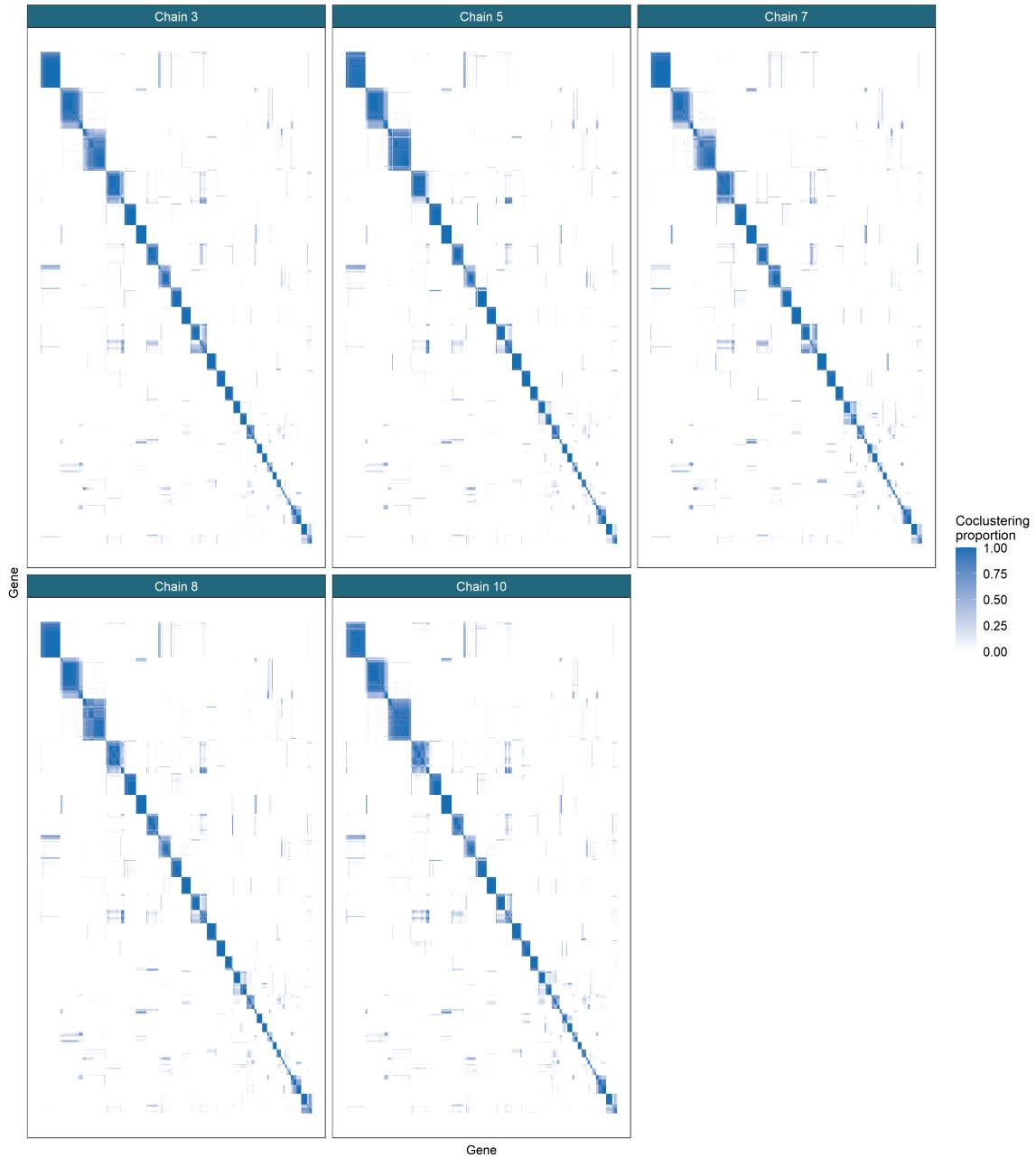


Figure 4: No marked difference.

ChIP-chip
Posterior similarity matrices

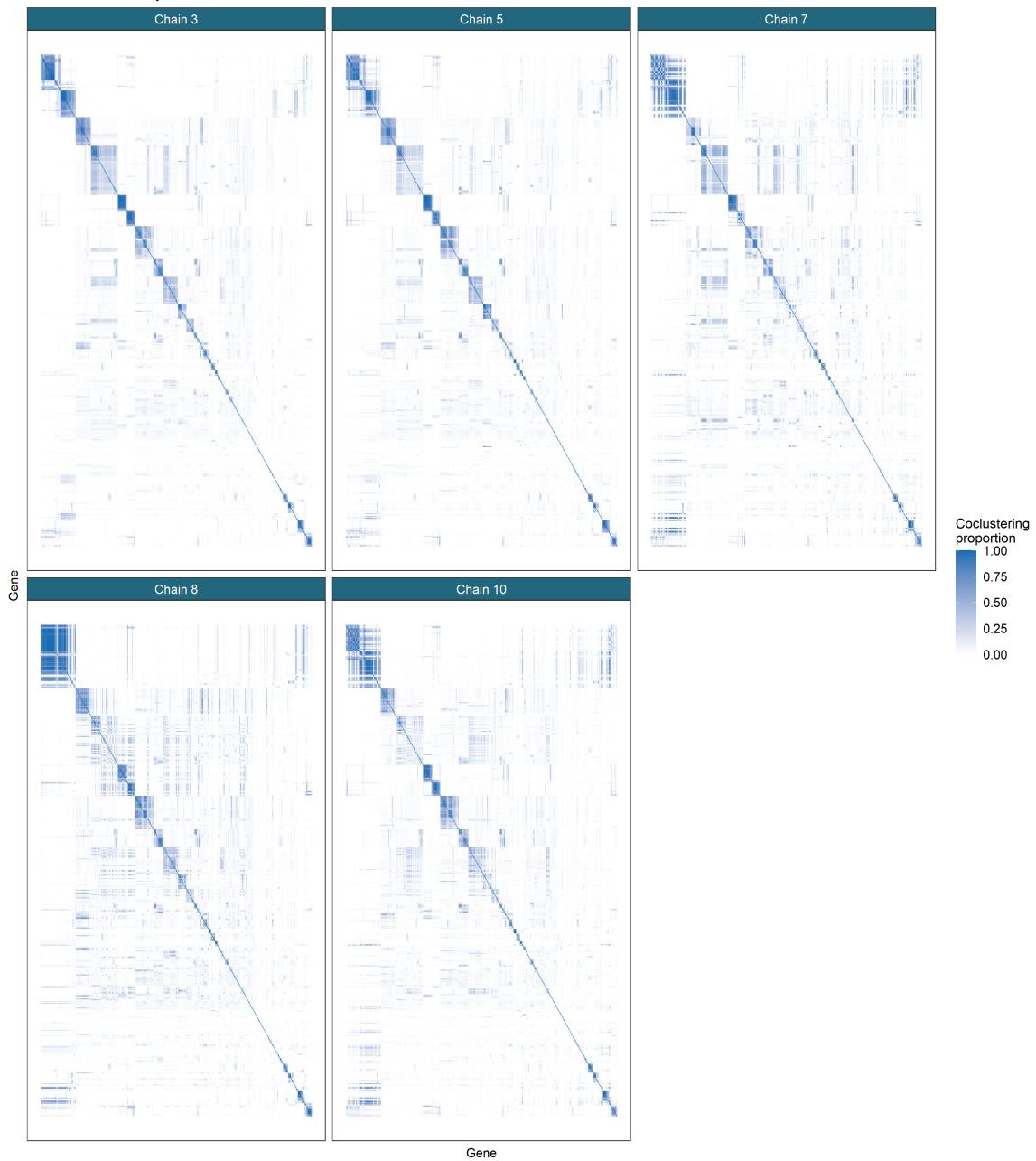


Figure 5: Some difference.

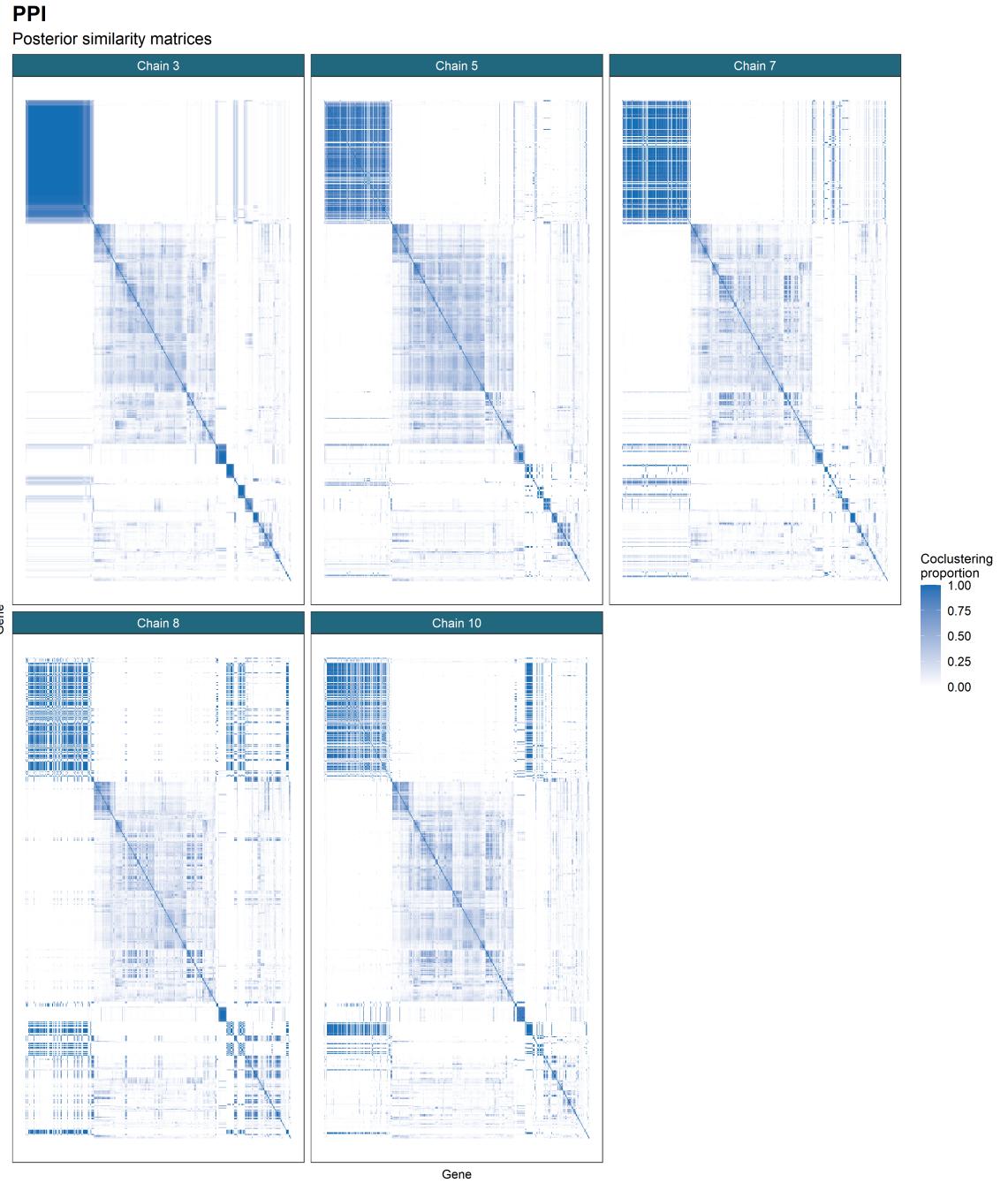


Figure 6: These PSMs have very large disagreements between each other. There is some common agreement in the square in the centre of each plot. However, the other sections (which consist of the most confident allocations) appear to completely fail to overlap. These sections appear to be approximately random in the partition defined.

Parameter density

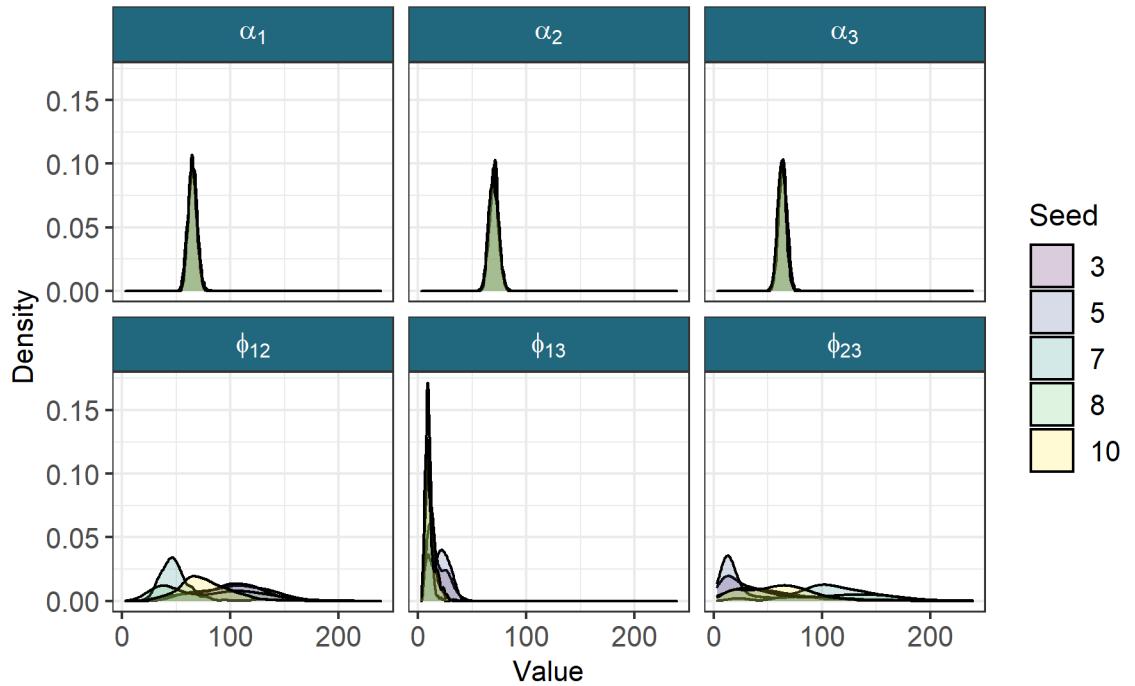


Figure 7: The densities of the continuous variables across the 5 chains kept for analysis. The mean sampled values are $\alpha_1 = 64.84$, $\alpha_2 = 69.85$, $\alpha_3 = 63.22$, $\phi_{12} = 81.76$, $\phi_{13} = 13.87$, and $\phi_{23} = 65.03$. It can be seen that different modes are being sampled for the ϕ parameters in each chain.

$S = (s, bs)$ (in our analysis we used $a = b = 0.5$, but the smaller the choice of a, b the more extreme the stopping criterion), then we consider the ensemble to have stabilised. This is inspired by the belief that a clustering method should produce stable results across similar datasets (Von Luxburg and Ben-David, 2005; Meinshausen and Bühlmann, 2010). We believe that if the method is still producing a partition that is visibly changing for additional chains and depth, than the random initialisation is influencing the result sufficiently that it is unlikely to be stable for similar datasets or reproducible for a random choice of seeds. An example of this logic can be seen in figures 9 and 10 (and to a lesser degree in figure 8). Here the decision to stop growing the ensemble is made as there is no apparent gain in increasing chain depth from $R = 5001$ to $R = 10001$, but it can be seen that a chain depth of $R = 1001$ is insufficient as there is a marked difference in the consensus matrices for the PPI dataset particularly between $R = 1001$ and $R = 5001$. The number of chains appears required appears to have stabilised quickly, as there is no obvious change in increasing S from 100.

If we compare the distribution of sampled values for the ϕ parameters for the Bayesian chains that we keep based upon their convergence diagnostics, the final ensemble used ($R = 10001$, $S = 1000$) and the pooled samples from the 5 long chains, then we see that the ensemble consisting of the long chains (which might be believed to sampling different parts of the posterior distribution) is closer in its appearance to the distributions sampled by the Consensus clustering than to any single chain.

1.2.1 GO term over-representation

To validate our analysis we Gene Ontology (GO) term over-representation. We test if the predicted clusters have a higher concentration of specific GO terms than would be expected by chance, conditioning on the background set of the 551 yeast genes in the data. The Bioconductor packages

References

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Timecourse

Consensus matrices

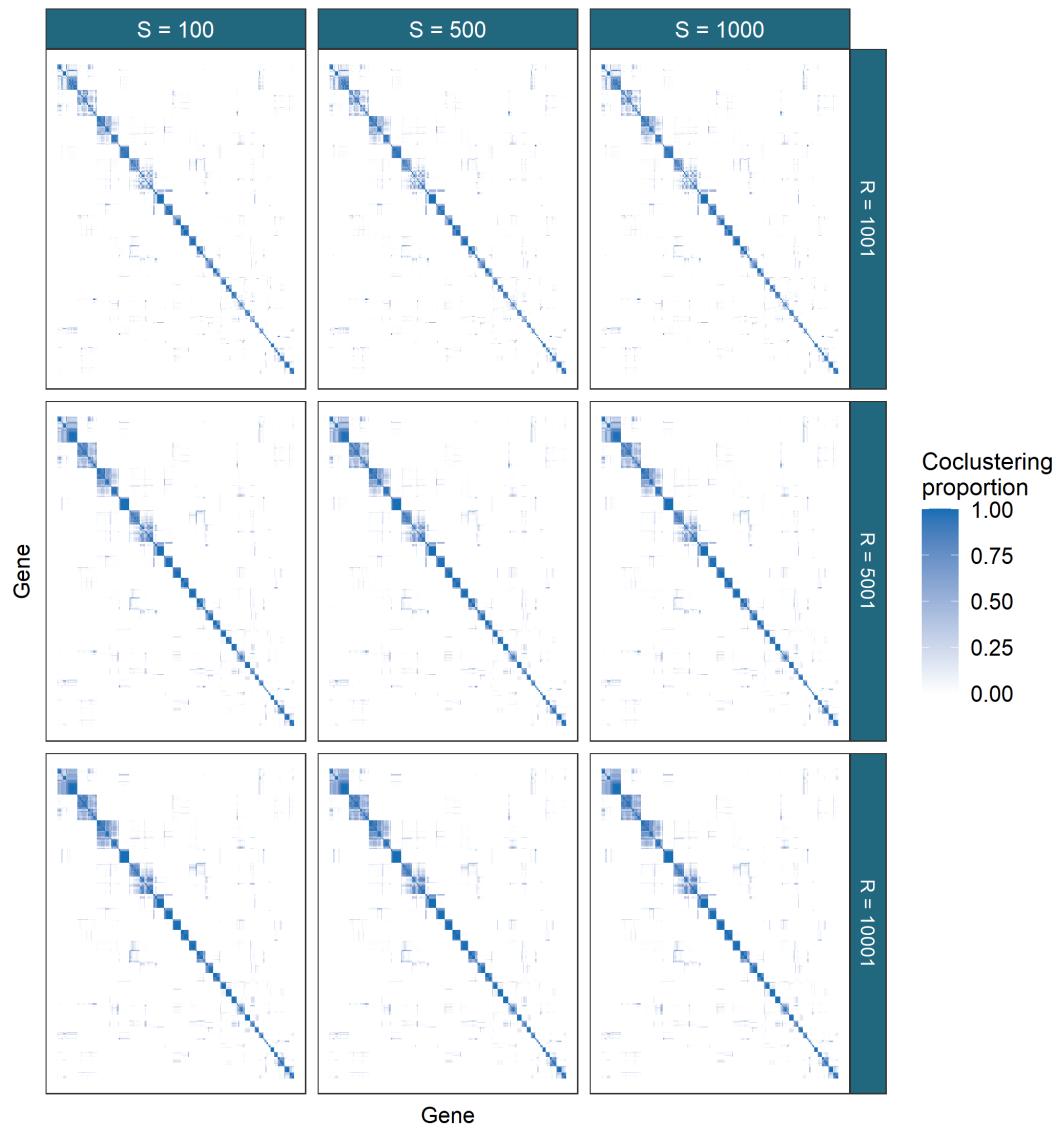


Figure 8: Consensus matrices for different ensembles of MDI for the Timecourse data. This dataset has stable clustering across the different choices of number of chains, S , and chain depth, R , with some components merging as the chain depth increases.

ChIP-chip

Consensus matrices

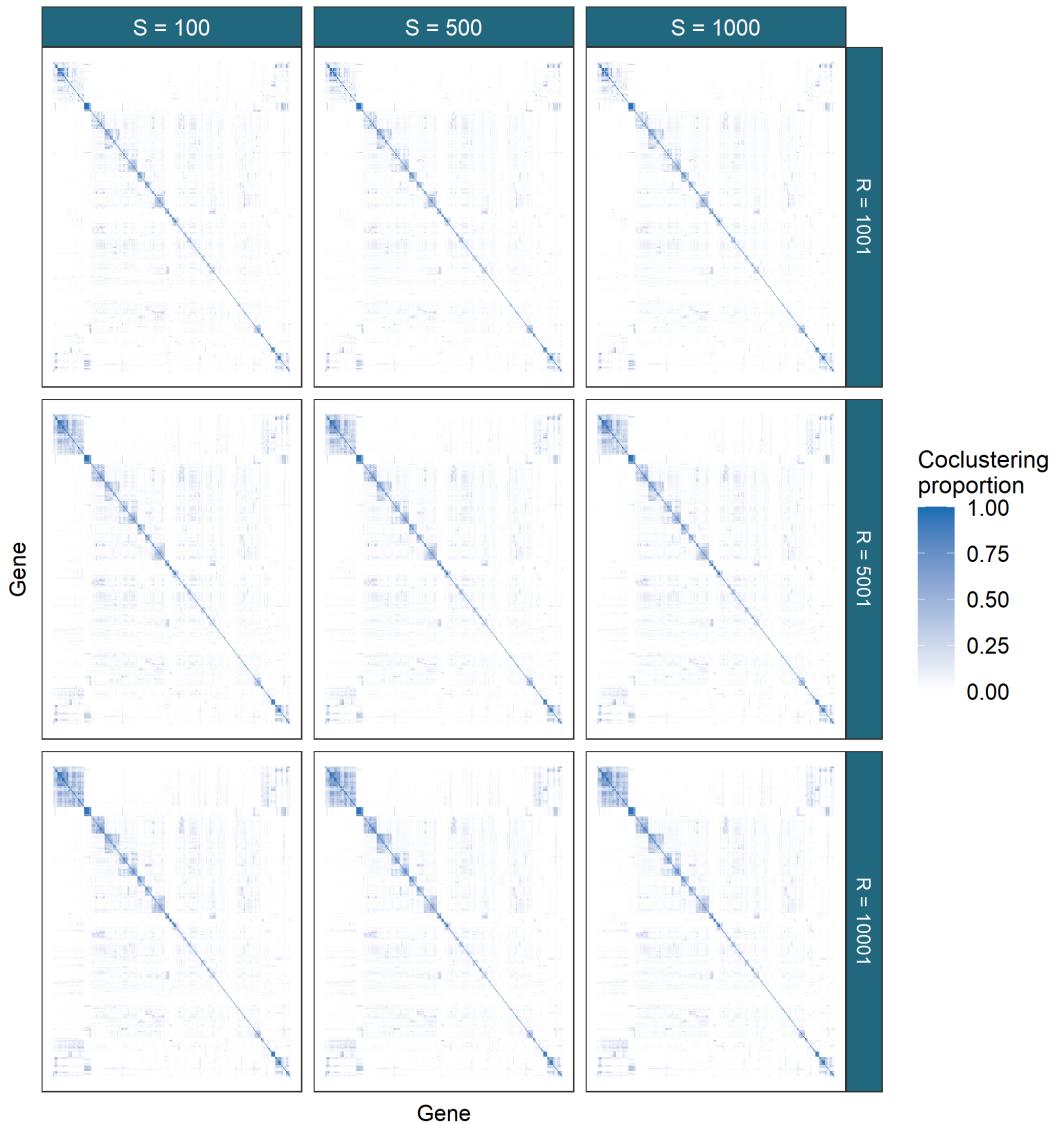


Figure 9: The ChIP-chip dataset is more sparse than the Timecourse data. In keeping with the results from the simulations for mixture models, deeper chains are required for better performance. It is only between $R = 5,001$ and $R = 10,001$ that no change in the clustering can be observed and the result is believed to be stable. In this dataset the number of chains used, S , appears relatively unimportant, with similar results for $S = 100, 500, 1000$.

PPI

Consensus matrices

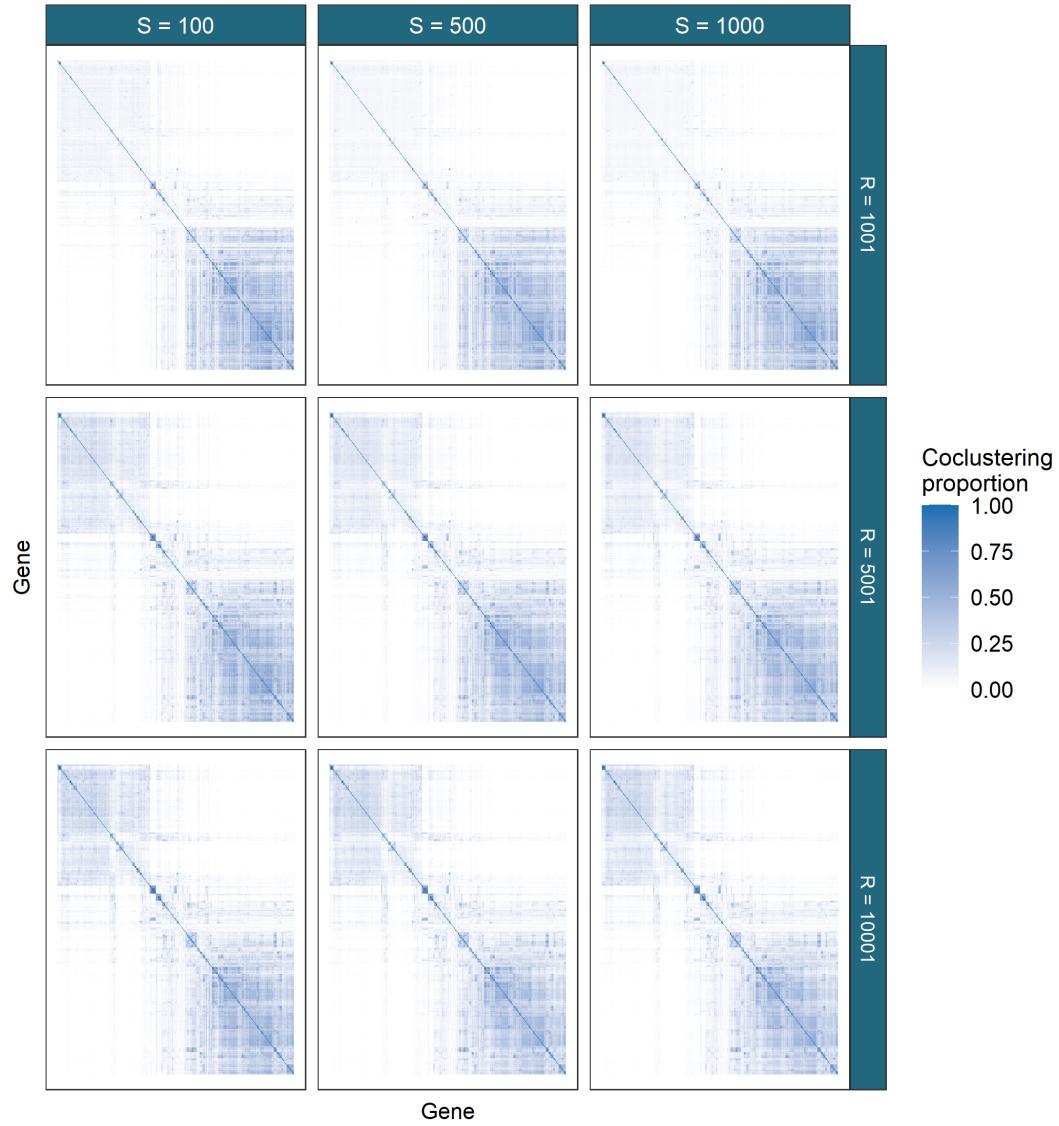


Figure 10: The PPI dataset has awkward characteristics for modelling. A wide, sparse dataset it is again chain depth that is the most important parameter for the ensemble. Similar to the results in figure 9, the matrices only stabilise from $R = 5001$ to $R = 10001$.

Parameter density

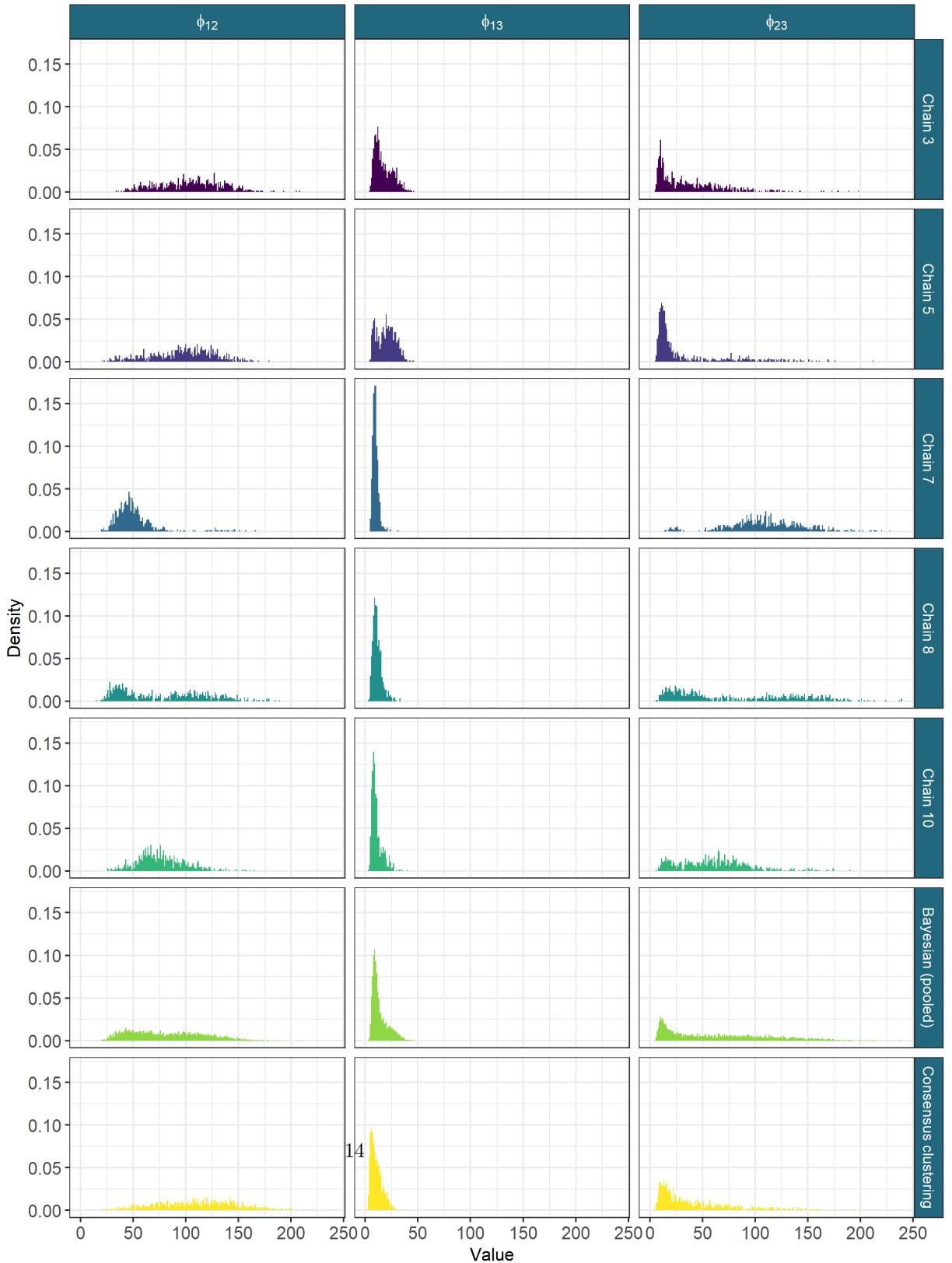


Figure 11: The sampled values for the ϕ parameters from the long chains, their pooled samples and the consensus using 1000 chains of depth 10.001. The long

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