

Consensus clustering for Bayesian mixture models: Supplementary materials

Stephen Coleman, Paul DW Kirk and Chris Wallace

November 9, 2020

Abstract

Description of models used and analyses performed.

1 Definitions

Definition 1 (Consensus matrix) *Given S clusterings for a dataset of N items, $c_s = (c_{s1}, \dots, c_{sN})$, the Consensus matrix is a $N \times N$ matrix where the $(i, j)^{th}$ entry records the proportions of clusterings for which items i and j are allocated the same label. More formally, it is the matrix \mathbb{C} such that*

$$\mathbb{C}(i, j) = \frac{1}{S} \sum_{s=1}^S \mathbf{I}(c_{si} = c_{sj}) \quad (1)$$

where $\mathbb{I}(\cdot)$ is the indicator function taking a value of 1 if the argument is true and 0 otherwise.

Definition 2 (Posterior similarity matrix) *A Consensus matrix for which all the clusterings are generated from a converged Markov chain for some Bayesian clustering model. Sometimes abbreviated to PSM.*

Definition 3 (Partition or Clustering) *For a dataset of items $X = (x_1, \dots, x_N)$, a partition or clustering is a set of disjoint sets covering X , normally indicated by a N -vector of integers indicating which set each item is associated with. Note that these labels only have meaning relative to each other, they are symbolic. Each set within the clustering is referred to as a cluster.*

2 The models

2.1 Individual dataset

In the simulations (see section 4) where individual datasets are modelled a *Bayesian mixture model* is used. We write the basic mixture model for inde-

pendent items $X = (x_1, \dots, x_N)$ as

$$x_n \sim \sum_{k=1}^K \pi_k f(x_n | \theta_k) \quad \text{independently for } n = 1, \dots, N \quad (2)$$

where $f(\cdot | \theta)$ is some family of densities parametrised by θ . A common choice is the Gaussian density function, with $\theta = (\mu, \sigma^2)$ (as in our simulation study). K , the number of subgroups in the population, $\{\theta_k\}_{k=1}^K$, the component parameters, and $\pi = (\pi_1, \dots, \pi_K)$, the component weights are the objects to be inferred. In the context of *clustering*, such a model arises due to the belief that the population from which the random sample under analysis has been drawn consists of K unknown groups proportional to π . In this setting it is natural to include a latent *allocation variable*, $c = (c_1, \dots, c_N)$, to indicate which group each item is drawn from, with each non-empty component of the mixture corresponds to a cluster. The model is

$$\begin{aligned} p(c_n = k) &= \pi_k \quad \text{for } k = 1, \dots, K, \\ x_n | c_n \sim f(x_n | \theta_k) &\quad \text{independently for } n = 1, \dots, N. \end{aligned} \quad (3)$$

The joint model can then be written

$$p(X, c, K, \pi, \theta) = p(X|c, \pi, K, \theta)p(\theta|c, \pi, K)p(c|\pi, K)p(\pi|K)p(K)$$

We assume conditional independence between certain parameters such that the model reduces to

$$p(X, c, \theta, \pi, K) = p(\pi|K)p(\theta|K)p(K) \prod_{n=1}^N p(x_n | c_n, \theta_{c_n})p(c_n | \pi, K). \quad (4)$$

Additional flexibility is provided by the inclusion of hyperparameters on the priors for π and θ , denoted α and η respectively. In our context where $\theta = (\mu, \sigma^2)$, we use

$$\sigma^2 \sim \Gamma^{-1}(a, b), \quad (5)$$

$$\mu \sim \mathcal{N}(\xi, \frac{1}{\lambda} \sigma^2), \quad (6)$$

$$\pi \sim \text{Dirichlet}(\alpha). \quad (7)$$

The directed acyclic graph (**DAG**) for this model is shown in figure 1. The value of the hyperparameters we use are

$$\alpha = 1, \quad (8)$$

$$\xi = 0.0, \quad (9)$$

$$\lambda = 1.0, \quad (10)$$

$$a = 2.0, \quad (11)$$

$$b = 2.0. \quad (12)$$

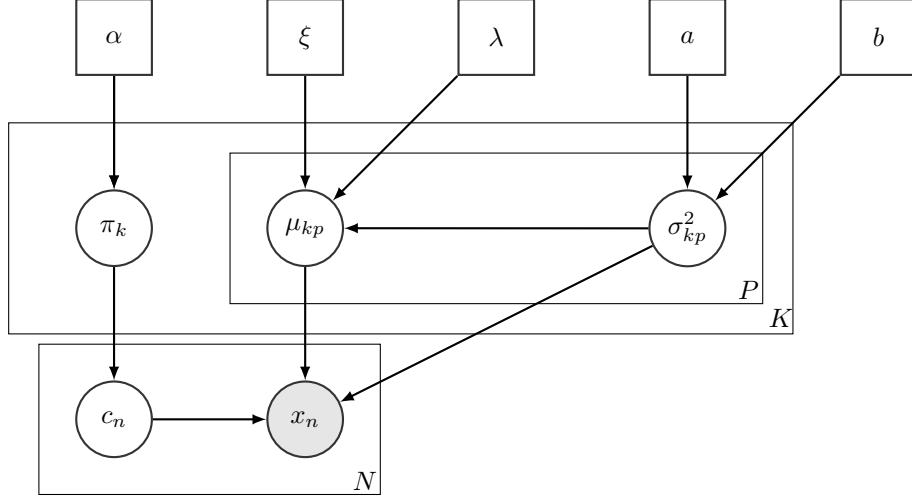


Figure 1: Directed acyclic graph for the mixture of Gaussians used.

2.2 Integrative clustering

We are interested in the use of Consensus clustering for integrative methods. We used Multiple Dataset Integration (**MDI**, Kirk et al., 2012) as an example of a Bayesian integrative clustering method. MDI models dataset specific clusterings, in contrast to, for example, Clusternomics (Gabasova et al., 2017) in which a *global clustering* is inferred.

The defining aspect of MDI is the prior on the allocation of the n^{th} item across the L datasets

$$p(c_{n1}, \dots, c_{nL}) \propto \prod_{l=1}^L \pi_{c_{nl}l} \prod_{l=1}^{L-1} \prod_{m=l+1}^L (1 + \phi_{lm} \mathbb{I}(c_{nl} = c_{nm})) \text{ for } n = 1, \dots, N. \quad (13)$$

ϕ_{lm} is the parameter defined by the similarity of the clusterings for the l^{th} and m^{th} datasets and is also sampled in each iteration. As ϕ_{lm} increases more mass is placed on the common partition for these datasets. Conversely, in the limit $\phi_{lm} \rightarrow 0$ we have independent mixture models. In other words, MDI allows datasets with similar clustering of the items to inform the clustering in each other more strongly than the clustering for an unrelated dataset. The DAG for this model for three datasets is shown in figure 2.

3 Consensus clustering

Consensus clustering is an ensemble approach to cluster analysis. Ensembles are often better able to explore the full parameter space than any individual

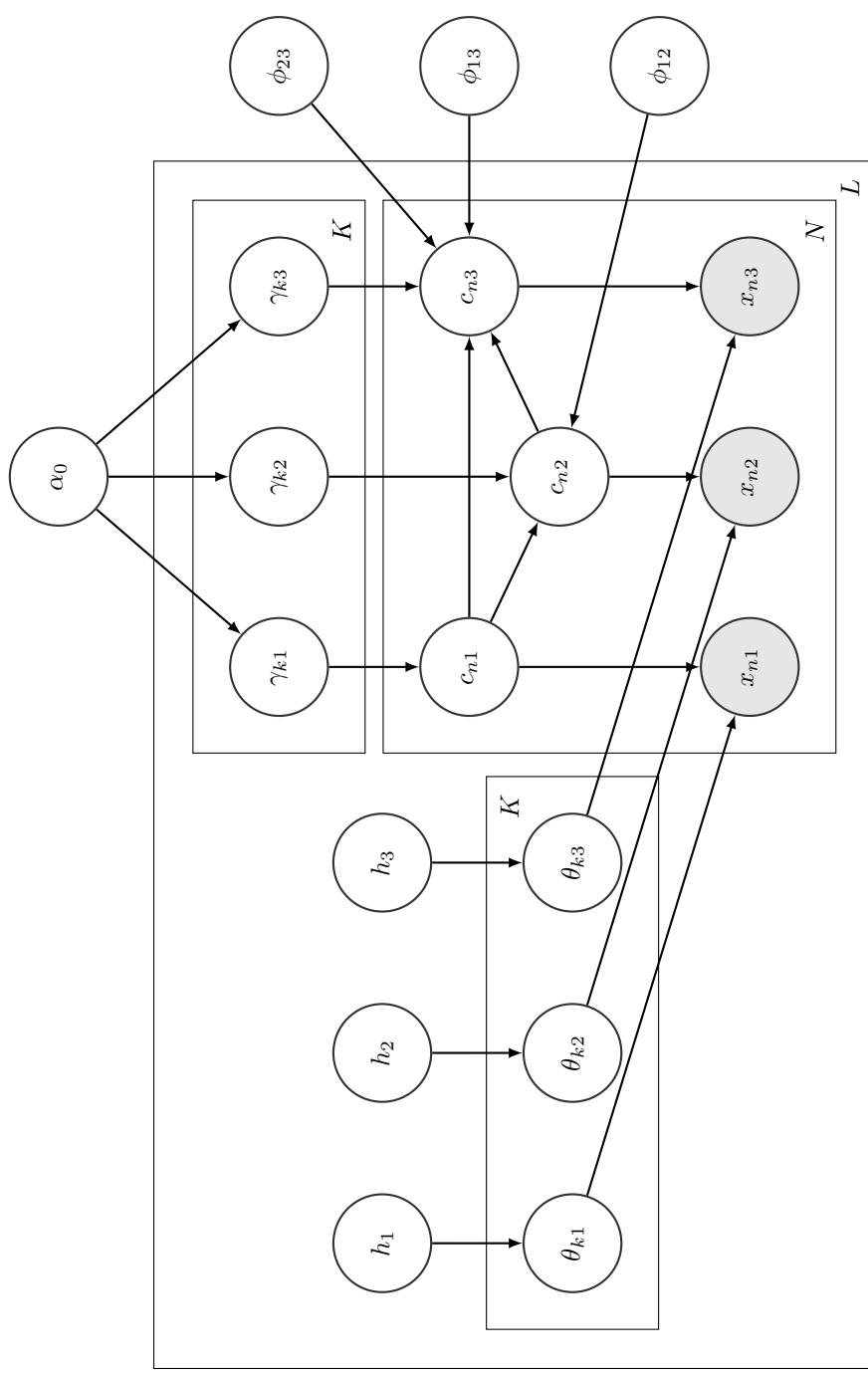


Figure 2: Directed acyclic graph for the Multiple Dataset Integration model for $L = 3$ datasets. h_l is the choice of hyperpriors for the l^{th} dataset.

learner in its composition, thus describing more modes within parameters than the individual learners (Ghaemi et al., 2011). Ensembles also offer reductions in computational runtime because most ensemble methods enable use of a parallel environment to improve computation speed (Ghaemi et al., 2009).

Consensus clustering (Monti et al., 2003) is an ensemble method for cluster analysis, previously implemented using k -means clustering as the base learner in the R package **ConsensusClusterPlus** (Wilkerson et al., 2010). Consensus clustering has been applied in a variety of biomedical setting such as cancer subtyping (Lehmann et al., 2011; Verhaak et al., 2010), identifying subclones in single cell analysis (Kiselev et al., 2017), and proteomic characterisation of tumours (Xu et al., 2020). Consensus clustering applies S independent runs of the underlying clustering algorithm to perturbed versions of the dataset and combines the S final partitions in a *Consensus matrix* which is used to infer a final clustering. An outline of this is described in algorithm 1.

The consensus matrix is a symmetric matrix with the $(i, j)^{th}$ entry being the proportions of model runs for which the i^{th} and j^{th} items are clustered together. For a single partition the *coclustering matrix* represents this information, being a binary matrix with the $(i, j)^{th}$ entry indicating if items i and j are allocated to the same cluster.

```

Data:  $X = (x_1, \dots, x_N)$ 
Input: A resampling scheme Resample
A clustering algorithm Cluster
Number of resampling iterations  $S$ 
Set of cluster numbers to try  $\mathcal{K} = \{K_1, \dots, K_{max}\}$ 
Output: A predicted clustering,  $\hat{Y}$ 
The predicted number of clusters present  $\hat{K}$ 
begin
  for  $K \in \mathcal{K}$  do
    /* initialise an empty Consensus Matrix */  

     $\mathbf{M}^{(K)} \leftarrow \mathbf{0}_{N \times N};$   

    for  $s = 1$  to  $S$  do
       $X^{(s)} \leftarrow \text{Resample}(X);$   

      /* Cluster the perturbed dataset, represented in a  

       coclustering matrix */  

       $\mathbf{B}^{(s)} \leftarrow \text{Cluster}(X^{(s)}, K);$   

       $\mathbf{M}^{(K)} \leftarrow \mathbf{M}^{(K)} + \mathbf{B}^{(s)};$ 
    end
     $\mathbf{M}^{(K)} \leftarrow \frac{1}{S} \mathbf{M}^{(K)};$ 
  end
   $\hat{K} \leftarrow \text{best } K \in \mathcal{K} \text{ based upon all } \mathbf{M}^{(K)};$ 
   $\hat{Y} \leftarrow \text{partition } X \text{ based upon } \mathbf{M}^{(\hat{K})};$ 
end
```

Algorithm 1: Consensus Clustering algorithm

Ensemble methods are rarely applied Bayesian models despite Monti et al. (2003) suggesting this. We believe that Bayesian methods are underexploited in the ensemble framework and propose applying Consensus clustering to Bayesian mixture models. Our implementation of this is described in algorithm 2.

```

Data:  $X = (x_1, \dots, x_N)$ 
Input: A Bayesian mixture model with membership vector
 $c = (c_1, \dots, c_N)$ 
A clustering algorithm that generates samples  $Cluster$ 
The number of chains to run,  $S$ 
The number of iterations within each chain,  $R$ 
Output: A predicted clustering,  $\hat{Y}$ 
The consensus matrix  $M$ 
begin
    /* initialise an empty Consensus Matrix */  

     $M \leftarrow \mathbf{0}_{N \times N};$   

    for  $s = 1$  to  $S$  do  

        /* set the random seed controlling initialisation and  

         MCMC moves */  

         $set.seed(s);$   

        /* initialise a random partition on  $X$  drawn from the  

         prior distribution */  

         $Y_{(0,s)} \leftarrow Initialise(X);$   

        for  $r = 1$  to  $R$  do  

            /* generate a markov chain for the membership  

             vector */  

             $Y_{(r,s)} \leftarrow Cluster(c, r);$   

        end  

        /* create a coclustering matrix from the  $R^{th}$  sample */  

         $B^{(s)} \leftarrow Y_{(R,s)};$   

         $M \leftarrow M + B^{(s)};$   

    end  

     $M \leftarrow \frac{1}{S}M;$   

     $\hat{Y} \leftarrow \text{partition } X \text{ based upon } M;$ 
end

```

Algorithm 2: Consensus clustering for Bayesian mixture models

We show via simulation that ensembles consisting of short chains are sufficient to uncover meaningful structure in a number of scenarios including some within which a Gibbs sampler becomes trapped in individual modes for any reasonable length of runtime. The chains are both short and independent, thus their individual runtime is far shorter than the chains traditionally used for Bayesian inference and may also be run in parallel. This means that Consensus clustering of Bayesian mixture models offers significant reductions in runtime without sacrifices in performance. As the ensemble can describe multiple modes,

the uncertainty present in the consensus matrix can be more representative of the data than the individual modes captured by any single chain.

We then considered the multiple dataset setting. We applied Consensus clustering to an integrative extension of Bayesian mixture models, Multiple Dataset Integration (MDI). We applied this ensemble to three 'omics datasets for *Saccharomyces cerevisiae* and uncovered clusters that have a biological interpretation. We then compared this result to performing Bayesian inference of MDI.

3.1 Stopping rule for ensemble growth

As our ensemble sidesteps the problem of convergence within each chain, we need an alternative stopping rule for growing the ensemble in chain depth, R , and number of chains, S . We propose a heuristic based upon the Consensus matrix to decide if a given value of R and S are sufficient. We suspect that increasing S and R might continuously improve the performance of the ensemble, but we believe that these improvements will become smaller and smaller for greater values, approaching some asymptote for each of S and R . Following this logic if the Consensus matrices for three ensembles define by the parameters (aR, S) , (R, bS) and (R, S) are not visibly different for some reasonable values of a, b, S and R than increasing ensemble size or depth will see at most marginal improvement in performance. We suggest bounds of $a, b \in (0, 0.5]$ and $R \geq 100, S \geq 50$, but make the general observation that large S and R are always better and that the closer a and b are to 0 the more strict the stopping criteria become.

This heuristic is partially 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.

4 Simulations

We defined a number of scenarios to test certain concepts of the method and to explore behaviour due to specific characteristics of real data. The parameters associated with each scenario in table 1 were used to generate individual simulations using algorithm 3. We compared Consensus clustering of Bayesian mixture models, a Bayesian inference of these models and **Mclust**, an implementation of mixture models that uses the maximum-likelihood estimator and an initialisation based upon hierarchical clustering.

- *2D*: a low dimensional scenario within which we expected **Mclust** to perform well and the long chains to converge and explore the full support of the posterior distribution.

Algorithm: Simulation generation

Input: Distance between means Δ_μ
A common standard deviation σ^2
A number of clusters K
The number of items to generate in total N
The number of features to generate in total P
An indicator vector of feature relevance $\phi = (\phi_1, \dots, \phi_P)$
The expected proportion of items in each cluster $\pi = (\pi_1, \dots, \pi_K)$
A method for sampling x times from the array y , with weights π :
 $Sample(y, x, \pi)$
A method for permuting a vector x : $Permute(x)$
A method for generating a value from a univariate Gaussian
distribution with mean μ and standard deviation σ^2 : $Gaussian(\mu, \sigma^2)$

Output: A dataset, X

The generating cluster labels $c = (c_1, \dots, c_N)$

```

begin
    /* initialise the empty data matrix */ 
     $X \leftarrow 0_{N \times P};$ 
    /* create a matrix of  $K$  means */ 
     $\mu \leftarrow (\Delta_\mu, \dots, K\Delta_\mu);$ 
    /* generate the allocation vector */ 
     $c \leftarrow Sample(1 : K, N, \pi);$ 
     $M \leftarrow 0_{N \times N};$ 
    for  $p = 1$  to  $P$  do
        /* Test if the feature is relevant, if relevant
           generate data from a mixture of univariate
           Gaussians, otherwise draw all items from the same
           distribution */ 
        if  $\phi_p = 1$  then
             $\nu \leftarrow Permute(\mu);$ 
            for  $n = 1$  to  $N$  do
                |  $X(n, p) \leftarrow Gaussian(\nu_{c_n}, \sigma^2)$ 
            end
        end
        if  $\phi_p = 0$  then
            for  $n = 1$  to  $N$  do
                |  $X(n, p) \leftarrow Gaussian(0, \sigma^2)$ 
            end
        end
    end
    /* Mean centre and scale the data */ 
     $X \leftarrow Normalise(X)$ 
end

```

Algorithm 3: Data generation for a mixture of Gaussian with independent features. This algorithm is implemented in the `generateSimulationDataset` function from the `mdiHelpR` package available at www.github.com/stcolema mdiHelpR.

Scenario	N	P_s	P_n	K	$\Delta\mu$	σ^2	π
2D	100	2	0	5	3.0	1	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
No structure	100	0	2	1	0.0	1	1
Base Case	200	20	0	5	1.0	1	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
Large standard deviation	200	20	0	5	1.0	9	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
Large standard deviation	200	20	0	5	1.0	25	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
Irrelevant features	200	20	10	5	1.0	1	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
Irrelevant features	200	20	20	5	1.0	1	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
Irrelevant features	200	20	100	5	1.0	1	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
Varying proportions	200	20	0	5	1.0	1	$(\frac{1}{2}, \frac{1}{4}, \frac{1}{8}, \frac{1}{16}, \frac{1}{16})$
Varying proportions	200	20	0	5	0.4	1	$(\frac{1}{2}, \frac{1}{4}, \frac{1}{8}, \frac{1}{16}, \frac{1}{16})$
Small N , large P	50	500	0	5	1.0	1	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$
Small N , large P	50	500	0	5	0.2	1	$(\frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5}, \frac{1}{5})$

Table 1: Parameters defining the simulation scenarios as used in generating data and labels.

- *No structure*: we included this scenario to reassure fears that Consensus clustering has a predilection to finding clusters where none exist (Şenbabaoğlu et al., 2014a,b).
- *Base case*: highly informative datasets within which we expected methods to find the true generating labels quite easily. We included this scenario to benchmark the others that are variations of this setting.
- *Large standard deviation*: these two scenarios investigated the degree of distinction required between clusters for the methods to uncover their structure.
- *Irrelevant features*: we included these scenarios to investigate how robust the methods are to irrelevant features.
- *Varying proportions*: these scenarios investigated how well each method uncovers clusters when the clusters have significantly different membership counts.
- *Small N , large P* : an investigation of behaviour when the number of features is far greater than the number of items.

4.1 Bayesian analysis

For each simulation we ran 10 chains for 1 million iterations, keeping every thousandth sample. We discarded the first 10,000 iterations to account for burn-in bias, leaving 990 samples per chain. To check if the chains were converged we used

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

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 (i.e. the chain is sampling the same distribution in both samples) than the scores are expected to be standard normally distributed. If a chain's Geweke convergence diagnostic passed a Shapiro-Wilks test for normality (Shapiro and Wilk, 1965) (based upon a threshold of 0.05), we considered it to have achieved stationarity and included it in the model performance analysis.

\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. We use their method as implemented in the R package `stableGR` (Knudson and Vats, 2020) as the final check of convergence. An example of the \hat{R} series across the 100 simulations for a scenario where chains are well-behaved is shown in figure 3.

We focused upon stationarity of the continuous variables as assessing convergence of the allocation labels is difficult due to label-switching. In our simulations the only recorded continuous variable is the concentration parameter of the Dirichlet distribution for the component weights.

We pooled the samples from the stationary chains and used these to form a PSM. This and the point estimate clustering found by applying the R function `maxpear` (Fritsch, 2012) to this PSM are used in model performance analysis in section 4.4. `maxpear` attempts to find the clustering that maximises the Adjusted Rand Index to the true clustering by using an approximation of the expected clustering under the posterior, $\mathbb{E}(c|X)$, believing that this converges to the true clustering. A sample average clustering is used to approximate the expected clustering. This is estimated from the PSM by maximising

$$\frac{\sum_{i < j} \mathbb{I}(c_i^* = c_j^*) p_{ij} - \sum_{i < j} \mathbb{I}(c_i^* = c_j^*) \sum_{i < j} p_{ij} / \binom{N}{2}}{\frac{1}{2} \left[\sum_{i < j} \mathbb{I}(c_i^* = c_j^*) + \sum_{i < j} p_{ij} \right] - \sum_{i < j} \mathbb{I}(c_i^* = c_j^*) \sum_{i < j} p_{ij} / \binom{N}{2}} \quad (14)$$

where p_{ij} is the $(i, j)^{th}$ entry of the PSM (Fritsch et al., 2009). When the chain has converged this maximises the posterior expected ARI to the true clustering.

There are three possibilities to consider the decision to pool the samples across chains under:

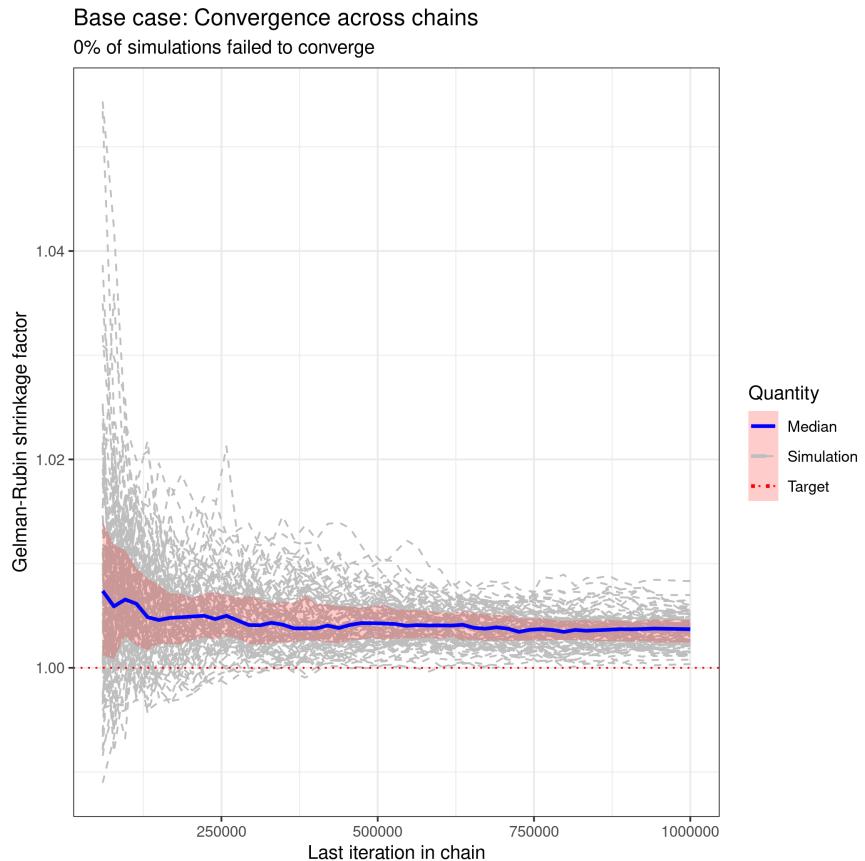


Figure 3: The \hat{R} values for each simulation (in dotted grey), the median value and the interquartile range across simulations. One can see that \hat{R} approaches 1.0, being below 1.01 for every simulation by the end of the chains. The “0% of simulations failed to converge” is a statement based upon the percentage of simulations which passed the test of stable \hat{R} .

- The chains are converged and agree upon the distribution sampled (see figure 4 for an example).
- The chains are not in agreement upon the partition sampled, becoming trapped in different modes. However, a mode does dominate being the mode present in a majority of chains (see figure 5 for an example of this behaviour).
- The chains are not in agreement and no one mode dominates among chains (see figure 6 for an example of this behaviour).

In the first case pooling has no effect upon the predicted clustering compared to using any one chain. In the second case it feels natural that one would use the mode that dominates. Pooling the samples effectively does this for the predictive performance of the method as the mode with the greatest number of samples across the chains dominates; however, the uncertainty for this mode is increased. In the third case the analysis is non-trivial and further thought, chains and samples would be required. In our simulations this case only arises in the most pathological form in the second *Large N, small P* scenario, where each chain remains trapped in the initial partition. The clustering inferred from any chain is not meaningful being a random clustering; thus the clustering predicted by pooling the PSMs is no more or less relevant as it too is random.

4.2 Consensus clustering analysis

We investigated a range of ensembles, using all combinations of chain depth, $R = (1, 10, 100, 1000, 10000)$, and the number of chains, $S = (1, 10, 30, 50, 100)$. This gave a total of 25 different ensembles. A Consensus matrix was constructed from the samples generated by each ensemble by finding the proportion of samples within which any pair of items are coclustered. An example of the Consensus matrices for each ensemble in a given simulation is shown in figure 7. We used the `maxpear` function from the R package `mcclust` to create a point clustering estimate from the Consensus matrix. In this context where we do not assume that the Consensus matrix of the samples is the Posterior similarity matrix we do not expect that the predicted clustering maximises the posterior expected ARI. Instead `maxpear` is used as calculating a sample average clustering which we believe is representative of the ensemble.

4.3 Mclust

We called `Mclust` using the default settings and a range of inputs for the choice of K . We used $K = (2, \dots, \min(\frac{N}{2}, 50))$ to mirror the choice of $K_{max} = 50$ used for the overfitted mixture models (the default in the software we used), with the bound of $\frac{N}{2}$ to avoid fitting 50 clusters in the *Small N, large P* scenario where $N = 50 = K_{max}$. In the *No structure* scenarios we extended to range to $K = (1, \dots, 50)$ to include the correct structure as an option. The model choice was performed using the Bayesian Information Criterion (Schwarz et al., 1978,



Figure 4: Posterior similarity matrices for the simulation generated using a random seed set to 1 for the first large standard deviation scenario from table 1. This is an example of all stationary chains agreeing in a simulation (and thus pooling of samples is no different to using any choice of chain for the performance analysis). Ordering of rows and columns is defined by hierarchical clustering of the first matrix in the series, in this case that from Chain 1.

Small N large P ($\Delta\mu = 1.0$)

Posterior similarity matrices (simulation 1)

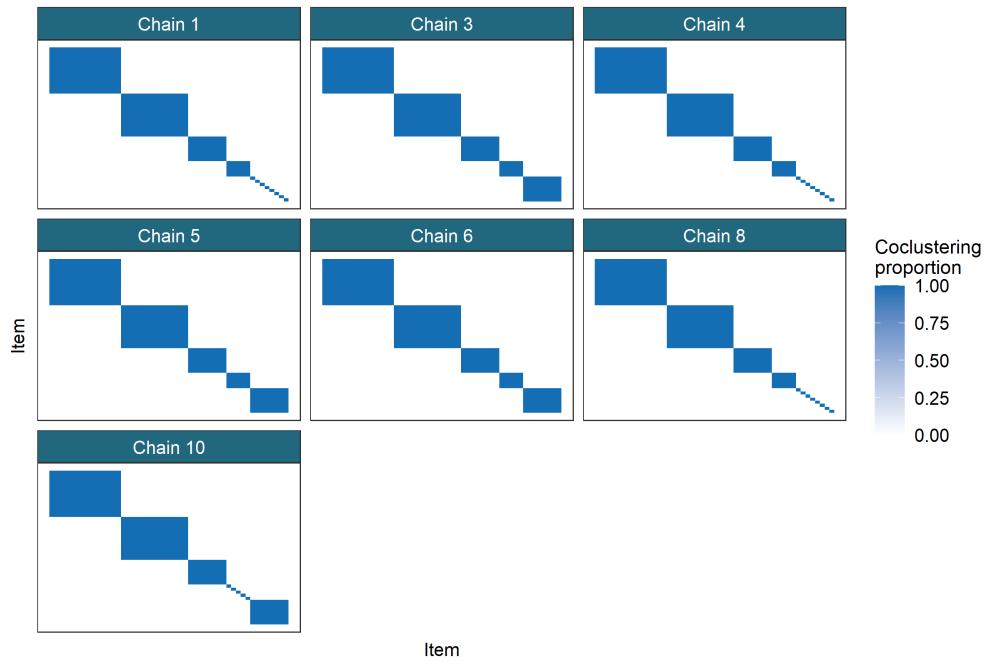


Figure 5: Posterior similarity matrices for the simulation generated using a random seed set to 1 for the first small N , large P scenario from table 1. This is an example of different chains becoming trapped in different modes, but one mode (which does represent the generating structure well) is dominant, being fully present in 3 of the 6 chains, with the two other modes present having significant overlap. Ordering of rows and columns is defined by hierarchical clustering of the first matrix in the series, in this case that from Chain 1.

Small N large P ($\Delta\mu = 0.2$)

Posterior similarity matrices (simulation 1)

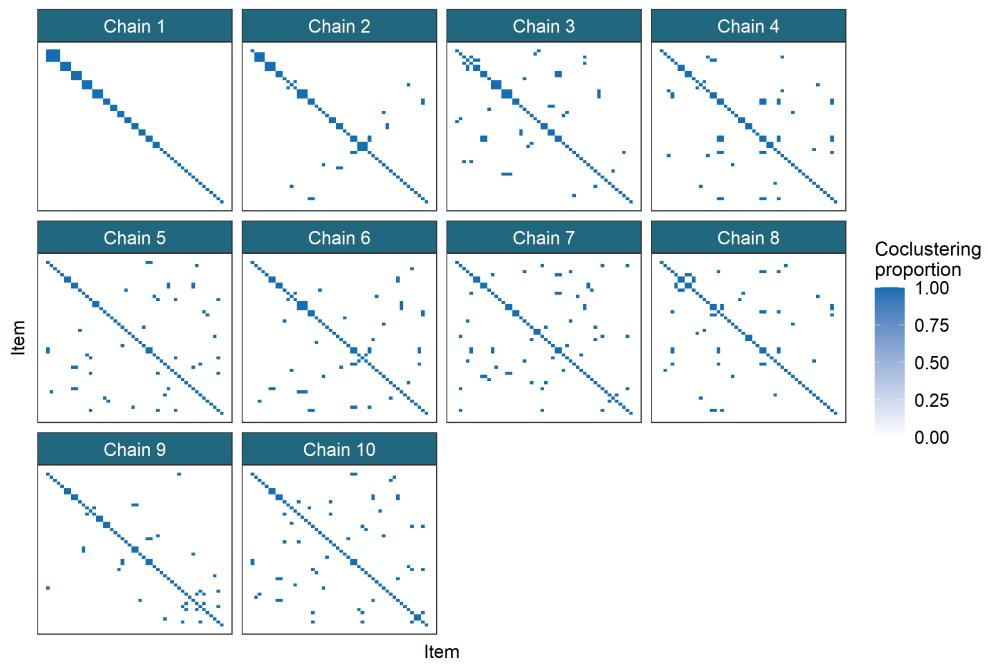


Figure 6: Posterior similarity matrices for the simulation generated using a random seed set to 1 for the second small N , large P scenario from table 1. This is an example of different chains becoming trapped in different modes with no mode being dominant. In this scenario each chain remains trapped in initialisation. Ordering of rows and columns is defined by hierarchical clustering of the first matrix in the series, in this case that from Chain 1.

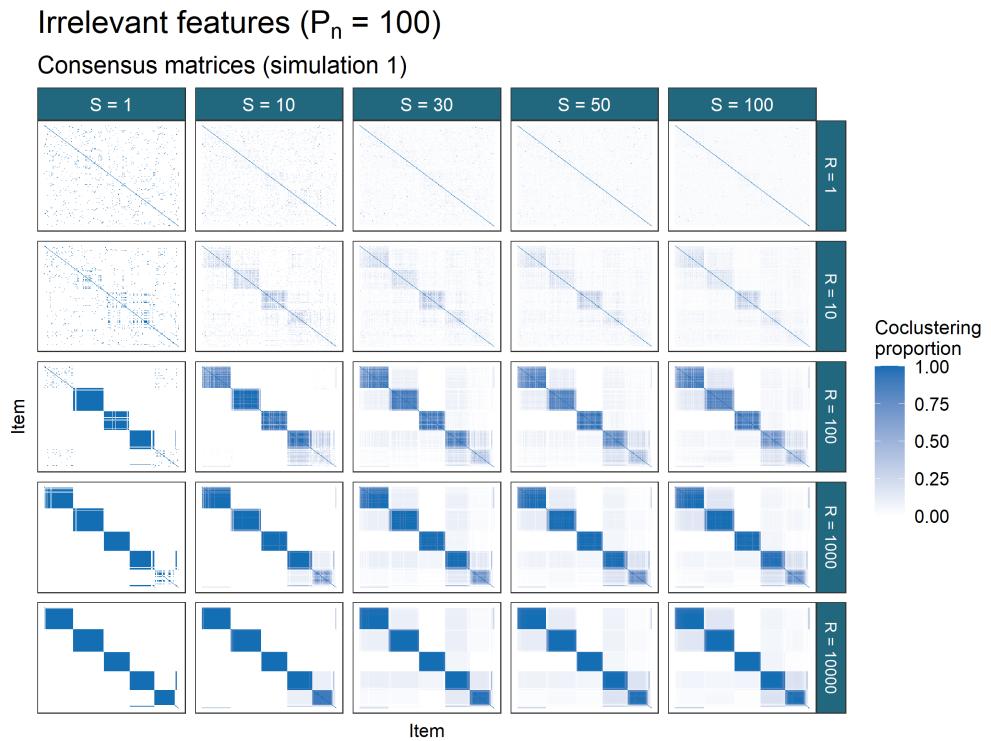


Figure 7: Consensus matrices for the simulation generated using a random seed set to 1 for the third irrelevant features scenario from table 1. R is the individual chain length and S is the number of chains used. In this example there are several modes present (as seen in the entries with values between 0 and 1) but one mode is clearly dominant (the 5 dark squares along the diagonal which correspond closely to the generating labels).

as implemented in **Mclust**). **Mclust** tries different covariance matrices and thus the model choice is not just between different values of K .

4.4 Model performance

The different models (Bayesian (pooled), **Mclust** and the 25 Consensus clustering ensembles) were compared under their ability to predict the generating clustering and their uncertainty about this quantity.

In figure 11 the ARI between the generating labels and the point estimate clustering from each method is shown. For two partitions c_1, c_2 ,

- $ARI(c_1, c_2) = 1.0$: a perfect match between the two partitions,
- $ARI(c_1, c_2) = 0.0$: c_1 is no more similar to c_2 than is expected for a random partition of the data.

In several scenarios **Mclust** performs the best under this metric (e.g. in the scenarios *2D*, *Small N, large P* ($\Delta\mu = 0.2$)). However when the number of irrelevant features is large **Mclust** performs less well (see *Irrelevant features* ($P_n = 20$) and ($P_n = 100$)) than the other methods. In the scenario that $P_n = 100$ failing to find structure is not inherently wrong as a majority of the features suggest that there are no subpopulations. We suspect that the initialisation based upon hierarchical clustering initialises the model in or very near to a small local mode in the likelihood surface and thus higher values of K are rejected as under the BIC as the model fit is not significantly improved and the model complexity is higher.

The pooled Bayesian samples act as an upper bound on the Consensus clustering ensembles in these simulations.

For the ensembles there are two parameters changing between each model, the iteration used to provide the clustering in the ensemble, R , and the number of chains (and hence samples) used, S . In many of the scenarios we find that the benefit of increasing R stabilises by approximately $R = 10$. We believe that in a low-dimensional dataset (such as *2D*), or a highly informative dataset (such as *Base case* or any of the higher dimensional scenarios with no irrelevant features where $\frac{\Delta\mu}{\sigma^2} \geq 1$) the chains quickly find a “sensible” partition of the data and thus increasing the depth within the chain does not increase the probability that any partition sampled will be closer to the generating partition. For example in figure 11 in the *Small N, large P* case, the distribution of the ARI across the ensembles for which $R \geq 10$ and $S = 1$ is nearly identical; this suggests that the chain is sampling a very similar partition again and again for 9,990 iterations (and possibly beyond based upon the PSMs shown in figure 5) and it is through adding more chains rather than using particularly long chains that we improve the ability to uncover the generating structure.

We also notice that even if the behaviour has not stabilised for R that the ensemble can uncover meaningful structure. The ARI for the ensembles of short chains can be quite high (as is the case in many of the scenarios). The behaviour

of the Consensus matrices also shows that low R is not a disqualifier from meaningful inference even if longer chains would be ideal, a result that might be useful in real applications with large datasets and complex models. Consider the Consensus matrices in figure 7, it can be seen that the behaviour has not stabilised before $R = 10000$ (and possibly there is still some benefit in increasing R beyond this value), but the structure being uncovered when there is a sufficient number of chains and R is small does correspond to the structure uncovered in the largest and deepest ensemble. We believe that the order in which components merge and items are co-clustered varies depending on initialisation, and thus if the chain is not sufficiently deep that all of the final mergings have occurred that a sufficiently large ensemble can still perform meaningful inference of the subpopulation structure despite the poor performance of any individual model. Even though each learner probably has too many clusters for small R the consensus among them will have less if the individual learners have low correlation between their partitions (something we might expect if the chains are stopped very early). This is why the entries of the Consensus matrix for $R = 100$ and $S = 100$ in figure 7 are more pale than in deeper ensembles; very few items correctly (possibly none) cocluster in every partition, it is only in observing the consensus that the global structure of interest emerges. Thus if there is some limit to the length of chains available for an analysis (e.g. computational or temporal constraints) than the inference obtained from the shorter chains can still be meaningful, with the caveat that the point clustering might have more clusters than the same analysis with longer chains would provide. Additional post-hoc merging of some clusters might be necessary in this case.

In contrast, when the dataset is sparse or contains many irrelevant features, we believe that deeper chains are required to reach this steady-state sampling where no single sample is expected to be better than any other (see the *Irrelevant features* ($P_n = 100$) facet of figure 11).

In some scenarios no method is successful in uncovering the generating labels. In the *Large standard deviation* ($\sigma^2 = 25$) and *Small N, large P* ($\Delta\mu = 0.2$) this is due to the lack of signal - the clusters overlap so significantly that it is not possible for any of these methods to uncover much of the generating structure. In the *No structure* case it is different (although **Mclust** does perform well here). In this case all items are generated from a common distribution. For the Bayesian chains and the ensembles, a clustering of singletons is predicted; each item is allocated a unique label (see figures 8 and 9). While failing to perform well under the ARI, this is a sensible result. Rather than indicating (as we did with the shared label) that no item is particularly distinct from the others and thus all share a common label, this clustering of singletons states that no item is more similar to any other and thus no two items should cluster together. It is an alternative statement of the same result, i.e. that there is no evidence for subpopulation structure. We consider this evidence that an ensemble of Bayesian mixture models is not as susceptible to predicting labels than an ensemble based upon K -means clustering as in Şenbabaoğlu et al. (2014a,b).

Increasing S is also required when the dimensionality of the dataset is large.

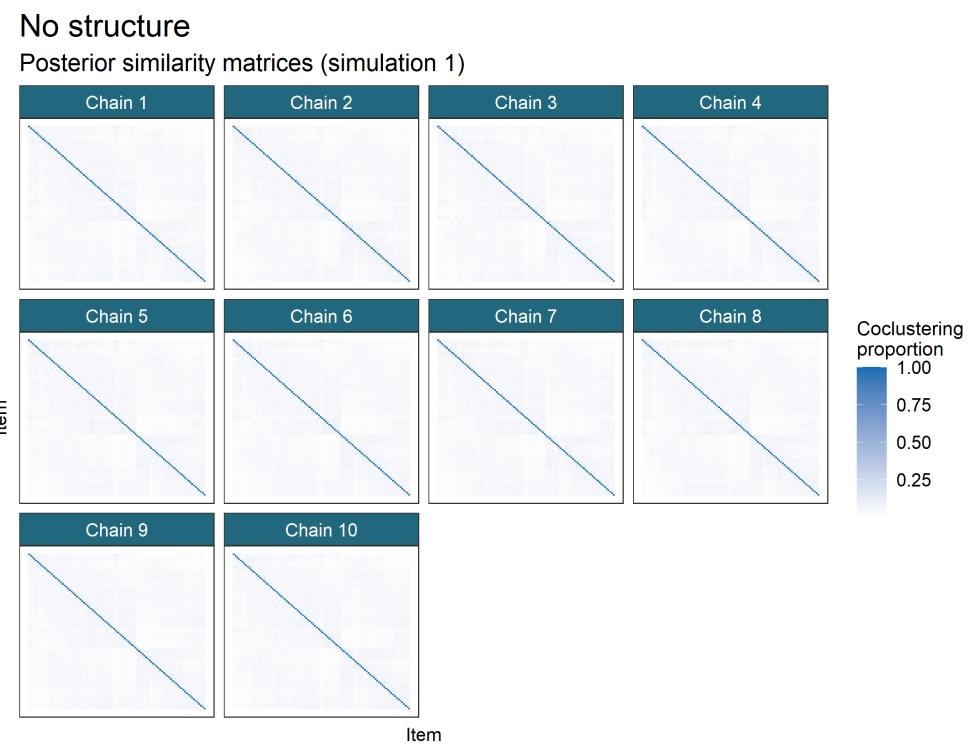


Figure 8: Posterior similarity matrices for simulation 1 of the *No structure* scenario. Each item is allocated to a singleton.

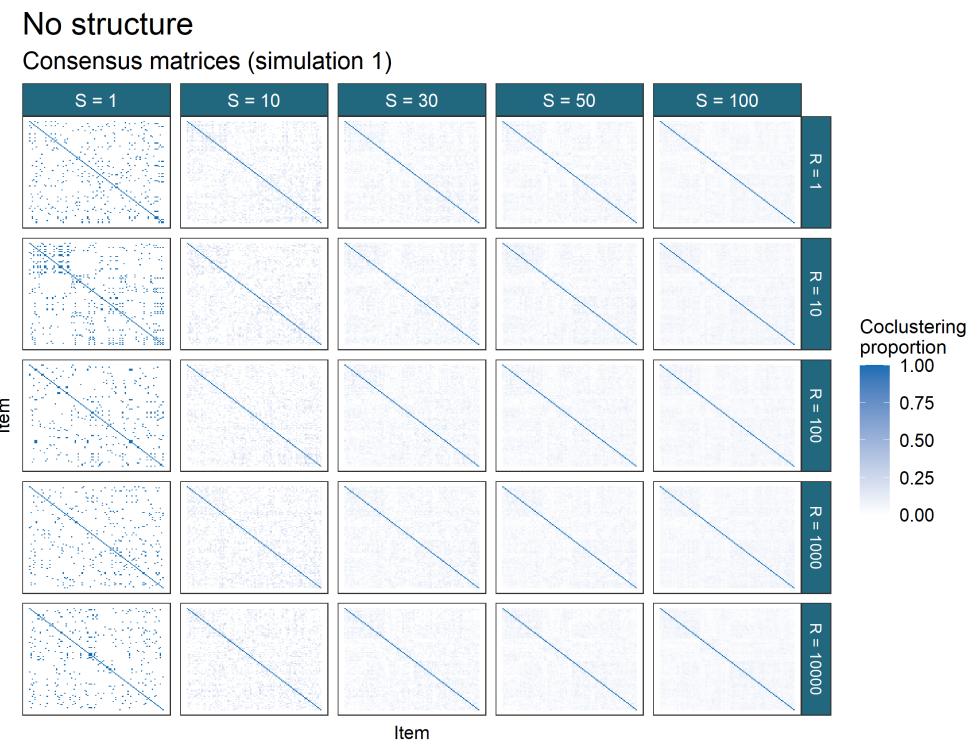


Figure 9: Consensus matrices for simulation 1 of the *No structure* scenario. Each item is allocated to a singleton in many of the Consensus matrices.

Small N large P ($\Delta\mu = 1.0$)

Consensus matrices (simulation 1)

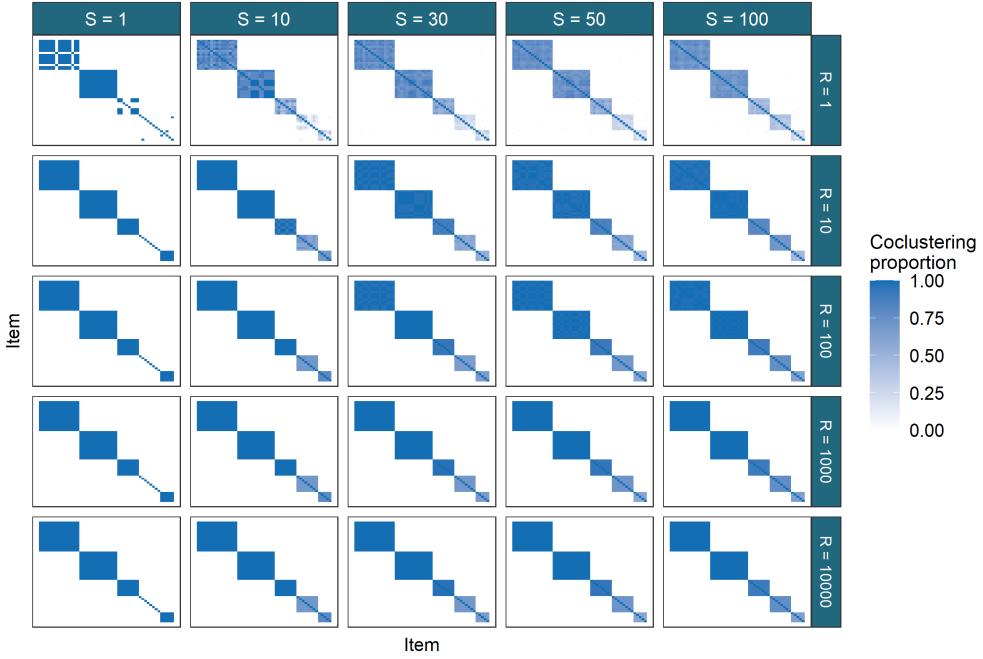


Figure 10: Consensus matrices for simulation 1 of the first *Large N, small P* scenario. One can see that by iteration ten the sample being drawn is from the mode (for $S = 1, R = 10$), and that an ensemble of chains does find structure that recalls the generating labels (see figure 11, the ARI for $CC(10, s)$ is 1.0 for $s > 1$, meaning that the true labels perfectly align with those predicted by the Consensus matrix).

In this case it is due to individual chains exploring only a single mode (as can be seen in figure 5 where each chain appears to sample only a single partition). In this example where each sample is a partition that appears to be a mode in the posterior distribution of the allocation vector from very early in the chain (based upon the stable performance for $R \geq 10$), increasing S allows each chain to “vote” on which mode is the global mode, as we believe that the mode that attracts the most chains is the global mode (although in real datasets the number of chains required might be greater than in our simulations). An example of this behaviour may be seen in figure 10.

In figure 11, limiting behaviour for increases of S and R can be seen for the ensemble. For most simulations there is no change in performance for greater choices of S and R after some stabilising values.

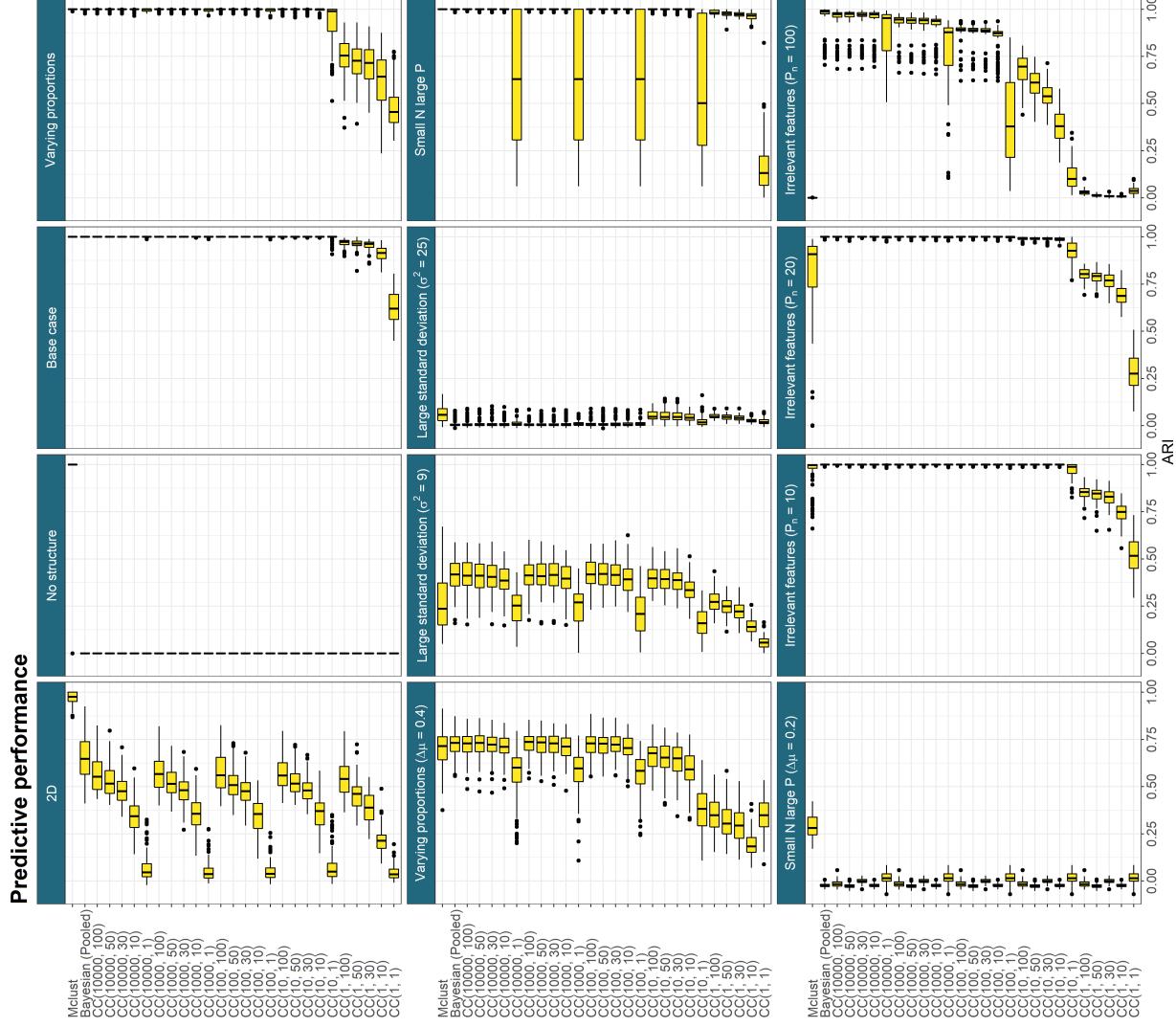


Figure 11: Predictive performance across all simulations. $CC(R, S)$ denotes Consensus clustering using the R^{th} sample from S different chains. In the cases where the generating structure is not exactly found, increasing R and S sees some improvement in the ARI between the truth and the predicted clusterings before some limiting behaviour emerges and further increase appears to have no change in the performance.

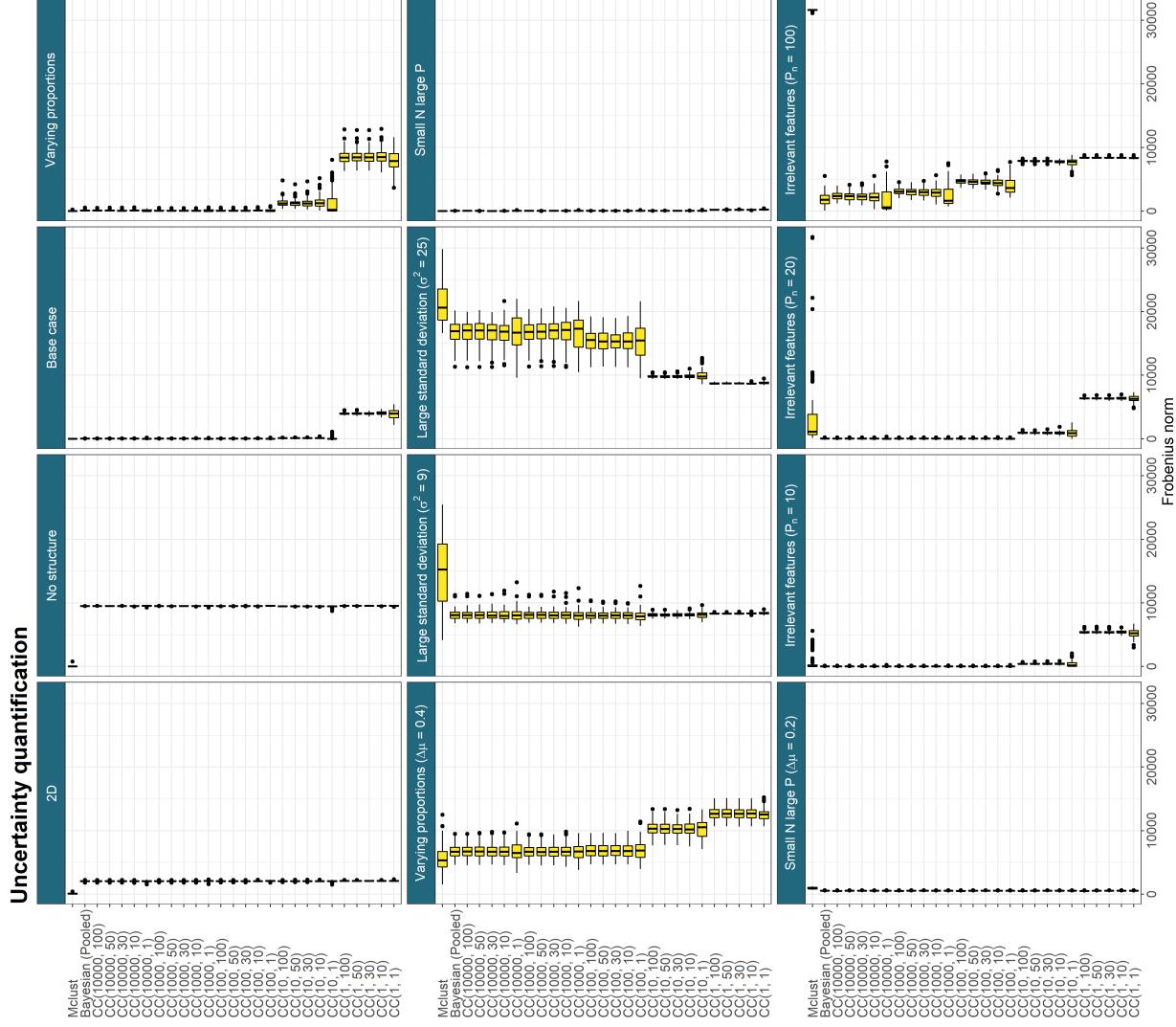


Figure 12: Frobenius norm across simulations. $CC(R, S)$ denotes Consensus clustering using the R^{th} sample from S different chains. Lower values are better. In the *Large standard deviation ($\sigma^2 = 25$) scenario, the very low valued entries from the ensembles of very short chains are rewarded. These ensembles are not closer to the true structure than the longer ensembles, but they are rewarded for the lack of certainty.*

5 Yeast

The cell cycle is the process by which a growing cell divides into two daughter cells. This involves virtually all cellular processes - metabolism, protein synthesis, secretion, DNA replication, organelle biogenesis, cytoskeletal dynamics and chromosome segregation - and diverse regulatory events (Granovskaia et al., 2010). The cell cycle is crucial to biological growth, repair, reproduction, and development; it is fundamental to sustaining life (Tyson et al., 2013; Chen et al., 2004; Alberts et al., 2018). The regulatory proteins of the system first appeared over a billion years ago and are so highly conserved among eukaryotes that many of them function perfectly when transferred from a human cell to a yeast cell (Alberts et al., 2018). This conservation means that a relatively simple eukaryote such as *Saccharomyces cerevisiae* can provide insight into a variety of cell cycle perturbations including those that occur in human cancer (Ingalls et al., 2007; Chen et al., 2004) and ageing (Jiménez et al., 2015). Budding yeast is particularly attractive for genetic analysis as it can proliferate as haploid cells, its genetic makeup can be easily altered by standard tools of molecular genetics, and large numbers of cells may be synchronised in a particular stage of the cell cycle (Tyson et al., 2013; Juanes, 2017).

To better understand the regulatory mechanisms and the genes most important in this process, we performed an integrative cluster analysis of gene products across three yeast datasets. These datasets were generated using different 'omics technologies and target different aspects of the molecular biology underpinning the cell cycle process.

- Microarray profiles of RNA expression from Granovskaia et al. (2010). This dataset comprises measurements of cell-cycle-regulated expression at 5-minute intervals for 41 time points (up to three cell division cycles) and is referred to as the **Timecourse** dataset. We include only the genes identified by Granovskaia et al. (2010) as having periodic expression profiles. This includes some non-coding RNAs (**ncRNAs**) of which the majority are anti-sense RNAs.
- Chromatin immunoprecipitation followed by microarray hybridization (**ChIP-chip**) data from Harbison et al. (2004). This dataset discretizes *p*-values from tests of association between 117 DNA-binding transcriptional regulators and a set of yeast genes. Based upon a significance threshold these *p*-values are represented as either a 0 (no interaction) or a 1 (an interaction).
- Protein-protein interaction (**PPI**) data from BioGrid (Stark et al., 2006). This database consists of physical and genetic interactions between gene and gene products. The interactions included are a collection of results observed in high throughput experiments and some computationally inferred interactions. The dataset we used contained 603 proteins as columns. An entry of 1 in the $(i, j)^{th}$ cell indicates that the i^{th} gene has a protein product that interacts with the j^{th} protein.

We used these datasets to construct sets of co-regulated genes that share biological functions in *Saccharomyces cerevisiae*. We believe such informed gene sets are more relevant to phenotypic traits and offer insight into more complex biological processes.

We believe that the integrative aspect of the experiments means that the clusters are more interpretable than in a standalone cluster analysis. Cluster analysis of a single dataset entails interpreting the clusters defined by similarity within a single experiment which often involves strong assumptions about the biological processes behind the result (e.g. correlation of transcripts implies co-regulation).

We used the MDI model for our integrative analysis. This jointly models the clustering in each dataset, inferring individual clusterings for each dataset that are informed by similarity in the other clusterings. As described in section 2, MDI learns the similarity between the datasets being analysed and does not assume global structure. This means that the similarity between datasets is not strongly assumed in our model. As the MDI model allows different clusters to align across datasets but does not enforce a global structure; this means that individual clusters or even genes can align across datasets based upon the evidence present in the data without forcing global alignment. Thus we can include the PPI data and expect it to contribute to our final clustering despite the expectation that the ncRNAs might not have common cluster allocation across the Timecourse and PPI datasets.

The datasets were reduced to 551 items by considering only the genes with no missing data in the PPI and ChIP-chip data. The choices to reduce the datasets to these 551 genes are the same steps as the original MDI paper (Kirk et al., 2012). The datasets are shown in figure 13.

We used these datasets to perform an integrative analysis as many of the protein encoding genes in the mitotic cell cycle have well studied genomic binding sites with mapped transcription factors that control phase-specific expression (Cho et al., 1998; Spellman et al., 1998); thus the inclusion of the ChIP-chip data means that the clusters that fuse across the datasets should include well studied regulatory proteins. If a cluster of genes are similarly expressed in the Timecourse, share associated regulatory protein in the ChIP-chip and are associated with common protein complexes in the PPI data, than this implies a gene set with strong biological significance.

For example, if we cluster the Timecourse dataset alone, any clusters that we find are defined by correlation across time. This might be assumed to be driven by shared regulatory mechanisms, but other sources of structure might be encouraging this, even experimental error. However, if a cluster aligns across both the Timecourse dataset and the ChIP-chip dataset we can be more certain that these genes are part of some regulatory network; if this cluster also emerges in the PPI dataset we might believe that the genes are co-regulated as part of the formation of some protein complex.

Thus we performed an integrative analysis using MDI to avoid aggressive assumptions about either the biology defining any clusters and modelling assumptions about the latent structure.

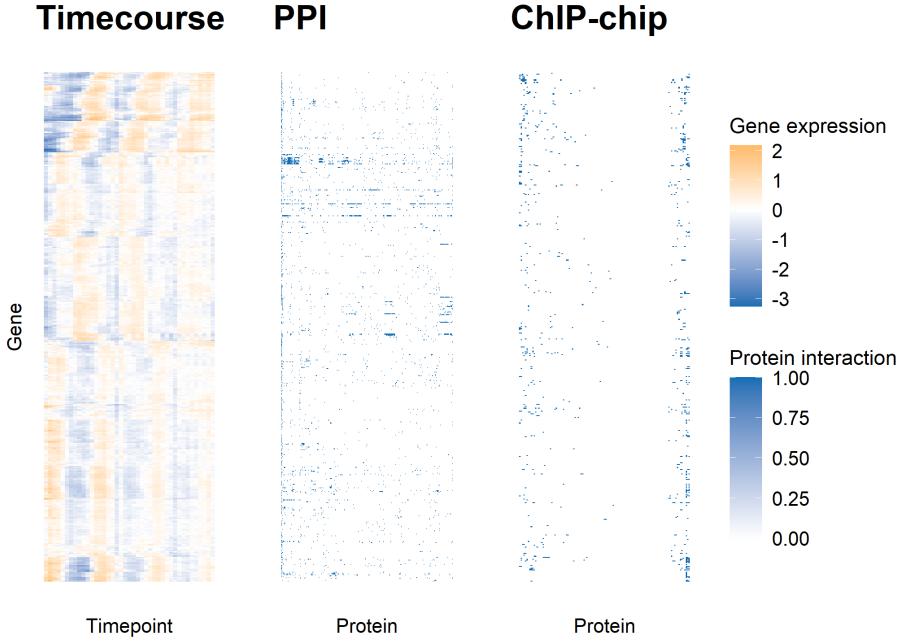


Figure 13: Heatmap of the yeast datasets. Each plot has a common row order corresponding to the gene products being clustered. This order was decided by a hierarchical clustering of the rows of the Timecourse expression matrix. The Timecourse data is associated with the “Gene expression” legend and the ChIP-chip and PPI data with “Protein interaction” legend.

We expect that the complexity of this data and model means that the time required for convergence of the MCMC algorithm would be very large. We avoid this problem by using Consensus clustering of MDI, instead basing our final ensemble choice on the stopping rule laid out in section 3.1.

The datasets were modelled using a mixture of Gaussian processes in the Timecourse dataset and Multinomial distributions in the ChIP-chip and PPI datasets. To ensure that our mixture model is initially overfitted we set $K_{max} = 275 \approx \frac{N}{2}$.

5.1 Consensus clustering analysis

5.1.1 Ensemble choice

We use an ensemble of depth $R = 10001$ and width $S = 1000$ with a base learner of MDI (using the software implementation from Mason et al., 2016). This ensemble depth and width were decided using the stopping rule from section 3.1. We include the Consensus matrices for this ensemble and those for

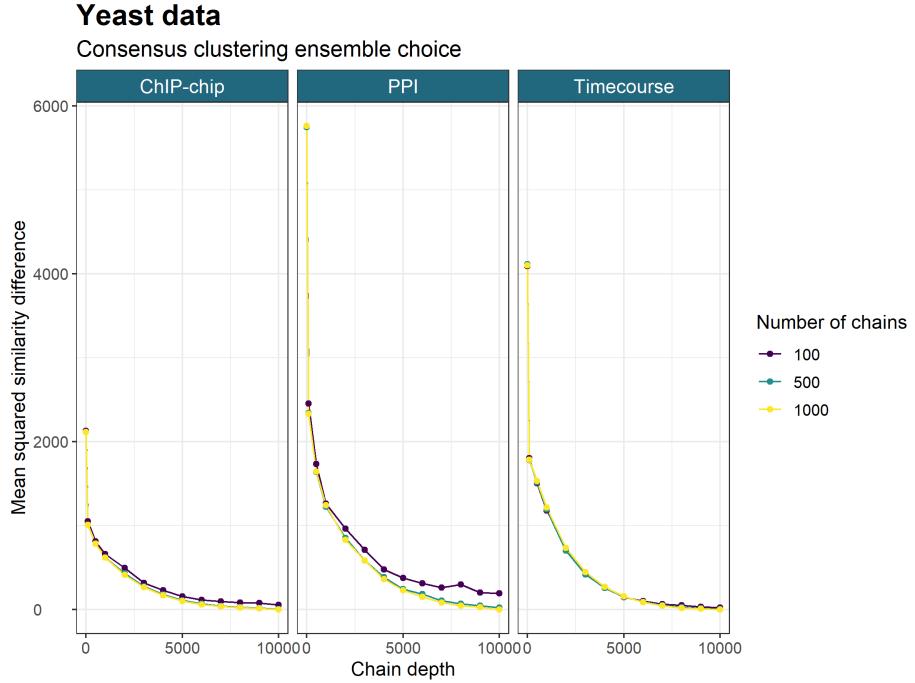


Figure 14: The mean squared difference between the Consensus matrix for chain depth R and S chains to the Consensus matrix for chain depth 10,001 and 1,000 chains. We find that increasing S beyond 100 has marginal effect except in the PPI dataset where values have stabilised by $S = 500$. The changes in item coclustering across the ensemble changes very slightly for chains deeper than 5,000.

the combinations of $R = (1001, 5001, 10001)$, $S = (100, 500, 1, 000)$ in the three datasets (shown in figures 17, 18 and 19) and a plot of the mean squared difference between the Consensus matrix for $R = 10001$ and $S = 1000$ to a range of smaller and shallower ensembles.

We decide to stop increasing at $R = 10001$ as there is little change between Consensus matrices for increasing chain depth from $R = 5001$ to $R = 10001$ across the three datasets. An example of insufficient depth can be seen for $R = 1001$ in figure 19; there is a marked difference in the Consensus matrices between $R = 1001$ and $R = 5001$.

In terms of the number of chains required, we believe this to have stabilised, as there is no obvious change in increasing S from 100 in any dataset.

5.2 Cluster analysis

We use `maxpear` to infer an estimate clustering from the Consensus matrices as in the Simulations except we set `k.max = 275`.

5.2.1 Fused genes

We wish to identify groups of genes that tend to be grouped together in multiple datasets. We use the concept of *fused genes* proposed by Savage et al. (2010) and used by Kirk et al. (2012), but to avoid confusion due to other possible ideas of fused genes (e.g. those that contribute to a common protein complex, the behaviour of TFs upon a gene) we use the term *integrated*. We define a gene to be integrated across some set of datasets if the gene has the same label in each of these datasets for at least half of the recorded clustering samples. Integrated genes are those most affected by the integrative aspect of the analysis and therefore we focus upon these in the following analysis. In our case we have the possible sets of:

- {Timecourse}, {ChIP-chip}, {PPI},
- {Timecourse, ChIP-chip}, {Timecourse, PPI}, {ChIP-chip, PPI}, and
- {Timecourse, ChIP-chip, PPI}.

Any set of a single dataset is the trivial case that all genes are considered integrated.

The number of integrated genes between any two datasets is indicative of how strongly they influence each other and is expected to align with the ϕ_{lm} parameters from the MDI model. We find the following number of unique genes integrated between each combination of datasets:

- Timecourse + ChIP-chip + PPI: 56,
- Timecourse + ChIP-chip: 205 (261 including the 56 integrated across all datasets),
- Timecourse + PPI: 12 (68),
- ChIP-chip + PPI: 43 (99). .

which aligns with the sampled ϕ_{lm} values in figure 15, which shows that the Timecourse and ChIP-chip datasets contain very similar structure, the ChIP-chip and PPI datasets have some similarity but significantly less and the Timecourse and PPI datasets have less similarity again.

Compare this to the original analysis of this data in Kirk et al. (2012), where the number of integrated genes in each combination is:

- Timecourse + ChIP-chip + PPI: 16,
- Timecourse + ChIP-chip: 32 (48),

Consensus clustering

Sampled ϕ densities

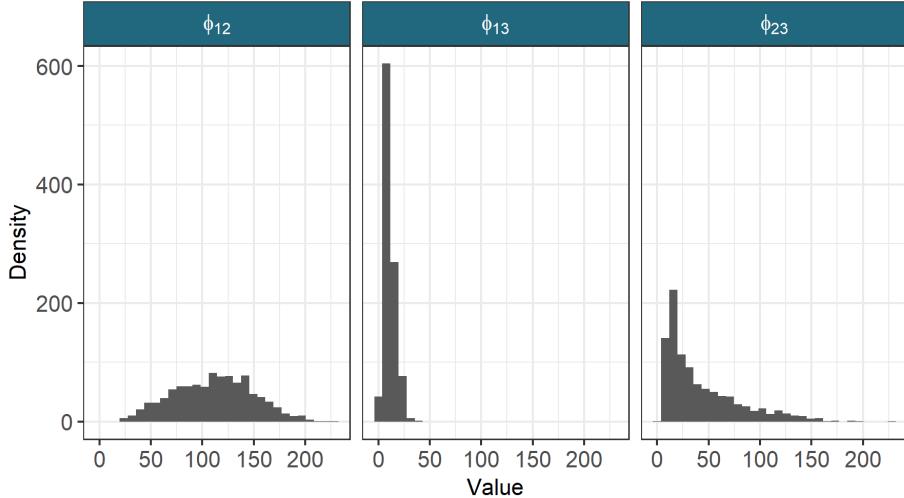


Figure 15: The sampled values for the ϕ parameters from the learners constituting the ensemble. High values indicate similar structure, low values indicate less, with 0 implying that the clustering models on each dataset are independent. The Timecourse dataset is represented by an index of 1, ChIP-chip by 2 and the PPI data by 3.

- Timecourse + PPI: 16 (32),
- ChIP-chip + PPI: 15 (31).

Our analysis has found significantly more shared structure.

In figure 16 we show the data from the Timecourse and ChIP-chip datasets for the genes that integrated between these datasets. In this plot we exclude the 15 clusters where more than half of the member genes have no interactions in the ChIP-chip data and any clusters of one. We find that a small number of transcription factors dominate, with different combinations emerging across the 10 clusters shown here in table 2. Many of these 10 correspond to transcription factors that are well known to regulate cell cycle expression, namely MBP1, SWI4, SWI6, MCM1, FKH1, FKH2, NDD1, SWI5, and ACE2 Simon et al. (2001).

Table 2: Table of transcription factors prominent in fused clusters for the Timecourse and ChIP-chip datasets.

Gene	Name	Description
------	------	-------------

YLR131C	ACE2	Transcription factor required for septum destruction after cytokinesis; phosphorylation by Cbk1p blocks nuclear exit during M/G1 transition; phosphorylation by cyclins Cdc28p and Pho85p prevents nuclear import during cell cycle phases other than cytokinesis; part of RAM network that regulates cellular polarity and morphogenesis; ACE2 has a paralog, SWI5, that arose from the whole genome duplication
YPL049C	DIG1	MAP kinase-responsive inhibitor of the Ste12p transcription factor; involved in the regulation of mating-specific genes and the invasive growth pathway; Dig1p and paralog Dig2p bind to Ste12p
YIL131C	FKH1	Forkhead family transcription factor; evolutionarily conserved lifespan regulator; binds multiple chromosomal elements with distinct specificities, cell cycle dynamics; regulates transcription elongation, chromatin silencing at mating loci, expression of G2/M phase genes; facilitates clustering, activation of early-firing replication origins; binds HML recombination enhancer, regulates donor preference during mating-type switching
YNL068C	FKH2	Forkhead family transcription factor; rate-limiting activator of replication origins; evolutionarily conserved regulator of lifespan; binds multiple chromosomal elements with distinct specificities, cell cycle dynamics; positively regulates transcriptional elongation; facilitates clustering, activation of early-firing replication origins; negative role in chromatin silencing at HML and HMR; major role in expression of G2/M phase genes; relocates to cytosol under hypoxia
YDL056W	MBP1	Transcription factor; involved in regulation of cell cycle progression from G1 to S phase, forms a complex with Swi6p that binds to MluI cell cycle box regulatory element in promoters of DNA synthesis genes
YMR043W	MCM1	Transcription factor; involved in cell-type-specific transcription and pheromone response; plays a central role in the formation of both repressor and activator complexes; relocates to the cytosol in response to hypoxia
YOR372C	NDD1	Transcriptional activator essential for nuclear division; localized to the nucleus; essential component of the mechanism that activates the expression of a set of late-S-phase-specific genes; turnover is tightly regulated during cell cycle and in response to DNA damage

YHR084W	STE12	Transcription factor that is activated by a MAPK signaling cascade; activates genes involved in mating or pseudohyphal/invasive growth pathways; cooperates with Tec1p transcription factor to regulate genes specific for invasive growth
YER111C	SWI4	DNA binding component of the SBF complex (Swi4p-Swi6p); a transcriptional activator that in concert with MBF (Mbp1-Swi6p) regulates late G1-specific transcription of targets including cyclins and genes required for DNA synthesis and repair
YDR146C	SWI5	Transcription factor that recruits Mediator and Swi/Snf complexes; activates transcription of genes expressed at the M/G1 phase boundary and in G1 phase; required for expression of the HO gene controlling mating type switching; localization to nucleus occurs during G1 and appears to be regulated by phosphorylation by Cdc28p kinase; SWI5 has a paralog, ACE2, that arose from the whole genome duplication
YLR182W	SWI6	Transcription cofactor; forms complexes with Swi4p (SBF) and Mbp1p (MBF) to regulate transcription at the G1/S transition (Simon et al., 2001); involved in meiotic gene expression; also binds Stb1p to regulate transcription at START; also required for the unfolded protein response, independently of its known transcriptional coactivators
YBR083W	TEC1	Transcription factor targeting filamentation genes and Ty1 expression; Ste12p activation of most filamentation gene promoters depends on Tec1p and Tec1p transcriptional activity is dependent on its association with Ste12p; binds to TCS elements upstream of filamentation genes, which are regulated by Tec1p/Ste12p/Dig1p complex; competes with Dig2p for binding to Ste12p/Dig1p; positive regulator of chronological life span
YML027W	YOX1	Homeobox transcriptional repressor; binds to Mcm1p and to early cell cycle boxes (ECBs) in the promoters of cell cycle-regulated genes expressed in M/G1 phase; phosphorylated by the cyclin Cdc28p; relocates from nucleus to cytoplasm upon DNA replication stress

Simon et al. (2001)

MBF (a complex of Mbp1 and Swi6) and SBF (a complex of Swi4 and Swi6) control late G1 genes.

Mcm1, together with Fkh1 or Fkh2, recruits the Ndd1 protein in late G2,

and thus controls the transcription of G2/M genes. Simon et al. (2001).

Mcm1 is also involved in the transcription of some M/G1 genes Simon et al. (2001).

Swi5 and Ace2 regulate genes at the end of M and early G1. It is not yet clear whether this model, developed using a small set of genes, will extrapolate to regulation of all cell cycle genes Simon et al. (2001).

Mcm1p regulates two consecutive waves of transcription controlling G1/S and G2/M cell-cycle transitions. Both FKH1 and FKH2 are also periodically transcribed and peak in S phase Zhu et al. (2000).

Iyer et al. (2001): SBF and MBF are sequence-specific transcription factors that activate gene expression during the G1/S transition of the cell cycle in yeast. SBF is a heterodimer of Swi4 and Swi6, and MBF is a heterodimer of Mbpl and Swi6. Our results support the hypothesis that SBF activated genes are predominantly involved in budding, and in membrane and cell-wall biosynthesis, whereas DNA replication and repair are the dominant functions among MBF activated genes.

- Cluster 1 has both AC2 and SWI5 emerge. M/G1 phase boundary? McBride et al. (1999) Swi5 and Ace2 activate expression of early G1-specific genes.
- Cluster 2 has SWI5 alone.
- Cluster 5 has MBP1 and some of SWI4 and SWI6. G1/S transisiton Iyer et al. (2001). The SBF complex (Swi4p-Swi6p) is a transcriptional activator that in concert with MBF (Mbpl-Swi6p) regulates late G1-specific transcription of targets including cyclins and genes required for DNA synthesis and repair;
- Cluster 9 has MBP1 and some SWI6 - these combine to form MBF .
- Cluster 11 has DIG1, SWI4, SWI6, and STE12 fully with some TEC1. DIG1 inhibits STE12 and regulates mating specific genes. STE12 activates genes involved in mating or pseudohyphal/invasive growth pathways; cooperates with Tec1p transcription factor to regulate genes specific for invasive growth. SWI6 involved in meiotic gene expression. Some sort of growth cluster?
- Cluster 12 is mainly SWI6 and MBP1 with some SWI4. Similar to cluster 5 (again SWI6 and MBP1 form MBF).
- Cluster 16 is all the histone folks - no clear TF in the ChIP-chip.
- Cluster 17 has FKH1 and FKH2. Transcription elongation and chromatin silencing, G2/M phase.
- Cluster 20 has NDD1 and MCM1 with some FKH2.Mcm1, together with Fkh1 or Fkh2, recruits the Ndd1 protein in late G2, and thus controls the transcription of G2/M genes. Simon et al. (2001). Breeden (2000)

NDD1 and FKH2 transcription is initiated in S phase and the nascent Ndd1 binds the Mcm1–Fkh2–DNA complex at that time. Koranda et al. (2000) find that NDD1, a positive regulator, becomes associated with G2/M promoter regions in manner that depends on the stage in cell cycle. Its recruitment depends on a permanent protein–DNA complex consisting of the MADS box protein, MCM1, and a recently identified partner Fkh2, a forkhead/winged helix related transcription factor. The lethality of Ndd1 depletion is suppressed by fkh2 null mutations, which indicates that Fkh2 may also have a negative regulatory role in the transcription of G2/M-induced RNAs. We conclude that Ndd1–Fkh2 interactions may be the transcriptionally important process targeted by Cdk activity.

- Cluster 26 has YOX1 and MCM1. YOX1 binds to Mcm1p and to early cell cycle boxes (ECBs) in the promoters of cell cycle-regulated genes expressed in M/G1 phase Pramila et al. (2002).

5.2.2 Timecourse - ChIP-chip fused

5.2.3 Cluster 16

Cluster 16 is nice! Histone proteins and then three others, GAS3, NRM1 and PDS1.

GAS3 is a poorly understood gene. We find that it is associated with HEK2 and SMT3 in the PPI data and SWI6, FKH2 and FKH1 in the ChIP-chip data.

Yox1p may function together with Nrm1p to confine MBF-dependent transcription to the G1/S transition of the cell cycle via negative feedback Aligianni et al. (2009). Is cluster 16 separated from cluster 12 due to the scaling of the timecourse data?

Evidence that they are the same: The divergently transcribed histone H3 and H4 genes (hht1 and hhf1, respectively) show enrichment of Yox1p (red), but not of Cdc10p (blue),

Two negative feedback loops have previously been reported to constrain transcription to G1/S by promoting timely repression of MBF-dependent genes: 1) the cyclin Cig2p, whose gene is activated by MBF, in turn inhibits MBF activity in G2-phase by phosphorylating Res1p [19]; and 2) Nrm1p, whose gene is also activated by MBF, in turn acts as a transcriptional co-repressor for MBF-dependent genes much like Yox1p.

these findings suggest that Yox1p and Nrm1p operate in the same negative feedback loop in which the role of Yox1p in transcriptional repression depends on Nrm1p. Whether Nrm1p depends on Yox1p for its association with MBF or is a connector protein required for Yox1p-dependent repression of MBF-regulated transcription remains to be determined.

Besides the negative feedback loop based on Yox1p, both yeasts also seem to apply positive feedback loops based on the SBF-regulated SWI4 in budding yeast McInerny et al. (1997); Foster et al. (1993)

In conclusion, we have uncovered an additional regulatory layer, based on the homeodomain protein Yox1p, to switch-off MBF-dependent transcription

Consensus clustering
Fused clusters across Timecourse and ChIP-chip datasets

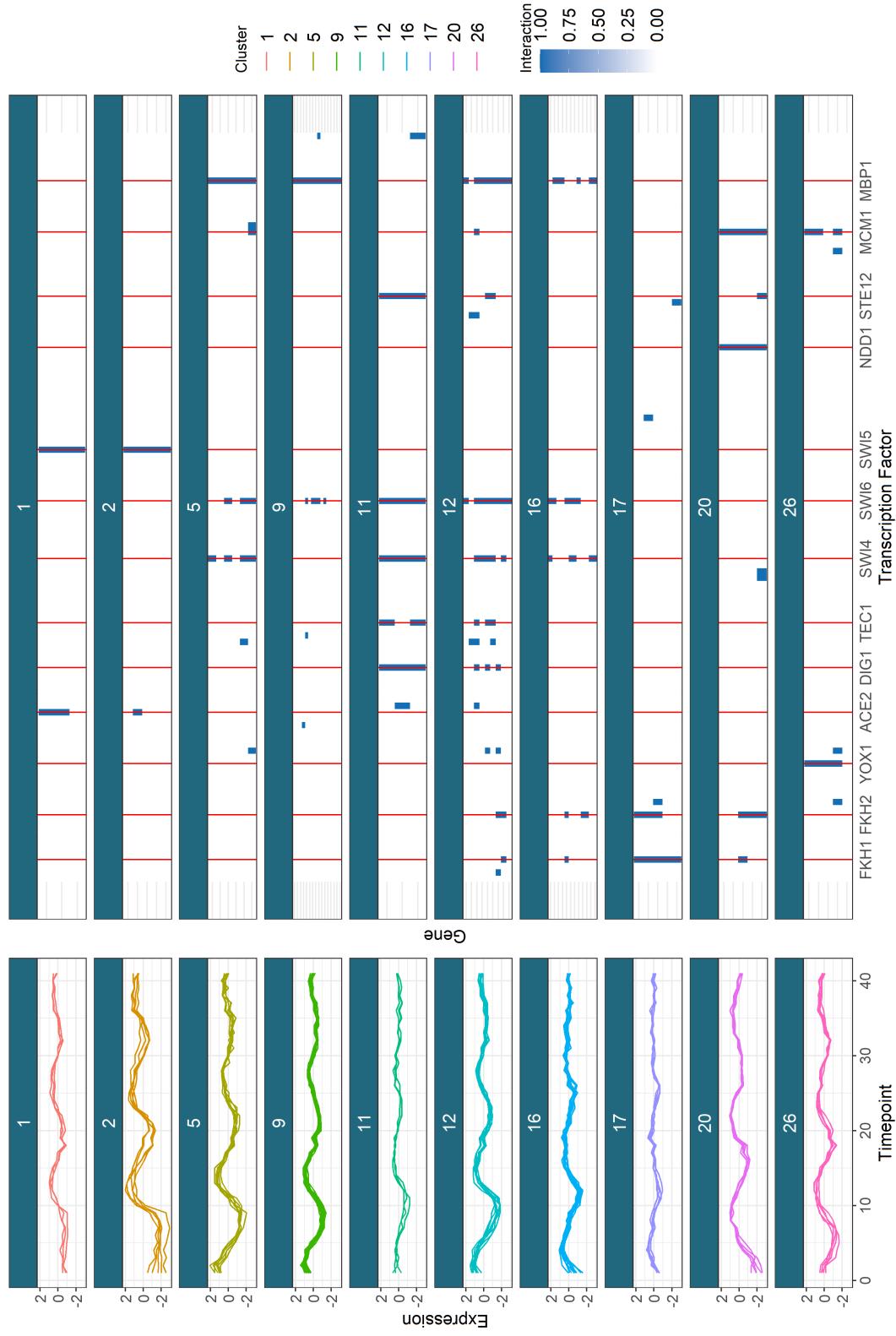


Figure 16: The fused clusters across the Timecourse and ChIP-chip datasets (as described in table 3). We exclude the clusters with no interactions in the ChIP-chip dataset and include a red line for the Transcription factors that dominate the clustering structure in the ChIP-chip dataset.

during S-phase progression. Similar roles have been identified for Cig2p and Nrm1p.

Kumar et al. (2000): Fkh1p and Fkh2p are required for cell-cycle regulation of transcription during G2–M. Forkhead transcription factors, Fkh1p and Fkh2p, collaborate with Mcm1p to control transcription required for M-phase

- FKH1: Fkh1p cooperates with Isw1p to remodel chromatin during G2/M. FKH1 has additional roles in the establishment of chromatin silencing at the silent mating-type cassette and in the regulation of donor preference during mating type switching. FKH1 and the Swi4p/Swi6p-containing SCB-binding factor (SBF - note that NRM1 also depends upon SBF) independently regulate donor preference through direct interactions with a cis-acting sequence called the recombination enhancer, with Fkh1p binding in the G2 phase and SBF binding in the G1 phase of the cell cycle.
- FKH2: negative role in chromatin silencing at HML and HMR.
- SWI6: Transcription cofactor. FKH1 and the Swi6p-containing SCB-binding factor (SBF) independently regulate donor preference through direct interactions with a cis-acting sequence called the recombination enhancer, with Fkh1p binding in the G2 phase and SBF binding in the G1 phase of the cell cycle.
- HEK2: RNA binding protein involved in asymmetric localization of ASH1 mRNA; represses translation of ASH1 mRNA, an effect reversed by Yck1p-dependent phosphorylation; regulates telomere position effect and length; similarity to hnRNP-K.
- SMT3: regulates chromatid cohesion, chromosome segregation, APC-mediated proteolysis, DNA replication and septin ring dynamics.

This suggests that GAS3 might be associated with chromosome/chromatin stuff. Not sure what this “donor preference” stuff is, but it might be important for this.

PDS1: The initial pds1-1 allele was identified by its inviability after transient exposure to microtubule inhibitors and its precocious dissociation of sister chromatids in the presence of these microtubule inhibitors. PDS1p is an important regulator of the onset of anaphase both for the Anaphase Promoting Complex and checkpoint pathways. (Yamamoto et al., 1996)

The DNA damage check-point(s) requires products encoded by RAD9, RAD17, RAD24, MEC1, MEC3, and RAD53 (MEC2/SAD1) genes while the spindle-damage checkpoint(s) requires a different set of products encoded by BUB1, BUB2, BUB3, MAD1, MAD2, and MAD3 genes (Weinert and Hartwell, 1988, 1993; Hoyt et al., 1991; Li and Murray, 1991; Allen et al., 1994; Weinert et al., 1994). (Yamamoto et al., 1996)

Pds1 is an anaphase inhibitor and plays an essential role in DNA damage and spindle checkpoint pathways. Pds1 is phosphorylated in response to DNA damage but not spindle disruption, indicating distinct mechanisms delaying

anaphase entry. Phosphorylation of Pds1 is Mec1 and Chk1 dependent *in vivo*. Here, we show that Pds1 is phosphorylated at multiple sites *in vivo* in response to DNA damage by Chk1. Wang et al. (2001).

An ESP1/PDS1 complex regulates loss of sister chromatid cohesion at the metaphase to anaphase transition in yeast (Ciosk et al., 1998).

NRM1: Transcriptional co-repressor of MBF-regulated gene expression; Nrm1p associates stably with promoters via MCB binding factor (MBF) to repress transcription upon exit from G1 phase. Approximately half of the members of cluster 16 have an interaction with MBP in the ChIP-chip data, and some have SWI6 too, so there might be something here.

NRM1, an MBF-specific transcriptional repressor acting at the transition from G1 to S phase of the cell cycle, is at the nexus between the cell cycle transcriptional program and the DNA replication checkpoint in fission yeast. Phosphorylation of Nrm1 by the Cds1 (Chk2) checkpoint protein kinase, which is activated in response to DNA replication stress, promotes its dissociation from the MBF transcription factor. De Bruin et al. (2008)

G1-specific transcription in yeast depends upon SBF and MBF. We have identified NRM1 (negative regulator of MBF targets 1), as a stable component of MBF. NRM1(YNR009w), an MBF-regulated gene expressed during late G1 phase, associates with G1-specific promoters via MBF. Transcriptional repression upon exit from G1 phase requires both NRM1 and MBF. Inactivation of NRM1 results in prolonged expression of MBF-regulated transcripts and leads to hydroxyurea (HU) resistance and enhanced bypass of RAD53D- and MEC1D-associated lethality. Constitutive expression of a stabilized form of Nrm1 represses MBF targets and leads to HU sensitivity. The fission yeast homolog SpNrm1, encoded by the MBF target genenrm1+(SPBC16A3.07c), binds to MBF target genes and acts as a corepressor. In both yeasts, MBF represses G1-specific transcription outside of G1 phase. A negative feedback loop involving Nrm1 bound to MBF leads to transcriptional repression as cells exit G1 phase. (de Bruin et al., 2006)

5.2.4 Cluster 26

Cluster 26 is also very consistent - 3 MCM complex genes and 2 others. Try to make a story.

5.2.5 Cluster 3

GO terms: Small molecule metabolic process. NAD+?

5.2.6 Cluster 9

GO terms: DNA replication, DNA-dependent DNA replication, DNA repair, DNA metabolic process, cellular response to DNA damage stimulus, cellular response to stress, response to stress. POL12, TOF1, DPB2, SEN34, SMC3, MSH6, ASF1, RFA1, MRC1, CDC45, POL1, RAD53, RAD27, IRR1, RFA2, CIN2

5.2.7 Cluster 12

The regulation of the G1- to S-phase transition is critical for cell-cycle progression. This transition is driven by a transient transcriptional wave regulated by transcription factor complexes termed MBF/SBF in yeast Aligianni et al. (2009). Yox1p homeodomain protein of fission yeast plays a critical role in confining MBF-dependent transcription to the G1/S transition of the cell cycle. Aligianni et al. (2009). Cluster 12 is g1/S? Associated with SWI6/MBP1 (i.e. MBF).

Aligianni et al. (2009): Transcript levels of many genes fluctuate periodically as a function of cell growth and division, peaking at specific phases of each cell cycle. Such cell cycle-regulated gene expression seems to be a universal feature of proliferating cells [1]–[3]. The best characterized transcriptional wave is induced during the G1/S transition, named ‘Start’ in yeast and ‘restriction point’ in mammalian cells, when cells commit to DNA replication and thus to a new cell-division cycle. E2F-DP complexes control G1/S transcription and are deregulated in most cancer cells, highlighting the importance of this regulation MBF activates transcription during the G1/S transition, binding to MCB promoter elements that are conserved from yeasts to humans.

Gene	Name	Cluster	Description
YIL009W	FAA3	1	Long chain fatty acyl-CoA synthetase; activates imported fatty acids with a preference for C16:0-C18:0 chain lengths; green fluorescent protein (GFP)-fusion protein localizes to the cell periphery
YNL328C	MDJ2	1	Constituent of the mitochondrial import motor; associated with the presequence translocase; function overlaps with that of Pam18p; stimulates the ATPase activity of Ssc1p to drive mitochondrial import; contains a J domain
YNL078W	NIS1	1	Protein localized in the bud neck at G2/M phase; physically interacts with septins; possibly involved in a mitotic signaling network
YPL158C	AIM44	2	Protein that regulates Cdc42p and Rho1p; functions in the late steps of cytokinesis and cell separation; sustains Rho1p at the cell division site after actomyosin ring contraction; inhibits the activation of Cdc42-Cla4 at the cell division site to prevent budding inside the old bud neck; transcription is regulated by Swi5p; null mutant displays elevated frequency of mitochondrial genome loss; relocates from bud neck to cytoplasm upon DNA replication stress

YKL185W	ASH1	2	Component of the Rpd3L histone deacetylase complex; zinc-finger inhibitor of HO transcription; mRNA is localized and translated in the distal tip of anaphase cells, resulting in accumulation of Ash1p in daughter cell nuclei and inhibition of HO expression; potential Cdc28p substrate
YNL327W	EGT2	2	Glycosylphosphatidylinositol (GPI)-anchored cell wall endoglucanase; required for proper cell separation after cytokinesis; expression is activated by Swi5p and tightly regulated in a cell cycle-dependent manner
YDL179W	PCL9	2	Cyclin; forms a functional kinase complex with Pho85p cyclin-dependent kinase (Cdk), expressed in late M/early G1 phase, activated by Swi5p; PCL9 has a paralog, PCL2, that arose from the whole genome duplication
YKL164C	PIR1	2	O-glycosylated protein required for cell wall stability; attached to the cell wall via beta-1,3-glucan; mediates mitochondrial translocation of Apn1p; expression regulated by the cell integrity pathway and by Swi5p during the cell cycle; PIR1 has a paralog, YJL160C, that arose from the whole genome duplication
YOR374W	ALD4	3	Mitochondrial aldehyde dehydrogenase; required for growth on ethanol and conversion of acetaldehyde to acetate; phosphorylated; activity is K ⁺ dependent; utilizes NADP ⁺ or NAD ⁺ equally as coenzymes; expression is glucose repressed; can substitute for cytosolic NADP-dependent aldehyde dehydrogenase when directed to the cytosol; human homolog ALDH2 can complement yeast ald4 mutant
YCL040W	GLK1	3	Glucokinase; catalyzes the phosphorylation of glucose at C6 in the first irreversible step of glucose metabolism; one of three glucose phosphorylating enzymes; expression regulated by non-fermentable carbon sources; GLK1 has a paralog, EMI2, that arose from the whole genome duplication
YFR053C	HXK1	3	Hexokinase isoenzyme 1; a cytosolic protein that catalyzes phosphorylation of glucose during glucose metabolism; expression is highest during growth on non-glucose carbon sources; glucose-induced repression involves hexokinase Hxk2p; HXK1 has a paralog, HXK2, that arose from the whole genome duplication

YGL037C	PNC1	3	Nicotinamidase that converts nicotinamide to nicotinic acid; part of the NAD(+) salvage pathway; required for life span extension by calorie restriction; lacks a peroxisomal targeting signal but is imported into peroxisomes via binding to Gpd1p; PNC1 expression responds to all known stimuli that extend replicative life span; protein increases in abundance and relative distribution to cytoplasmic foci decreases upon DNA replication stress
YDR440W	DOT1	4	Nucleosomal histone H3-Lys79 methylase; methylation is required for telomeric silencing, meiotic checkpoint control, and DNA damage response
YGR289C	MAL11	4	High-affinity maltose transporter (alpha-glucoside transporter); inducible; encoded in the MAL1 complex locus; broad substrate specificity that includes maltotriose; required for isomaltose utilization
YBR098W	MMS4	4	Subunit of structure-specific Mms4p-Mus81p endonuclease; cleaves branched DNA; involved in recombination, DNA repair, and joint molecule formation/resolution during meiotic recombination; phosphorylation of the non-catalytic subunit Mms4p by Cdc28p and Cdc5p during mitotic cell cycle activates the function of Mms4p-Mus81p
YGR042W	MTE1	4	Protein of unknown function; involved in maintenance of proper telomere length; green fluorescent protein (GFP)-fusion protein localizes to both the cytoplasm and the nucleus; forms nuclear foci upon DNA replication stress
YLR457C	NBP1	4	Spindle pole body (SPB) component; required for the insertion of the duplication plaque into the nuclear membrane during SPB duplication; essential for bipolar spindle formation; component of the Mps2p-Bbp1p complex; NBP1 has a paralog, YPR174C, that arose from the whole genome duplication
YDL102W	POL3	4	Catalytic subunit of DNA polymerase delta; required for chromosomal DNA replication during mitosis and meiosis, intragenic recombination, repair of double strand DNA breaks, and DNA replication during nucleotide excision repair (NER)
YOR342C		4	Protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm and the nucleus; relocates from nucleus to cytoplasm upon DNA replication stress; YOR342C has a paralog, YAL037W, that arose from the whole genome duplication

	YBL010C	4	Putative protein of unknown function; green fluorescent protein (GFP)-fusion protein colocalizes with clathrin-coated vesicles
	YHR127W	4	Protein of unknown function; localizes to the nucleus; required for asymmetric localization of Kar9p during mitosis
YPL267W	ACM1	5	Pseudosubstrate inhibitor of the APC/C; suppresses APC/C [Cdh1]-mediated proteolysis of mitotic cyclins; associates with Cdh1p, Bmh1p and Bmh2p; cell cycle regulated protein; the anaphase-promoting complex/cyclosome is also known as APC/C
YPL014W	CIP1	5	Cyclin-dependent kinase inhibitor; interacts with and inhibits the Cdc28p/Cln2p, G1/S phase cyclin-dependent kinase complex but not S-phase, or M-phase complexes; overexpression blocks cells in G1 phase and stabilizes the Cdc28p inhibitor Sic1p, while disruption accelerates the G1/S phase transition; phosphorylated during S phase in a Cdc28p-dependent manner; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm and to the nucleus
YGR109C	CLB6	5	B-type cyclin involved in DNA replication during S phase; activates Cdc28p to promote initiation of DNA synthesis; functions in formation of mitotic spindles along with Clb3p and Clb4p; most abundant during late G1; CLB6 has a paralog, CLB5, that arose from the whole genome duplication
YKR077W	MSA2	5	Putative transcriptional activator; interacts with G1-specific transcription factor MBF and G1-specific promoters; MSA2 has a paralog, MSA1, that arose from the whole genome duplication
YMR179W	SPT21	5	Protein with a role in transcriptional silencing; required for normal transcription at several loci including HTA2-HTB2 and HHF2-HHT2, but not required at the other histone loci; functionally related to Spt10p; localizes to nuclear foci that become diffuse upon DNA replication stress
YER111C	SWI4	5	DNA binding component of the SBF complex (Swi4p-Swi6p); a transcriptional activator that in concert with MBF (Mbp1-Swi6p) regulates late G1-specific transcription of targets including cyclins and genes required for DNA synthesis and repair; Slt2p-independent regulator of cold growth; acetylation at two sites, K1016 and K1066, regulates interaction with Swi6p

YNL233W	BNI4	6	Targeting subunit for Glc7p protein phosphatase; localized to the bud neck, required for localization of chitin synthase III to the bud neck via interaction with the chitin synthase III regulatory subunit Skt5p; phosphorylation by Slt2p and Kss1p involved in regulating Bni4p in septum assembly
YDL156W	CMR1	6	Nuclear protein with a role in protein quality control; localizes to the intranuclear quality control compartment (INQ) in response to proteasome inhibition or DNA replication stress; INQ likely sequesters proteins involved in DNA metabolism for degradation or re-folding; DNA-binding protein with preference for UV-damaged DNA; contains three WD domains (WD-40 repeat); human ortholog WDR76 also exhibits perinuclear localization under similar stress conditions
YFR027W	ECO1	6	Acetyltransferase; required for establishment of sister chromatid cohesion; acetylates Mps3p to regulate nuclear organization; modifies Smc3p at replication forks and Mcd1p in response to dsDNA breaks; phosphorylated by three kinases (Cdc28p, Cdc7p, Mck1p) to generate pair of phosphates spaced precisely for recognition by ubiquitin ligase SCF-Cdc4; mutations in human homolog ESCO2 cause Roberts syndrome; relative distribution to nucleus increases upon DNA replication stress
YOR144C	ELG1	6	Subunit of an alternative replication factor C complex; important for DNA replication and genome integrity; suppresses spontaneous DNA damage; involved in homologous recombination-mediated repair and telomere homeostasis; required for PCNA (Pol30p) unloading during DNA replication
YOR033C	EXO1	6	5'-3' exonuclease and flap-endonuclease; involved in recombination, double-strand break repair, MMS2 error-free branch of the post replication (PRR) pathway and DNA mismatch repair; role in telomere maintenance; member of the Rad2p nuclease family, with conserved N and I nuclease domains; relative distribution to the nucleus increases upon DNA replication stress; EXO1 has a paralog, DIN7, that arose from the whole genome duplication
YNL262W	POL2	6	Catalytic subunit of DNA polymerase (II) epsilon; a chromosomal DNA replication polymerase that exhibits processivity and proofreading exonuclease activity; participates in leading-strand synthesis during DNA replication; also involved in DNA synthesis during DNA repair; interacts extensively with Mrc1p

YLR032W	RAD5	6	DNA helicase/Ubiquitin ligase; involved in error-free DNA damage tolerance (DDT), replication fork regression during postreplication repair by template switching, error-prone translesion synthesis; promotes synthesis of free and PCNA-bound polyubiquitin chains by Ubc13p-Mms2p; forms nuclear foci upon DNA replication stress; associates with native telomeres, cooperates with homologous recombination in senescent cells; human homolog HLTf can complement yeast null mutant
YJL181W	RBH1	6	Putative protein of unknown function; expression is cell-cycle regulated as shown by microarray analysis; potential regulatory target of Mbp1p, which binds to the YJL181W promoter region; contains a PH-like domain; RBH1 has a paralog, RBH2, that arose from the whole genome duplication
YKL108W	SLD2	6	Single-stranded DNA origin-binding and annealing protein; required for initiation of DNA replication; phosphorylated in S phase by cyclin-dependent kinases (Cdks), promoting origin binding, DNA replication and Dpb11p complex formation; component of the preloading complex; binds the Mcm2-7p complex to prevent inappropriate Mcm2-7p interaction with the GINS complex in G1; required for S phase checkpoint; relative distribution to the nucleus increases upon DNA replication stress
YFL008W	SMC1	6	Subunit of the multiprotein cohesin complex; essential protein involved in chromosome segregation and in double-strand DNA break repair; SMC chromosomal ATPase family member, binds DNA with a preference for DNA with secondary structure
YNL309W	STB1	6	Protein with role in regulation of MBF-specific transcription at Start; phosphorylated by Cln-Cdc28p kinases in vitro; unphosphorylated form binds Swi6p, which is required for Stb1p function; expression is cell-cycle regulated; STB1 has a paralog, YOL131W, that arose from the whole genome duplication
YJR155W	AAD10	7	Putative aryl-alcohol dehydrogenase; similar to <i>P. chrysosporium</i> aryl-alcohol dehydrogenase; mutational analysis has not yet revealed a physiological role; members of the AAD gene family comprise three pairs (AAD3 + AAD15, AAD6/AAD16 + AAD4, AAD10 + AAD14) whose two genes are more related to one another than to other members of the family

YER170W	ADK2	7	Mitochondrial adenylate kinase; catalyzes the reversible synthesis of GTP and AMP from GDP and ADP; may serve as a back-up for synthesizing GTP or ADP depending on metabolic conditions; 3' sequence of ADK2 varies with strain background
YEL064C	AVT2	7	Putative transporter; member of a family of seven <i>S. cerevisiae</i> genes (AVT1-7) related to vesicular GABA-glycine transporters
YKL092C	BUD2	7	GTPase activating factor for Rsr1p/Bud1p; plays a role in spindle position checkpoint distinct from its role in bud site selection; required for both axial and bipolar budding patterns; mutants exhibit random budding in all cell types; contains two PH-like domains
YBR042C	CST26	7	Acylation transferase; enzyme mainly responsible for the introduction of saturated very long chain fatty acids into neo-synthesized molecules of phosphatidylinositol; required for incorporation of stearic acid into phosphatidylinositol; affects chromosome stability when overexpressed; CST26 has a paralog, YDR018C, that arose from the whole genome duplication
YLR233C	EST1	7	TLC1 RNA-associated factor involved in telomere length regulation; recruitment subunit of telomerase; has G-quadruplex promoting activity required for telomere elongation; role in activating telomere-bound Est2p-TLC1-RNA; EST1 has a paralog, EBS1, that arose from the whole genome duplication
YOR176W	HEM15	7	Ferrochelatase; a mitochondrial inner membrane protein, catalyzes insertion of ferrous iron into protoporphyrin IX, the eighth and final step in the heme biosynthetic pathway; human homolog FECH can complement yeast mutant and allow growth of haploid null after sporulation of a heterozygous diploid
YOR288C	MPD1	7	Member of the protein disulfide isomerase (PDI) family; interacts with and inhibits the chaperone activity of Cne1p; MPD1 overexpression in a pdi1 null mutant suppresses defects in Pdi1p functions such as carboxypeptidase Y maturation
YJL019W	MPS3	7	Nuclear envelope protein; required for SPB insertion, SPB duplication, Kar5p localization near the SPB and nuclear fusion; interacts with Mps2p to tether half-bridge to core SPB; N-terminal acetylation by Eco1p regulates its role in nuclear organization; localizes to the SPB half bridge and telomeres during meiosis; required with Ndj1p and Csm4p for meiotic bouquet formation and telomere-led rapid prophase movement; member of the SUN protein family (Sad1-UNC-84 homology)

YLR382C	NAM2	7	Mitochondrial leucyl-tRNA synthetase; also has direct role in splicing of several mitochondrial group I introns; indirectly required for mitochondrial genome maintenance; human homolog LARS2 can complement yeast null mutant, and is implicated in Perrault syndrome
YDR481C	PHO8	7	Repressible vacuolar alkaline phosphatase; regulated by levels of Pi and by Pho4p, Pho9p, Pho80p, Pho81p and Pho85p; dephosphorylates phosphotyrosyl peptides; contributes to NAD ⁺ metabolism by producing nicotinamide riboside from NMN
YDL103C	QRI1	7	UDP-N-acetylglucosamine pyrophosphorylase; catalyzes the formation of UDP-N-acetylglucosamine (UDP-GlcNAc), which is important in cell wall biosynthesis, protein N-glycosylation, and GPI anchor biosynthesis; protein abundance increases in response to DNA replication stress
YBR073W	RDH54	7	DNA-dependent ATPase; DNA recombination/repair translocase, supercoils DNA and promotes DNA strand opening; stimulates strand exchange by modifying ds-DNA topology; involved in recombinational repair of DNA double-strand breaks (DSBs) during mitosis and meiosis; phosphorylated in Mec1p-, Rad53p-dependent way in response to one DSB; contributes to remodelling of nucleosomes; proposed to be involved in crossover interference; interacts with Dmc1p; stimulates Dmc1p and Rad51p
YBR275C	RIF1	7	Protein that binds to the Rap1p C-terminus; acts synergistically with Rif2p to help control telomere length and establish telomeric silencing; involved in control of DNA replication; contributes to resection of DNA double strand breaks (DSBs); deletion results in telomere elongation
YPL208W	RKM1	7	SET-domain lysine-N-methyltransferase; catalyzes the formation of dimethyllysine residues on the large ribosomal subunit proteins L23 (Rpl23Ap and Rpl23Bp) and monomethyllysine residues on L18 (Rps18Ap and Rps18Bp)
YLL002W	RTT109	7	Histone acetyltransferase; critical for cell survival in presence of DNA damage during S phase, required for recovery after DSB repair; acetylates H3K56, H3K9; H3K56 acetylation activity required for expression homeostasis, buffering of mRNA synthesis rate against changes in gene dosage during S phase; involved in non-homologous end joining and regulation of Ty1 transposition; prevents hyper-amplification of rDNA; interacts physically with Vps75p

YAR003W	SWD1	7	Subunit of the COMPASS (Set1C) complex; COMPASS methylates histone H3 on lysine 4 and is required in transcriptional silencing near telomeres; WD40 beta propeller superfamily member with similarity to mammalian Rbbp7
YHR159W	TDA11	7	Putative protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm; potential Cdc28p substrate; null mutant is sensitive to expression of the top1-T722A allele
YLR212C	TUB4	7	Gamma-tubulin; involved in nucleating microtubules from both the cytoplasmic and nuclear faces of the spindle pole body; protein abundance increases in response to DNA replication stress
YNL304W	YPT11	7	Rab GTPase; Myo2p-binding protein implicated in mother-to-bud transport of cortical endoplasmic reticulum (ER), late Golgi, and mitochondria during cell division; function is regulated at multiple levels; abundance of active Ypt11p forms is controlled by phosphorylation status and degradation; normally a low-abundance protein whose ER localization is only detected when protein is highly over expressed
YNL310C	ZIM17	7	Protein co-chaperone with a zinc finger motif; essential for protein import into mitochondria; may act with Pam18p to facilitate recognition and folding of imported proteins by Ssc1p (mtHSP70) in the mitochondrial matrix; required for the maintenance of Ssc1p solubility and assists in the functional interaction of Ssc1p with substrate proteins
YML020W		7	Putative protein of unknown function
YJR154W		7	Putative protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm
YFL054C	AQY3	8	Putative channel-like protein; similar to Fps1p; mediates passive diffusion of glycerol in the presence of ethanol
YAL007C	ERP2	8	Member of the p24 family involved in ER to Golgi transport; similar to Emp24p and Erv25p; role in misfolded protein quality control; forms a heterotrimeric complex with Erp1p, Emp24p, and Erv25p; localized to COPII-coated vesicles; ERP2 has a paralog, ERP4, that arose from the whole genome duplication
YHR188C	GPI16	8	Subunit of the glycosylphosphatidylinositol transamidase complex; transmembrane protein; adds GPIs to newly synthesized proteins; human PIG-Tp homolog

YDR517W	GRH1	8	Acetylated cis-Golgi protein, involved in ER to Golgi transport; homolog of human GRASP65; forms a complex with the coiled-coil protein Bug1p; mutants are compromised for the fusion of ER-derived vesicles with Golgi membranes; protein abundance increases in response to DNA replication stress
YDR348C	PAL1	8	Protein of unknown function thought to be involved in endocytosis; physically interacts with Ede1p and is found at endocytic sites at cell periphery during early stages of endocytosis; green fluorescent protein (GFP)-fusion protein localizes to bud neck; potential Cdc28p substrate; similar to <i>S. pombe</i> Pall1 protein; relocates from bud neck to cytoplasm upon DNA replication stress; PAL1 has a paralog, YHR097C, that arose from the whole genome duplication
YDL095W	PMT1	8	Protein O-mannosyltransferase of the ER membrane; transfers mannose from dolichyl phosphate-D-mannose to protein serine and threonine residues; 1 of 7 related proteins involved in O-glycosylation which is essential for cell wall rigidity; involved in ER quality control; amino terminus faces cytoplasm, carboxyl terminus faces ER lumen
YER104W	RTT105	8	Protein with a role in regulation of Ty1 transposition
YJL115W	ASF1	9	Nucleosome assembly factor; involved in chromatin assembly, disassembly; required for recovery after DSB repair; role in H3K56 acetylation required for expression homeostasis, buffering mRNA synthesis rate against gene dosage changes in S phase; anti-silencing protein, derepresses silent loci when overexpressed; role in regulating Ty1 transposition; relocates to cytosol under hypoxia; growth defect of asf1 null is functionally complemented by either human ASF1A or ASF1B
YLR103C	CDC45	9	DNA replication initiation factor; recruited to MCM pre-RC complexes at replication origins; promotes release of MCM from Mcm10p, recruits elongation machinery; binds tightly to ssDNA, which disrupts interaction with the MCM helicase and stalls it during replication stress; mutants in human homolog may cause velocardiofacial and DiGeorge syndromes
YPL241C	CIN2	9	GTPase-activating protein (GAP) for Cin4p; tubulin folding factor C involved in beta-tubulin (Tub2p) folding; mutants display increased chromosome loss and benomyl sensitivity; human homolog RP2 complements yeast null mutant

YPR175W	DPB2	9	Second largest subunit of DNA polymerase II (DNA polymerase epsilon); required for maintenance of fidelity of chromosomal replication; essential motif in C-terminus is required for formation of the four-subunit Pol epsilon; expression peaks at the G1/S phase boundary; Cdc28p substrate
YIL026C	IRR1	9	Subunit of the cohesin complex; which is required for sister chromatid cohesion during mitosis and meiosis and interacts with centromeres and chromosome arms; relocates to the cytosol in response to hypoxia; essential for viability
YCL061C	MRC1	9	S-phase checkpoint protein required for DNA replication; couples DNA helicase and polymerase; interacts with and stabilizes Pol2p at stalled replication forks during stress, where it forms a pausing complex with Tof1p and is phosphorylated by Mec1p; defines a novel S-phase checkpoint with Hog1p that coordinates DNA replication and transcription upon osmostress; protects uncapped telomeres; Dia2p-dependent degradation mediates checkpoint recovery; mammalian claspin homolog
YDR097C	MSH6	9	Protein required for mismatch repair in mitosis and meiosis; forms a complex with Msh2p to repair both single-base and insertion-deletion mispairs; also involved in interstrand cross-link repair; potentially phosphorylated by Cdc28p
YNL102W	POL1	9	Catalytic subunit of the DNA polymerase I alpha-primase complex; required for the initiation of DNA replication during mitotic DNA synthesis and premeiotic DNA synthesis
YBL035C	POL12	9	B subunit of DNA polymerase alpha-primase complex; required for initiation of DNA replication during mitotic and premeiotic DNA synthesis; also functions in telomere capping and length regulation
YKL113C	RAD27	9	5' to 3' exonuclease, 5' flap endonuclease; required for Okazaki fragment processing and maturation, for long-patch base-excision repair and large loop repair (LLR), ribonucleotide excision repair; member of the <i>S. pombe</i> RAD2/FEN1 family; relocates to the cytosol in response to hypoxia

YPL153C	RAD53	9	DNA damage response protein kinase; required for cell-cycle arrest, regulation of copper genes in response to DNA damage; phosphorylates nuclear pores to counteract gene gating, preventing aberrant transitions at forks approaching transcribed genes; activates downstream kinase Dun1p; differentially senses mtDNA depletion, mitochondrial ROS; relocates to cytosol under hypoxia; human homolog CHEK2 implicated in breast cancer can complement yeast null mutant
YAR007C	RFA1	9	Subunit of heterotrimeric Replication Protein A (RPA); RPA is a highly conserved single-stranded DNA binding protein involved in DNA replication, repair, and recombination; RPA protects against inappropriate telomere recombination, and upon telomere uncapping, prevents cell proliferation by a checkpoint-independent pathway; role in DNA catenation/decatenation pathway of chromosome disentangling; relocates to the cytosol in response to hypoxia
YNL312W	RFA2	9	Subunit of heterotrimeric Replication Protein A (RPA); RPA is a highly conserved single-stranded DNA binding protein involved in DNA replication, repair, and recombination; RPA protects against inappropriate telomere recombination, and upon telomere uncapping, prevents cell proliferation by a checkpoint-independent pathway; in concert with Sgs1p-Top2p-Rmi1p, stimulates DNA catenation/decatenation activity of Top3p; protein abundance increases in response to DNA replication
YAR008W	SEN34	9	Subunit of the tRNA splicing endonuclease; tRNA splicing endonuclease (Sen complex) is composed of Sen2p, Sen15p, Sen34p, and Sen54p; Sen complex also cleaves the CBP1 mRNA at the mitochondrial surface; Sen34p contains the active site for tRNA 3' splice site cleavage and has similarity to Sen2p and to Archaeal tRNA splicing endonuclease
YJL074C	SMC3	9	Subunit of the multiprotein cohesin complex; required for sister chromatid cohesion in mitotic cells; also required, with Rec8p, for cohesion and recombination during meiosis; phylogenetically conserved SMC chromosomal ATPase family member

YNL273W	TOF1	9	Subunit of a replication-pausing checkpoint complex; Tof1p-Mrc1p-Csm3p acts at the stalled replication fork to promote sister chromatid cohesion after DNA damage, facilitating gap repair of damaged DNA; interacts with the MCM helicase; relocates to the cytosol in response to hypoxia
YFL025C	BST1	10	GPI inositol deacylase of the endoplasmic reticulum (ER); negatively regulates COPII vesicle formation; prevents production of vesicles with defective subunits; required for proper discrimination between resident ER proteins and Golgi-bound cargo molecules; functional ortholog of human PGAP1, mutation of which is associated with intellectual disability and encephalopathy
YIL132C	CSM2	10	Component of Shu complex (aka PCSS complex); Shu complex also includes Psy3, Shu1, Shu2, and promotes error-free DNA repair; Shu complex mediates inhibition of Srs2p function; promotes formation of Rad51p filaments; Psy3p and Csm2p contain similar DNA-binding regions which work together to form a single DNA binding site; required for accurate chromosome segregation during meiosis
YLR381W	CTF3	10	Outer kinetochore protein that forms a complex with Mcm16p and Mcm22p; may bind the kinetochore to spindle microtubules; required for the spindle assembly checkpoint; orthologous to human centromere constitutive-associated network (CCAN) subunit CENP-I and fission yeast mis6
YGL027C	CWH41	10	Processing alpha glucosidase I; ER type II integral membrane N-glycoprotein involved in assembly of cell wall beta 1,6 glucan and asparagine-linked protein glycosylation; also involved in ER protein quality control and sensing of ER stress
YDR518W	EUG1	10	Protein disulfide isomerase of the endoplasmic reticulum lumen; EUG1 has a paralog, PDI1, that arose from the whole genome duplication; function overlaps with that of Pdi1p; may interact with nascent polypeptides in the ER
YKL165C	MCD4	10	Protein involved in GPI anchor synthesis; multimembrane-spanning protein that localizes to the endoplasmic reticulum; highly conserved among eukaryotes; GPI stands for glycosylphosphatidylinositol

YKL089W	MIF2	10	Protein required for structural integrity of elongating spindles; localizes to the kinetochore; interacts with histones H2A, H2B, and H4; phosphorylated by Ipl1p; orthologous to human centromere constitutive-associated network (CCAN) subunit CENP-C and fission yeast cnp3
YAL034W-A	MTW1	10	Essential component of the MIND kinetochore complex; joins kinetochore subunits contacting DNA to those contacting microtubules; critical to kinetochore assembly; complex consists of Mtw1p Including Nnf1p-Nsl1p-Dsn1p (MIND)
YGL094C	PAN2	10	Catalytic subunit of the Pan2p-Pan3p poly(A)-ribonuclease complex; complex acts to control poly(A) tail length and regulate the stoichiometry and activity of postreplication repair complexes
YLR151C	PCD1	10	8-oxo-dGTP diphosphatase; prevents spontaneous mutagenesis via sanitization of oxidized purine nucleoside triphosphates; can also act as peroxisomal pyrophosphatase with specificity for coenzyme A and CoA derivatives, may function to remove potentially toxic oxidized CoA disulfide from peroxisomes to maintain the capacity for beta-oxidation of fatty acids; nudix hydrolase family member; similar E. coli MutT and human, rat and mouse MTH1
YML061C	PIF1	10	DNA helicase, potent G-quadruplex DNA binder/unwinder; possesses strand annealing activity; promotes DNA synthesis during break-induced replication; important for crossover recombination; translation from different start sites produces mitochondrial and nuclear forms; nuclear form is a catalytic inhibitor of telomerase; mitochondrial form involved in DNA repair and recombination; mutations affect Zn, Fe homeostasis; regulated by Rad53p-dependent phosphorylation in rho0 cells
YDL093W	PMT5	10	Protein O-mannosyltransferase; transfers mannose residues from dolichyl phosphate-D-mannose to protein serine/threonine residues; acts in a complex with Pmt3p, can instead interact with Pmt2p in some conditions; target for new antifungals

YGL175C	SAE2	10	Endonuclease required for telomere elongation; required for telomeric 5' C-rich strand resection; involved in ds-break repair and processing hairpin DNA structures with the MRX complex; function requires sumoylation and phosphorylation; exists as inactive oligomers that are transiently released into smaller active units by phosphorylation; DNA damage triggers Sae2p removal, so active Sae2p is present only transiently; sequence and functional similarity with human CtIP/RBBP8
YOR081C	TGL5	10	Bifunctional triacylglycerol lipase and LPA acyltransferase; lipid particle-localized triacylglycerol (TAG) lipase involved in triacylglycerol mobilization; catalyzes acylation of lysophosphatidic acid (LPA); potential Cdc28p substrate; TGL5 has a paralog, TGL4, that arose from the whole genome duplication
YLR234W	TOP3	10	DNA Topoisomerase III; conserved protein that functions in a complex with Sgs1p and Rmi1p to relax single-stranded negatively-supercoiled DNA preferentially; DNA catenation/decatenation activity is stimulated by RPA and Sgs1p-Top3p-Rmi1p; involved in telomere stability and regulation of mitotic recombination
YKL067W	YNK1	10	Nucleoside diphosphate kinase; catalyzes the transfer of gamma phosphates from nucleoside triphosphates, usually ATP, to nucleoside diphosphates by a mechanism that involves formation of an autophosphorylated enzyme intermediate; protein abundance increases in response to DNA replication stress
YLR120C	YPS1	10	Aspartic protease; hyperglycosylated member of the yapsin family of proteases, attached to the plasma membrane via a glycosylphosphatidylinositol (GPI) anchor; involved in nutrient limitation-induced cleavage of the extracellular inhibitory domain of signaling mucin Msb2p, resulting in activation of the filamentous growth MAPK pathway; involved with other yapsins in the cell wall integrity response; role in KEX2-independent processing of the alpha factor precursor
YNL165W		10	Putative protein of unknown function; YNL165W is not an essential gene

YGR014W	MSB2	11	Mucin family member involved in various signaling pathways; functions as osmosensor in the Sho1p-mediated HOG pathway; functions in Cdc42p- and MAP kinase-dependent filamentous growth signaling pathway; processed into secreted and cell-associated forms by aspartyl protease Yps1p; potential Cdc28p substrate
YKR013W	PRY2	11	Sterol binding protein involved in the export of acetylated sterols; secreted glycoprotein and member of the CAP protein superfamily (cysteine-rich secretory proteins (CRISP), antigen 5, and pathogenesis related 1 proteins); sterol export function is redundant with that of PRY1; may be involved in detoxification of hydrophobic compounds; PRY2 has a paralog, PRY1, that arose from the whole genome duplication
YPL163C	SVS1	11	Cell wall and vacuolar protein; required for wild-type resistance to vanadate; SVS1 has a paralog, SRL1, that arose from the whole genome duplication
YOR074C	CDC21	12	Thymidylate synthase; required for de novo biosynthesis of pyrimidine deoxyribonucleotides; expression is induced at G1/S; human homolog TYMSOS can complement yeast cdc21 temperature-sensitive mutant at restrictive temperature
YOL007C	CSI2	12	Protein of unknown function; green fluorescent protein (GFP)- fusion protein localizes to the mother side of the bud neck and the vacuole; YOL007C is not an essential gene
YDL003W	MCD1	12	Essential alpha-kleisin subunit of the cohesin complex; required for sister chromatid cohesion in mitosis and meiosis; apoptosis induces cleavage and translocation of a C-terminal fragment to mitochondria; expression peaks in S phase
YNL289W	PCL1	12	Cyclin, interacts with cyclin-dependent kinase Pho85p; member of the Pcl1,2-like subfamily, involved in the regulation of polarized growth and morphogenesis and progression through the cell cycle; is ubiquitinated by Dma1p; phosphorylation by Pho85p targets it for degradation; localizes to sites of polarized cell growth
YER095W	RAD51	12	Strand exchange protein; forms a helical filament with DNA that searches for homology; involved in the recombinational repair of double-strand breaks in DNA during vegetative growth and meiosis; homolog of Dmc1p and bacterial RecA protein

YER070W	RNR1	12	Major isoform of large subunit of ribonucleotide-diphosphate reductase; the RNR complex catalyzes rate-limiting step in dNTP synthesis, regulated by DNA replication and DNA damage checkpoint pathways via localization of small subunits; relative distribution to the nucleus increases upon DNA replication stress; RNR1 has a paralog, RNR3, that arose from the whole genome duplication
YJL187C	SWE1	12	Protein kinase that regulates the G2/M transition; negative regulator of the Cdc28p kinase; morphogenesis checkpoint kinase; positive regulator of sphingolipid biosynthesis via Orm2p; phosphorylates a tyrosine residue in the N-terminus of Hsp90 in a cell-cycle associated manner, thus modulating the ability of Hsp90 to chaperone a selected clientele; localizes to the nucleus and to the daughter side of the mother-bud neck; homolog of <i>S. pombe</i> Wee1p; potential Cdc28p substrate
YGR221C	TOS2	12	Protein involved in localization of Cdc24p to the site of bud growth; may act as a membrane anchor; localizes to the bud neck and bud tip; potentially phosphorylated by Cdc28p; TOS2 has a paralog, SKG6, that arose from the whole genome duplication
YML027W	YOX1	12	Homeobox transcriptional repressor; binds to Mcm1p and to early cell cycle boxes (ECBs) in the promoters of cell cycle-regulated genes expressed in M/G1 phase; expression is cell cycle-regulated; phosphorylated by Cdc28p; relocates from nucleus to cytoplasm upon DNA replication stress; YOX1 has a paralog, YHP1, that arose from the whole genome duplication
YDL197C	ASF2	13	Anti-silencing protein; causes derepression of silent loci when overexpressed
YHR110W	ERP5	13	Protein with similarity to Emp24p and Erv25p; member of the p24 family involved in ER to Golgi transport
YDL010W	GRX6	13	Cis-golgi localized monothiol glutaredoxin, binds Fe-S cluster; more similar in activity to dithiol than other monothiol glutaredoxins; involved in the oxidative stress response; GRX6 has a paralog, GRX7, that arose from the whole genome duplication
YDR503C	LPP1	13	Lipid phosphate phosphatase; catalyzes Mg(2+)-independent dephosphorylation of phosphatidic acid (PA), lysophosphatidic acid, and diacylglycerol pyrophosphate; involved in control of the cellular levels of phosphatidylinositol and PA

YML060W	OGG1	13	Nuclear and mitochondrial glycosylase/lyase; specifically excises 7,8-dihydro-8-oxoguanine residues located opposite cytosine or thymine residues in DNA, repairs oxidative damage to mitochondrial DNA, contributes to UVA resistance
YDR501W	PLM2	13	Putative transcription factor, contains Forkhead Associated domain; found associated with chromatin; target of SBF transcription factor; induced in response to DNA damaging agents and deletion of telomerase; PLM2 has a paralog, TOS4, that arose from the whole genome duplication
YOR321W	PMT3	13	Protein O-mannosyltransferase; transfers mannose residues from dolichyl phosphate-D-mannose to protein serine/threonine residues; acts in a complex with Pmt5p, can instead interact with Pmt1p in some conditions; antifungal drug target; PMT3 has a paralog, PMT2, that arose from the whole genome duplication
YNL072W	RNH201	13	Ribonuclease H2 catalytic subunit; removes RNA primers during Okazaki fragment synthesis and errant ribonucleotides misincorporated during DNA replication; role in ribonucleotide excision repair; homolog of RNase HI; related to human AGS4 which causes Aicardi-Goutieres syndrome
YLR383W	SMC6	13	Component of the SMC5-SMC6 complex; this complex plays a key role in the removal of X-shaped DNA structures that arise between sister chromatids during DNA replication and repair; homologous to <i>S. pombe</i> rad18
YKL042W	SPC42	13	Central plaque component of spindle pole body (SPB); involved in SPB duplication, may facilitate attachment of the SPB to the nuclear membrane
YHR153C	SPO16	13	Meiosis-specific protein involved in synaptonemal complex assembly; implicated in regulation of crossover formation; required for sporulation
YPL057C	SUR1	13	Mannosylinositol phosphorylceramide (MIPC) synthase catalytic subunit; forms a complex with regulatory subunit Csg2p; function in sphingolipid biosynthesis is overlapping with that of Csh1p; SUR1 has a paralog, CSH1, that arose from the whole genome duplication
YDR400W	URH1	13	Uridine nucleosidase (uridine-cytidine N-ribohydrolase); cleaves N-glycosidic bonds in nucleosides; involved in the pyrimidine salvage and nicotinamide riboside salvage pathways
YOL019W		13	Protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the cell periphery and vacuole; YOL019W has a paralog, DCV1, that arose from the whole genome duplication

YDL211C		13	Protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the vacuole; YDL211C has a paralog, TDA7, that arose from the whole genome duplication
YOR114W		13	Putative protein of unknown function; null mutant is viable
YLR050C		13	Putative protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the endoplasmic reticulum; YLR050C is not an essential gene
YJL091C	GWT1	14	Protein involved in the inositol acylation of GlcN-PI; the inositol acylation of glucosaminyl phosphatidylinositol (GlcN-PI) forms glucosaminyl(acyl)phosphatidylinositol (GlcN(acyl)PI), an intermediate in the biosynthesis of glycosylphosphatidylinositol (GPI) anchors
YBL009W	ALK2	15	Protein kinase; along with its paralog, ALK1, required for proper spindle positioning and nuclear segregation following mitotic arrest, proper organization of cell polarity factors in mitosis, proper localization of formins and polarity factors, and survival in cells that activate spindle assembly checkpoint; phosphorylated in response to DNA damage; ALK2 has a paralog, ALK1, that arose from the whole genome duplication; similar to mammalian haspins
YNL166C	BNI5	15	Linker protein responsible for recruitment of myosin to the bud neck; interacts with the C-terminal extensions of septins Cdc11p and Shs1p and binds Myo1p to promote cytokinesis
YGR188C	BUB1	15	Protein kinase involved in the cell cycle checkpoint into anaphase; in complex with Mad1p and Bub3p, prevents progression into anaphase in presence of spindle damage; Cdc28p-mediated phosphorylation at Bub1p-T566 is important for degradation in anaphase and adaptation of checkpoint to prolonged mitotic arrest; associates with centromere DNA via Skp1p; involved in Sgo1p relocalization in response to sister kinetochore tension; paralog MAD3 arose from whole genome duplication
YDR480W	DIG2	15	MAP kinase-responsive inhibitor of the Ste12p transcription factor; involved in the regulation of mating-specific genes and the invasive growth pathway; related regulators Dig1p and Dig2p bind to Ste12p; DIG2 has a paralog, DIG1, that arose from the whole genome duplication

YMR144W	FDO1	15	Protein involved in directionality of mating type switching; acts with Fkh1p to control which donor mating-type locus is inserted into MAT locus during mating type switching; localized to the nucleus; not an essential gene
YER019W	ISC1	15	Inositol phosphosphingolipid phospholipase C; mitochondrial membrane localized; hydrolyzes complex sphingolipids to produce ceramide; activates genes required for non-fermentable carbon source metabolism during diauxic shift; activated by phosphatidylserine, cardiolipin, and phosphatidylglycerol; mediates Na ⁺ and Li ⁺ halotolerance; ortholog of mammalian neutral sphingomyelinase type 2
YPR141C	KAR3	15	Minus-end-directed microtubule motor; functions in mitosis and meiosis, localizes to the spindle pole body and localization is dependent on functional Cik1p, required for nuclear fusion during mating; potential Cdc28p substrate
YDR488C	PAC11	15	Dynein intermediate chain, microtubule motor protein; required for intracellular transport and cell division; acts in cytoplasmic dynein pathway; forms complex with dynein light chain Dyn2p that promotes Dyn1p homodimerization and potentiates motor processivity; Dyn2p-Pac11p complex is also important for interaction of dynein motor complex with dynactin complex; forms cortical cytoplasmic microtubule capture site with Num1p; essential in the absence of CIN8
YER003C	PMI40	15	Mannose-6-phosphate isomerase; catalyzes the interconversion of fructose-6-P and mannose-6-P; required for early steps in protein mannosylation
YBL031W	SHE1	15	Mitotic spindle protein; interacts with components of the Dam1 (DASH) complex, its effector Sli15p, and microtubule-associated protein Bim1p; also localizes to nuclear microtubules and to the bud neck in a ring-shaped structure; inhibits dynein function
YOR195W	SLK19	15	Kinetochore-associated protein; required for chromosome segregation and kinetochore clustering; required for normal segregation of chromosomes in meiosis and mitosis; component of the FEAR regulatory network, which promotes Cdc14p release from the nucleolus during anaphase; potential Cdc28p substrate

YLL021W	SPA2	15	Component of the polarisome; functions in actin cytoskeletal organization during polarized growth; acts as a scaffold for Mkk1p and Mpklp cell wall integrity signaling components; potential Cdc28p substrate; coding sequence contains length polymorphisms in different strains; SPA2 has a paralog, SPH1, that arose from the whole genome duplication
YGL093W	SPC105	15	Subunit of a kinetochore-microtubule binding complex; complex bridges centromeric heterochromatin and kinetochore MAPs and motors; required for sister chromatid bi-orientation and kinetochore binding of SAC components; complex also includes Kre28p; modified by sumoylation
YDR356W	SPC110	15	Inner plaque spindle pole body (SPB) component; ortholog of human kendrin; gamma-tubulin small complex (gamma-TuSC) receptor that interacts with Spc98p to recruit the complex to the nuclear side of the SPB, connecting nuclear microtubules to the SPB; promotes gamma-TuSC assembly and oligomerization to initiate microtubule nucleation; interacts with Tub4p-complex and calmodulin; phosphorylated by Mps1p in cell cycle-dependent manner
YHR172W	SPC97	15	Component of the microtubule-nucleating Tub4p (gamma-tubulin) complex; interacts with Spc110p at the spindle pole body (SPB) inner plaque and with Spc72p at the SPB outer plaque
YNL088W	TOP2	15	Topoisomerase II; relieves torsional strain in DNA by cleaving and re-sealing phosphodiester backbone of both positively and negatively supercoiled DNA; cleaves complementary strands; localizes to axial cores in meiosis; required for replication slow zone (RSZ) breakage following Mec1p inactivation; human homolog TOP2A implicated in cancers, and can complement yeast null mutant
YOR083W	WHI5	15	Repressor of G1 transcription; binds to SCB binding factor (SBF) at SCB target promoters in early G1; dilution of Whi5p concentration during cell growth determines cell size; phosphorylation of Whi5p by the CDK, Cln3p/Cdc28p relieves repression and promoter binding by Whi5, and contributes to both the determination of critical cell size at START and cell fate; periodically expressed in G1

YMR215W	GAS3	16	Putative 1,3-beta-glucanosyltransferase; has similarity to other GAS family members; low abundance, possibly inactive member of the GAS family of GPI-containing proteins; localizes to the cell wall; mRNA induced during sporulation
YBR009C	HHF1	16	Histone H4; core histone protein required for chromatin assembly and chromosome function; one of two identical histone proteins (see also HHF2); contributes to telomeric silencing; N-terminal domain involved in maintaining genomic integrity
YNL030W	HHF2	16	Histone H4; core histone protein required for chromatin assembly and chromosome function; one of two identical histone proteins (see also HHF1); contributes to telomeric silencing; N-terminal domain involved in maintaining genomic integrity
YPL127C	HHO1	16	Histone H1, linker histone with roles in meiosis and sporulation; decreasing levels early in sporulation may promote meiosis, and increasing levels during sporulation facilitate compaction of spore chromatin; binds to promoters and within genes in mature spores; may be recruited by Ume6p to promoter regions, contributing to transcriptional repression outside of meiosis; suppresses DNA repair involving homologous recombination
YBR010W	HHT1	16	Histone H3; core histone protein required for chromatin assembly, part of heterochromatin-mediated telomeric and HM silencing; one of two identical histone H3 proteins (see HHT2); regulated by acetylation, methylation, and phosphorylation; H3K14 acetylation plays an important role in the unfolding of strongly positioned nucleosomes during repair of UV damage
YNL031C	HHT2	16	Histone H3; core histone protein required for chromatin assembly, part of heterochromatin-mediated telomeric and HM silencing; one of two identical histone H3 proteins (see HHT1); regulated by acetylation, methylation, and phosphorylation; H3K14 acetylation plays an important role in the unfolding of strongly positioned nucleosomes during repair of UV damage
YDR225W	HTA1	16	Histone H2A; core histone protein required for chromatin assembly and chromosome function; one of two nearly identical subtypes (see also HTA2); DNA damage-dependent phosphorylation by Mec1p facilitates DNA repair; acetylated by Nat4p; N-terminally propionylated in vivo

YBL003C	HTA2	16	Histone H2A; core histone protein required for chromatin assembly and chromosome function; one of two nearly identical (see also HTA1) subtypes; DNA damage-dependent phosphorylation by Mec1p facilitates DNA repair; acetylated by Nat4p
YDR224C	HTB1	16	Histone H2B; core histone protein required for chromatin assembly and chromosome function; nearly identical to HTB2; Rad6p-Bre1p-Lge1p mediated ubiquitination regulates reassembly after DNA replication, transcriptional activation, meiotic DSB formation and H3 methylation
YBL002W	HTB2	16	Histone H2B; core histone protein required for chromatin assembly and chromosome function; nearly identical to HTB1; Rad6p-Bre1p-Lge1p mediated ubiquitination regulates reassembly after DNA replication, transcriptional activation, meiotic DSB formation and H3 methylation
YNR009W	NRM1	16	Transcriptional co-repressor of MBF-regulated gene expression; Nrm1p associates stably with promoters via MCB binding factor (MBF) to repress transcription upon exit from G1 phase
YDR113C	PDS1	16	Securin; inhibits anaphase by binding separin Esp1p; blocks cyclin destruction and mitotic exit, essential for meiotic progression and mitotic cell cycle arrest; localization is cell-cycle dependent and regulated by Cdc28p phosphorylation
YLR210W	CLB4	17	B-type cyclin involved in cell cycle progression; activates Cdc28p to promote the G2/M transition; may be involved in DNA replication and spindle assembly; accumulates during S phase and G2, then targeted for ubiquitin-mediated degradation; CLB4 has a paralog, CLB3, that arose from the whole genome duplication
YPL116W	HOS3	17	Trichostatin A-insensitive homodimeric histone deacetylase (HDAC); specificity in vitro for histones H3, H4, H2A, and H2B; similar to Hda1p, Rpd3p, Hos1p, and Hos2p; deletion results in increased histone acetylation at rDNA repeats
YMR117C	SPC24	17	Component of the kinetochore-associated Ndc80 complex; involved in chromosome segregation, spindle checkpoint activity, and kinetochore clustering; evolutionarily conserved; other members include Ndc80p, Nuf2p, Spc24p, and Spc25p

YNL176C	TDA7	17	Cell cycle-regulated gene of unknown function; promoter bound by Fkh2p; null mutant is sensitive to expression of the top1-T722A allele; TDA7 has a paralog, YDL211C, that arose from the whole genome duplication
YGR099W	TEL2	17	Subunit of the ASTRA complex, involved in chromatin remodeling; subunit of the telomere cap complex DNA-binding protein specific to single-stranded yeast telomeric DNA repeats, required for telomere length regulation and telomere position effect; involved in the stability or biogenesis of PIKKs such as TORC1
YLR209C	PNP1	18	Purine nucleoside phosphorylase; specifically metabolizes inosine and guanosine nucleosides; involved in the nicotinamide riboside salvage pathway
YOR129C	AFI1	19	Arf3p polarization-specific docking factor; required for the polarized distribution of the ADP-ribosylation factor, Arf3p; participates in polarity development and maintenance of a normal haploid budding pattern; interacts with Cnm7p
YPR004C	AIM45	19	Putative ortholog of mammalian ETF-alpha; interacts with frataxin, Yfh1p; null mutant displays elevated frequency of mitochondrial genome loss; may have a role in oxidative stress response; ETF-alpha is an electron transfer flavoprotein complex subunit
YBL097W	BRN1	19	Subunit of the condensin complex; required for chromosome condensation and for clustering of tRNA genes at the nucleolus; may influence multiple aspects of chromosome transmission
YJR076C	CDC11	19	Component of the septin ring that is required for cytokinesis; present at the ends of rod-like septin heterooligomers; C-terminal extension is important for recruitment of Bni5p to the mother-bud neck, which in turn is required for Myo1p recruitment and cytokinesis; septin rings at the mother-bud neck act as scaffolds for recruiting cell division factors and as barriers to prevent diffusion of specific proteins between mother and daughter cells
YHR146W	CRP1	19	Protein that binds to cruciform DNA structures; CRP1 has a paralog, MDG1, that arose from the whole genome duplication

YGR113W	DAM1	19	Essential subunit of the Dam1 complex (aka DASH complex); cooperates with Duo1p to connect the DASH complex with the microtubules (MT); couples kinetochores to the force produced by MT depolymerization thereby aiding in chromosome segregation; Ipl1p target for regulating kinetochore-MT attachments
YPR111W	DBF20	19	Ser/Thr kinase involved in late nuclear division; one of the mitotic exit network (MEN) proteins; necessary for the execution of cytokinesis; also plays a role in regulating the stability of SWI5 and CLB2 mRNAs; DBF20 has a paralog, DBF2, that arose from the whole genome duplication
YIR010W	DSN1	19	Essential component of the MIND kinetochore complex; joins kinetochore subunits contacting DNA to those contacting microtubules; Dsn1p phosphorylation promotes interaction between outer and inner kinetochore proteins; kinetochore receptor for monopolin, via interaction with subunit Csm1p; essential for meiotic but not mitotic chromosome segregation; MIND complex consists of Mtw1p, Nnf1p, Nsl1p and Dsn1p; modified by sumoylation; phosphorylated by monopolin subunit Hrr25p
YMR299C	DYN3	19	Dynein light intermediate chain (LIC); localizes with dynein, null mutant is defective in nuclear migration
YKL048C	ELM1	19	Serine/threonine protein kinase; regulates the orientation checkpoint, the morphogenesis checkpoint and the metabolic switch from fermentative to oxidative metabolism by phosphorylating the activation loop of Kin4p, Hsl1p and Snf4p respectively; cooperates with Hsl7p in recruiting Hsl1p to the septin ring, a prerequisite for subsequent recruitment, phosphorylation, and degradation of Swe1p; forms part of the bud neck ring; regulates cytokinesis
YDR130C	FIN1	19	Spindle pole body-related intermediate filament protein; forms cell cycle-specific filaments between spindle pole bodies in dividing cells; localizes to poles and microtubules of spindle during anaphase and contributes to spindle stability; involved in Glc7p localization and regulation; relative distribution to the nucleus increases upon DNA replication stress

YNL068C	FKH2	19	Forkhead family transcription factor; rate-limiting activator of replication origins; evolutionarily conserved regulator of lifespan; binds multiple chromosomal elements with distinct specificities, cell cycle dynamics; positively regulates transcriptional elongation; facilitates clustering, activation of early-firing replication origins; negative role in chromatin silencing at HML and HMR; major role in expression of G2/M phase genes; relocates to cytosol under hypoxia
YFL017C	GNA1	19	Glucosamine-6-phosphate acetyltransferase; evolutionarily conserved; required for multiple cell cycle events including passage through START, DNA synthesis, and mitosis; involved in UDP-N-acetylglucosamine synthesis, forms GlcNAc6P from AcCoA
YKL183W	LOT5	19	Protein of unknown function; gene expression increases in cultures shifted to a lower temperature; protein abundance increases in response to DNA replication stress
YLR288C	MEC3	19	DNA damage and meiotic pachytene checkpoint protein; subunit of a heterotrimeric complex (Rad17p-Mec3p-Ddc1p) that forms a sliding clamp, loaded onto partial duplex DNA by a clamp loader complex; homolog of human and <i>S. pombe</i> Hus1
YDL028C	MPS1	19	Dual-specificity kinase; autophosphorylation required for function; required for spindle pole body (SPB) duplication and spindle checkpoint function; contributes to bi-orientation by promoting formation of force-generating kinetochore-microtubule attachments in meiosis I; substrates include SPB proteins Spc42p, Spc110p, and Spc98p, mitotic exit network protein Mob1p, kinetochore protein Cnn1p, and checkpoint protein Mad1p; substrate of APCC(Cdh1); similar to human Mps1p
YML065W	ORC1	19	Largest subunit of the origin recognition complex; involved in directing DNA replication by binding to replication origins; also involved in transcriptional silencing; exhibits ATPase activity; ORC1 has a paralog, SIR3, that arose from the whole genome duplication
YML125C	PGA3	19	Putative cytochrome b5 reductase, localized to the plasma membrane; may be involved in regulation of lifespan; required for maturation of Gas1p and Pho8p, proposed to be involved in protein trafficking; PGA3 has a paralog, AIM33, that arose from the whole genome duplication
YMR006C	PLB2	19	Phospholipase B (lysophospholipase) involved in lipid metabolism; displays transacylase activity in vitro; over-production confers resistance to lysophosphatidylcholine

YMR190C	SGS1	19	RecQ family nucleolar DNA helicase; role in genome integrity maintenance, chromosome synapsis, meiotic joint molecule/crossover formation; stimulates activity of Top3p; rapidly lost in response to rapamycin in Rrd1p-dependent manner; forms nuclear foci upon DNA replication stress; yeast SGS1 complements mutations in human homolog BLM implicated in Bloom syndrome; also similar to human WRN implicated in Werner syndrome; human BLM and WRN can each complement yeast null mutant
YBR130C	SHE3	19	Protein adaptor between Myo4p and the She2p-mRNA complex; part of the mRNA localization machinery that restricts accumulation of certain proteins to the bud; also required for cortical ER inheritance
YDR227W	SIR4	19	SIR protein involved in assembly of silent chromatin domains; silent information regulator (SIR) along with SIR2 and SIR3; involved in assembly of silent chromatin domains at telomeres and the silent mating-type loci; some alleles of SIR4 prolong lifespan; required for telomere hypercluster formation in quiescent yeast cells
YML058W	SML1	19	Ribonucleotide reductase inhibitor; involved in regulating dNTP production; regulated by Mec1p and Rad53p during DNA damage and S phase; SML1 has a paralog, DIF1, that arose from the whole genome duplication
YDR346C	SVF1	19	Protein with a potential role in cell survival pathways; required for the diauxic growth shift; expression in mammalian cells increases survival under conditions inducing apoptosis; mutant has increased aneuploidy tolerance
YBR123C	TFC1	19	Subunit of RNA polymerase III transcription initiation factor complex; one of six subunits of the RNA polymerase III transcription initiation factor complex (TFIIC); part of the TauA globular domain of TFIIC that binds DNA at the BoxA promoter sites of tRNA and similar genes; human homolog is TFIIC-63
YDR325W	YCG1	19	Subunit of the condensin complex; required for establishment and maintenance of chromosome condensation, chromosome segregation and chromatin binding by the complex; required for tRNA genes clustering at the nucleolus; required for replication slow zone breakage following Mec1p inactivation; transcription is cell cycle regulated, peaking in mitosis and declining in G1; protein is constitutively degraded by the proteasome; rate limiting for condensin recruitment to chromatin

YGL101W		19	Protein of unknown function; non-essential gene; interacts with the DNA helicase Hpr5p; YGL101W has a paralog, YBR242W, that arose from the whole genome duplication
YKL069W		19	Methionine-R-sulfoxide reductase; reduces the R enantiomer of free Met-SO, in contrast to Ycl033Cp which reduces Met-R-SO in a peptide linkage; has a role in protection against oxidative stress; relative distribution to the nucleus increases upon DNA replication stress
YGL021W	ALK1	20	Protein kinase; along with its paralog, ALK2, required for proper spindle positioning and nuclear segregation following mitotic arrest, proper organization of cell polarity factors in mitosis, proper localization of formins and polarity factors, and survival in cells that activate spindle assembly checkpoint; phosphorylated in response to DNA damage; ALK1 has a paralog, ALK2, that arose from the whole genome duplication; similar to mammalian haspins
YJR092W	BUD4	20	Anillin-like protein involved in bud-site selection; required for the axial budding pattern; required for the formation and disassembly of the double septin ring structure, and generally for septin organization; functions as a platform linking the cytokinesis tag septins to the axial landmark through its multiple domains; in vivo substrate of Cdc28p/Clb2p
YMR001C	CDC5	20	Polo-like kinase; controls targeting and activation of Rho1p at cell division site via Rho1p guanine nucleotide exchange factors; regulates Spc72p; also functions in adaptation to DNA damage during meiosis; regulates the shape of the nucleus and expansion of the nuclear envelope during mitosis; similar to Xenopus Plx1 and S. pombe Plo1p; human homologs PLK1, PLK3 can each complement yeast cdc5 thermosensitive mutants
YLR190W	MMR1	20	Phosphorylated protein of the mitochondrial outer membrane; localizes only to mitochondria of the bud; interacts with Myo2p to mediate mitochondrial distribution to buds; mRNA is targeted to the bud via the transport system involving She2p

YDR146C	SWI5	20	Transcription factor that recruits Mediator and Swi/Snf complexes; activates transcription of genes expressed at the M/G1 phase boundary and in G1 phase; required for expression of the HO gene controlling mating type switching; localization to nucleus occurs during G1 and appears to be regulated by phosphorylation by Cdc28p kinase; SWI5 has a paralog, ACE2, that arose from the whole genome duplication
YDR389W	SAC7	21	GTPase activating protein (GAP) for Rho1p; regulator of a Tor2p-mediated, Rho1p GTPase switch that controls organization of the actin cytoskeleton; negative regulator of the RHO1-PKC1-MAPK cell integrity (CWI) and membrane fluidity homeostasis signaling pathways; potential Cdc28p substrate; SAC7 has a paralog, BAG7, that arose from the whole genome duplication
YMR009W	ADI1	22	Acireductone dioxygenase involved in methionine salvage pathway; transcribed as polycistronic mRNA with YMR010W and regulated post-transcriptionally by RNase III (Rnt1p) cleavage; ADI1 mRNA is induced in heat shock conditions; human ortholog ADI1 can complement yeast adi1 mutant
YKR021W	ALY1	22	Alpha arrestin, substrate of calcineurin; controls nutrient-mediated intracellular sorting of permease Gap1p; interacts with AP-1 subunit Apl4p; dephosphorylation of Aly1p required for the endocytosis of Dip5p; may regulate endocytosis of plasma membrane proteins by recruiting ubiquitin ligase Rsp5p to plasma membrane targets; ALY1 has a paralog, ALY2, that arose from the whole genome duplication
YGR177C	ATF2	22	Alcohol acetyltransferase; may play a role in steroid detoxification; forms volatile esters during fermentation, which is important for brewing and winemaking
YDR020C	DAS2	22	Putative protein of unknown function; non-essential gene identified in a screen for mutants with increased levels of rDNA transcription; weak similarity with uridine kinases and with phosphoribokinases
YNL024C	EFM6	22	Putative S-adenosylmethionine-dependent lysine methyltransferase; responsible for modifying Lys-390 in translational elongation factor EF-1 alpha (eEF1A); has seven beta-strand methyltransferase motif; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm

YER140W	EMP65	22	Integral membrane protein of the ER; forms an ER-membrane associated protein complex with Slp1p; identified along with SLP1 in a screen for mutants defective in the unfolded protein response (UPR); proposed to function in the folding of integral membrane proteins; interacts genetically with MPS3; the authentic, non-tagged protein is detected in highly purified mitochondria in high-throughput studies
YOL158C	ENB1	22	Endosomal ferric enterobactin transporter; expressed under conditions of iron deprivation; member of the major facilitator superfamily; expression is regulated by Rcs1p and affected by chloroquine treatment
YOR319W	HSH49	22	U2-snRNP associated splicing factor; similar to the mammalian splicing factor SAP49; proposed to function as a U2-snRNP assembly factor along with Hsh155p and binding partner Cus1p; contains two RNA recognition motifs (RRM)
YHR046C	INM1	22	Inositol monophosphatase; involved in biosynthesis of inositol and in phosphoinositide second messenger signaling; INM1 expression increases in the presence of inositol and decreases upon exposure to antibipolar drugs lithium and valproate
YMR294W	JNM1	22	Component of the yeast dynein complex; consisting of Nip100p, Jnm1p, and Arp1p; required for proper nuclear migration and spindle partitioning during mitotic anaphase B
YLR057W	MNL2	22	Putative mannosidase involved in ER-associated protein degradation; localizes to the endoplasmic reticulum; sequence similarity with seven-hairpin glycosidase (GH47) family members, such as Mns1p and Mnl1p, that hydrolyze 1,2-linked alpha-D-mannose residues; non-essential gene
YJR003C	MRX12	22	Protein that associates with mitochondrial ribosome; detected in highly purified mitochondria in high-throughput studies; predicted to be involved in ribosome biogenesis
YBR255W	MTC4	22	Protein of unknown function; required for normal growth rate at 15 degrees C; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm in a punctate pattern; mtc4 is synthetically sick with cdc13-1
YDL044C	MTF2	22	Mitochondrial protein that interacts with mitochondrial RNA polymerase; interacts with an N-terminal region of mitochondrial RNA polymerase (Rpo41p) and couples RNA processing and translation to transcription

YFR039C	OSW7	22	Protein involved in outer spore wall assembly; likely involved directly in dityrosine layer assembly; may be involved in response to high salt and changes in carbon source; SWAT-GFP, seamless-GFP and mCherry fusion proteins localize to the endoplasmic reticulum; deletion mutant has decreased spore survival in <i>Drosophila</i> feces; OSW7 has a paralog, SHE10, that arose from the whole genome duplication; paralogs are redundant for spore wall dityrosine assembly
YOR104W	PIN2	22	Exomer-dependent cargo protein; induces appearance of [PIN+] prion when overproduced; prion-like domain serves as a retention signal in the trans-Golgi network; predicted to be palmitoylated
YCR024C-A	PMP1	22	Regulatory subunit for the plasma membrane H(+)-ATPase Pma1p; small single-membrane span proteolipid; forms unique helix and positively charged cytoplasmic domain that is able to specifically segregate phosphatidylserines; PMP1 has a paralog, PMP2, that arose from the whole genome duplication
YDR198C	RKM2	22	Ribosomal protein lysine methyltransferase; responsible for trimethylation of the lysine residue at position 3 of Rpl12Ap and Rpl12Bp
YER139C	RTR1	22	CTD phosphatase; dephosphorylates S5-P in the C-terminal domain of Rpo21p; has a cysteine-rich motif required for function and conserved in eukaryotes; shuttles between the nucleus and cytoplasm; RTR1 has a paralog, RTR2, that arose from the whole genome duplication
YPL183C	RTT10	22	WD40 domain-containing protein involved in endosomal recycling; forms a complex with Rrt2p that functions in the retromer-mediated pathway for recycling internalized cell-surface proteins; interacts with Trm7p for 2'-O-methylation of N34 of substrate tRNAs; has a role in regulation of Ty1 transposition; human ortholog is WDR6
YIL167W	SDL1	22	Blocked reading frame otherwise encoding L-serine dehydratase
YKL130C	SHE2	22	RNA-binding protein that binds specific mRNAs and interacts with She3p; part of the mRNA localization machinery that restricts accumulation of certain proteins to the bud; binds to ER-derived membranes and targets mRNAs to cortical ER

YNR004W	SWM2	22	Protein with a role in snRNA and snoRNA cap trimethylation; interacts with Tgs1p and shows similar phenotypes; required for trimethylation of the caps of spliceosomal snRNAs and the U3 snoRNA, and for efficient 3' end processing of U3 snoRNA; may act as a specificity factor for Tgs1p
YLR237W	THI7	22	Plasma membrane transporter responsible for the uptake of thiamine; contributes to uptake of 5-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (acadesine); member of the major facilitator superfamily of transporters; mutation of human ortholog causes thiamine-responsive megaloblastic anemia
YLL028W	TPO1	22	Polyamine transporter of the major facilitator superfamily; member of the 12-spanner drug:H(+) antiporter DHA1 family; recognizes spermine, putrescine, and spermidine; catalyzes uptake of polyamines at alkaline pH and excretion at acidic pH; during oxidative stress exports spermine, spermidine from the cell, which controls timing of expression of stress-responsive genes; phosphorylation enhances activity and sorting to the plasma membrane
YBL067C	UBP13	22	Ubiquitin-specific protease that cleaves Ub-protein fusions; UBP13 has a paralog, UBP9, that arose from the whole genome duplication
YDR324C	UTP4	22	Subunit of U3-containing 90S preribosome and SSU processome complexes; involved in production of 18S rRNA and assembly of small ribosomal subunit; member of t-Utp subcomplex involved with transcription of 35S rRNA transcript; Small Subunit processome is also known as SSU processome
YBR242W		22	Putative protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm and nucleus; YBR242W is not an essential gene; YBR242W has a paralog, YGL101W, that arose from the whole genome duplication
YDR514C		22	Protein of unknown function that localizes to mitochondria; overexpression affects endocytic protein trafficking; YDR514C has a paralog, GFD2, that arose from the whole genome duplication
YIL092W		22	Putative protein of unknown function; green fluorescent protein (GFP)-fusion protein localizes to the cytoplasm and to the nucleus
YOL014W		22	Putative protein of unknown function; mCherry fusion protein localizes to the cytosol and nucleus

YAL059W	ECM1	23	Pre-ribosomal factor involved in 60S ribosomal protein subunit export; associates with the pre-60S particle; shuttles between the nucleus and cytoplasm
YMR132C	JLP2	23	Protein of unknown function; contains sequence that closely resembles a J domain (typified by the <i>E. coli</i> DnaJ protein)
YFR001W	LOC1	23	Nuclear protein involved in asymmetric localization of ASH1 mRNA; binds double-stranded RNA in vitro; constituent of 66S pre-ribosomal particles; required at post-transcriptional step for efficient retrotransposition; absence results in decreased Ty1 Gag:GFP protein levels; relocates from nucleus to cytoplasm upon DNA replication stress
YDR493W	MZM1	23	Protein required for assembly of the cytochrome bc(1) complex; acts as a chaperone for Rip1p and facilitates its insertion into the complex at a late stage of assembly; localized to the mitochondrial matrix; null mutant exhibits a respiratory growth defect and reduced mitochondrial zinc levels, which is characteristic of mutations affecting bc(1) complex assembly; member of the LYR protein family; human LYRM7 is a functional ortholog
YNL110C	NOP15	23	Constituent of 66S pre-ribosomal particles; involved in 60S ribosomal subunit biogenesis; localizes to both nucleolus and cytoplasm
YNL032W	SIW14	23	Tyrosine phosphatase involved in actin organization and endocytosis; localized to the cytoplasm
YDR308C	SRB7	23	Subunit of the RNA polymerase II mediator complex; associates with core polymerase subunits to form the RNA polymerase II holoenzyme; essential for transcriptional regulation; target of the global repressor Tup1p
YLR003C	CMS1	24	Putative subunit of the 90S preribosome processome complex; overexpression rescues suppressor mutant of mcm10; null mutant is viable; relocates from nucleus to cytoplasm upon DNA replication stress
YLR276C	DBP9	24	DEAD-box protein required for 27S rRNA processing; exhibits DNA, RNA and DNA/RNA helicase activities; ATPase activity shows preference for DNA over RNA; DNA helicase activity abolished by mutation in RNA-binding domain
YKL078W	DHR2	24	Predominantly nucleolar DEAH-box ATP-dependent RNA helicase; required for 18S rRNA synthesis

YHR148W	IMP3	24	Component of the SSU processome; SSU processome is required for pre-18S rRNA processing, essential protein that interacts with Mpp10p and mediates interactions of Imp4p and Mpp10p with U3 snoRNA
YNL308C	KRI1	24	Essential nucleolar protein required for 40S ribosome biogenesis; associate with snR30; physically and functionally interacts with Krr1p
YOR056C	NOB1	24	Protein involved in proteasomal and 40S ribosomal subunit biogenesis; required for cleavage of the 20S pre-rRNA to generate the mature 18S rRNA; cleavage is activated by Fun12p, a GTPase and translation initiation factor; relocates from nucleus to nucleolus upon DNA replication stress
YOL144W	NOP8	24	Nucleolar protein required for 60S ribosomal subunit biogenesis
YBR267W	REI1	24	Cytoplasmic pre-60S factor; required for the correct recycling of shuttling factors Alb1, Arx1 and Tif6 at the end of the ribosomal large subunit biogenesis; involved in bud growth in the mitotic signaling network
YNL151C	RPC31	24	RNA polymerase III subunit C31
YKR081C	RPF2	24	Essential protein involved in rRNA maturation and ribosomal assembly; involved in the processing of pre-rRNA and the assembly of the 60S ribosomal subunit; interacts with ribosomal protein L11; localizes predominantly to the nucleolus; constituent of 66S pre-ribosomal particles
YDL153C	SAS10	24	Subunit of U3-containing Small Subunit (SSU) processome complex; involved in production of 18S rRNA and assembly of small ribosomal subunit; disrupts silencing when overproduced; mutant has increased aneuploidy tolerance; essential gene
YOL124C	TRM11	24	Catalytic subunit of adoMet-dependent tRNA methyltransferase complex; required for the methylation of the guanosine nucleotide at position 10 (m2G10) in tRNAs; contains a THUMP domain and a methyltransferase domain; another complex member is Trm112p
YJL084C	ALY2	25	Alpha arrestin; controls nutrient-mediated intracellular sorting of permease Gap1p; interacts with AP-1 subunit Apl4p; phosphorylated by Npr1p and also by cyclin-CDK complex Pcl7p-Pho85p; promotes endocytosis of plasma membrane proteins; ALY2 has a paralog, ALY1, that arose from the whole genome duplication

YGR068C	ART5	25	Protein proposed to regulate endocytosis of plasma membrane proteins; regulates by recruiting the ubiquitin ligase Rsp5p to its target in the plasma membrane; SWAT-GFP and mCherry fusion proteins localize to the cytosol
YOR228C	MCP1	25	Mitochondrial protein of unknown function involved in lipid homeostasis; integral membrane protein that localizes to the mitochondrial outer membrane; involved in mitochondrial morphology; interacts genetically with MDM10, and other members of the ERMES complex; contains five predicted transmembrane domains
YOR018W	ROD1	25	Alpha-arrestin involved in ubiquitin-dependent endocytosis; activating dephosphorylation relays glucose signaling to transporter endocytosis; calcineurin dephosphorylation is required for Rsp5p-dependent internalization of agonist-occupied Ste2p, as part of signal desensitization; recruits Rsp5p to Ste2p via its 2 PPXY motifs; protein abundance increases in response to DNA replication stress; ROD1 has a paralog, ROG3, that arose from the whole genome duplication
YGR070W	ROM1	25	Guanine nucleotide exchange factor (GEF) for Rho1p; mutations are synthetically lethal with mutations in rom2, which also encodes a GEP; ROM1 has a paralog, ROM2, that arose from the whole genome duplication
YDR191W	HST4	26	NAD(+-)-dependent protein deacetylase; deacetylation targets are primarily mitochondrial proteins; involved along with Hst3p in silencing at telomeres, cell cycle progression, radiation resistance, genomic stability and short-chain fatty acid metabolism; accumulates in mitochondria in response to biotin starvation and may link biotin metabolism with energy homeostasis; member of the Sir2 family and may be the functional equivalent of human SIRT3 - SIRT3 is a nuclear NAD+-dependent histone deacetylase that translocates to the mitochondria upon cellular stress citepscher2007sirt3
YEL032W	MCM3	26	Protein involved in DNA replication; component of the Mcm2-7 hexameric helicase complex that binds chromatin as a part of the pre-replicative complex
YLR274W	MCM5	26	Component of the Mcm2-7 hexameric helicase complex; MCM complex is important for priming origins of DNA replication in G1 and becomes an active ATP-dependent helicase that promotes DNA melting and elongation when activated by Cdc7p-Dbf4p in S-phase

YBR202W	MCM7	26	Component of the Mcm2-7 hexameric helicase complex; MCM2-7 primes origins of DNA replication in G1 and becomes an active ATP-dependent helicase that promotes DNA melting and elongation in S-phase; forms an Mcm4p-6p-7p subcomplex
YLR273C	PIG1	26	Putative targeting subunit for type-1 protein phosphatase Glc7p; tethers Glc7p to Gsy2p glycogen synthase; PIG1 has a paralog, GAC1, that arose from the whole genome duplication

Table 3: Genes that fused across the Timecourse and ChIP-chip datasets.

5.3 Bayesian analysis

We ran 10 chains of MDI for 36 hours saving every thousandth sample. This resulted in chains of varying length. We reduced the chains to 666 samples as this was the number of samples achieved by the slowest chain. Similar to section 4.1 these chains were then investigated for

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

Again we focus upon stationarity of the continuous variables. In the implementation of MDI we used, the recorded continuous variables are 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 20. No chain is perfectly behaved; as we cannot reduce to the set of stationary chains we thus exclude the most poorly behaved chains. Our lack of belief in the convergence of these chains is fortified by the behaviour of \hat{R} (which can be seen in figure 21) and the different distributions sampled for the ϕ_{lm} parameters shown in figure 22.

We visualise the the PSMs for each dataset in figure 23.

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. There is no consistent distribution across the chains, but it appears that Consensus clustering is producing a distribution that does have similar behaviour to the overlap of the chains.

Timecourse

Consensus matrices

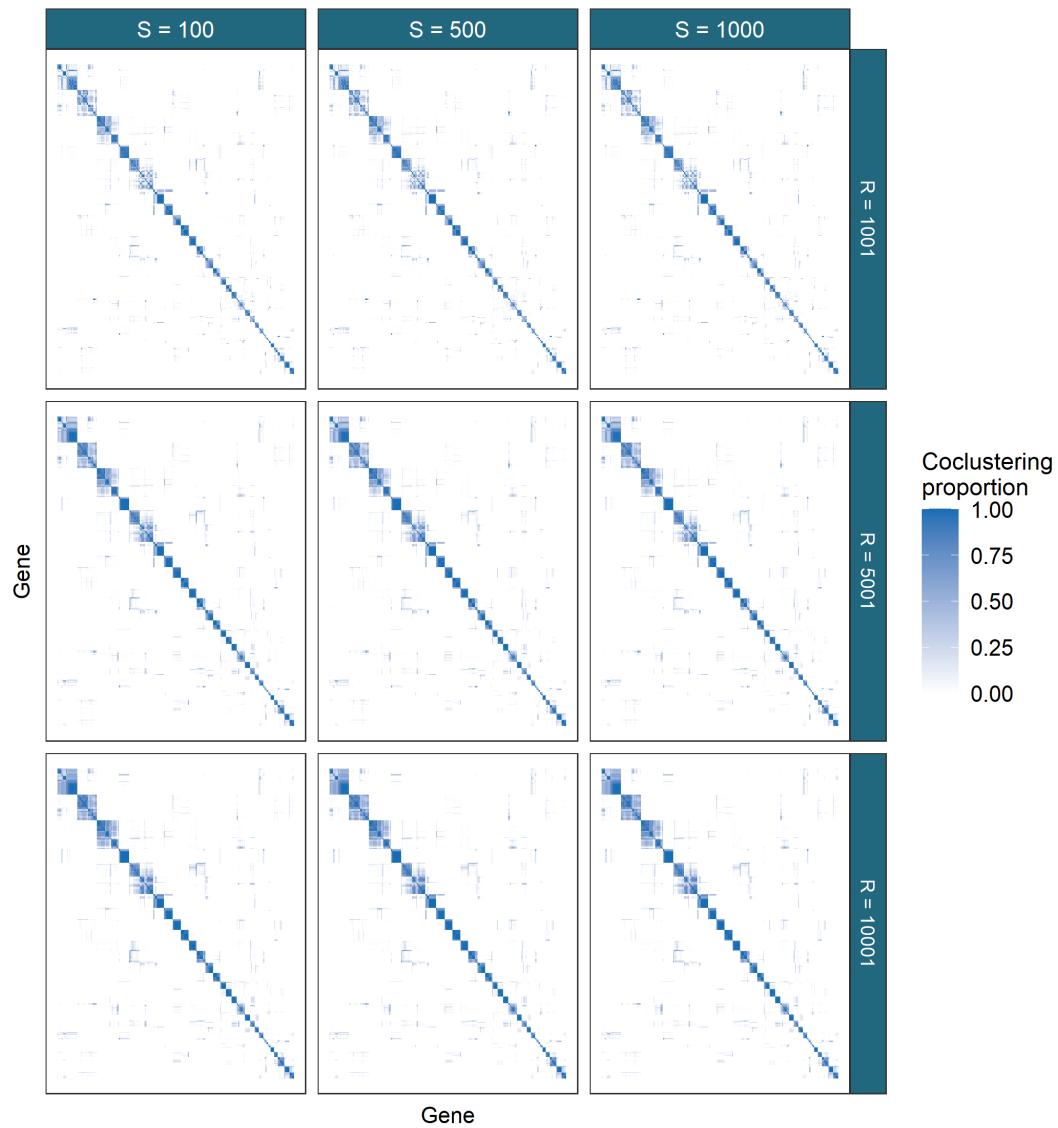


Figure 17: Consensus matrices for different ensembles of MDI for the Timecourse data. This dataset has stable clustering across the different choices of number of chains, S , and chain depth, R , with some components merging as the chain depth increases.

ChIP-chip

Consensus matrices

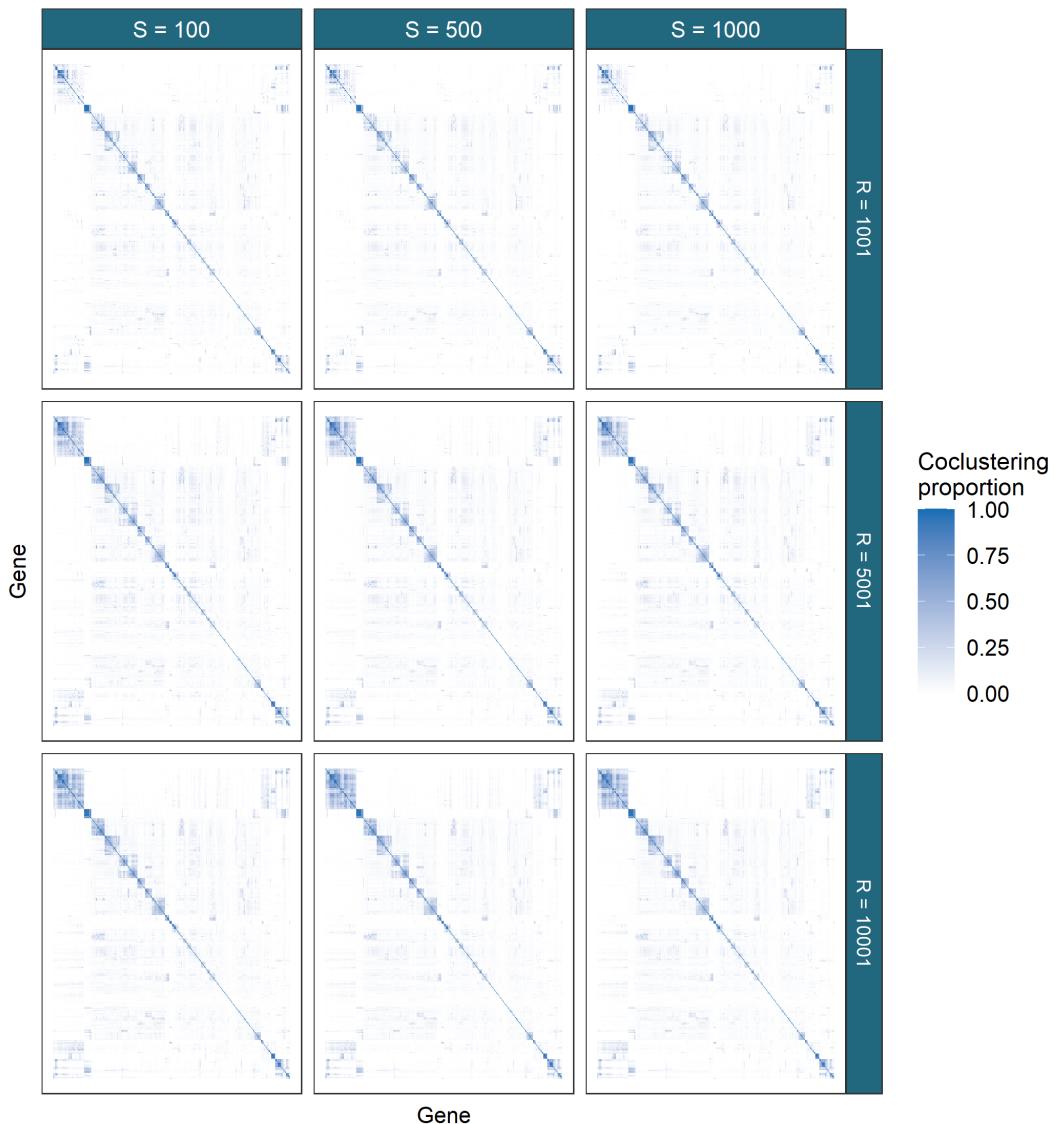


Figure 18: The ChIP-chip dataset is more sparse than the Timecourse data. In keeping with the results from the simulations for mixture models, deeper chains are required for better performance. It is only between $R = 5,001$ and $R = 10,001$ that no change in the clustering can be observed and the result 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

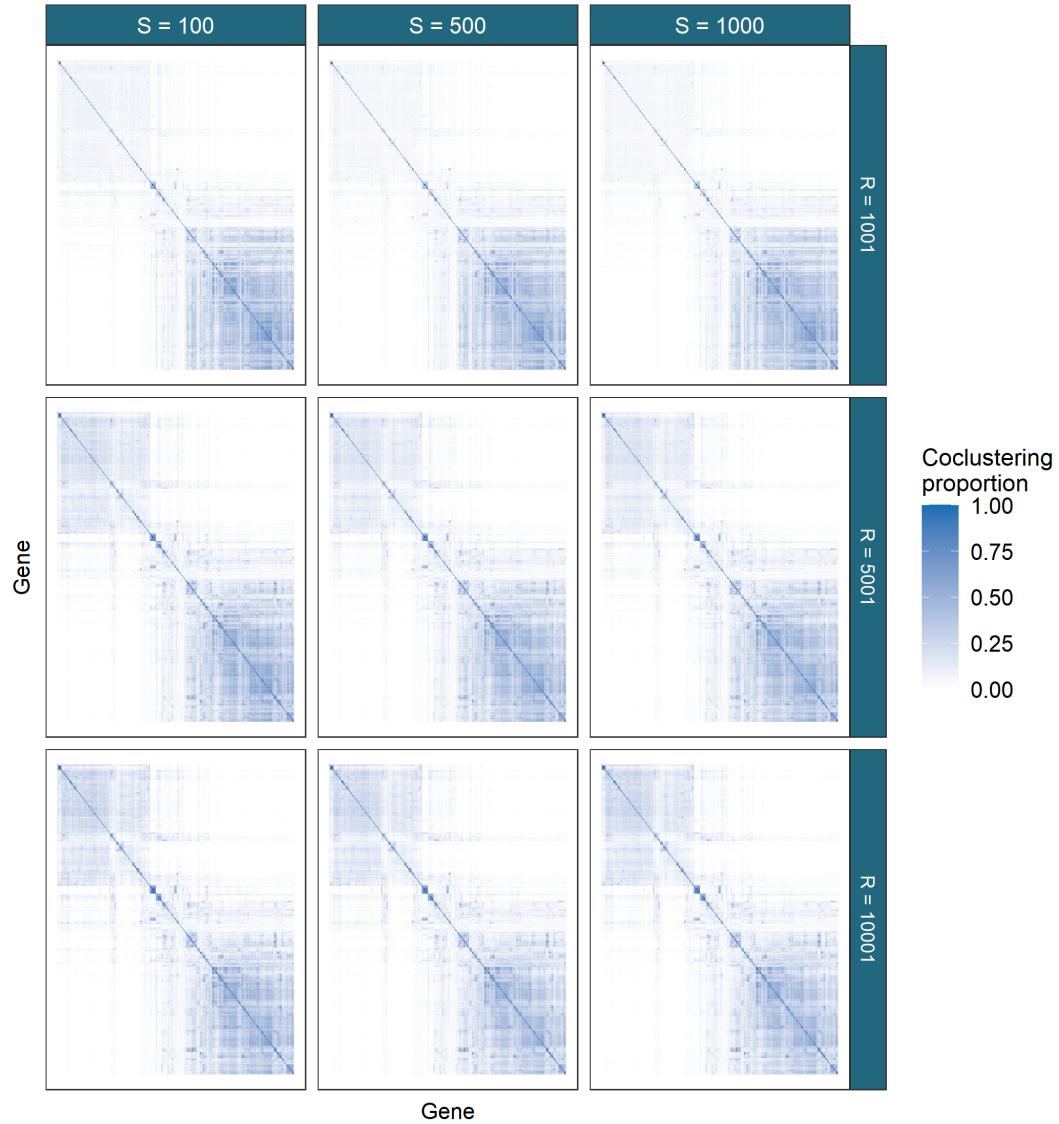


Figure 19: The PPI dataset has awkward characteristics for modelling. A wide, sparse dataset it is chain depth that we found to be the most important parameter for the ensemble. Similar to the results in figure 18, the matrices only stabilise from $R = 5001$ to $R = 10001$.

Within chain convergence

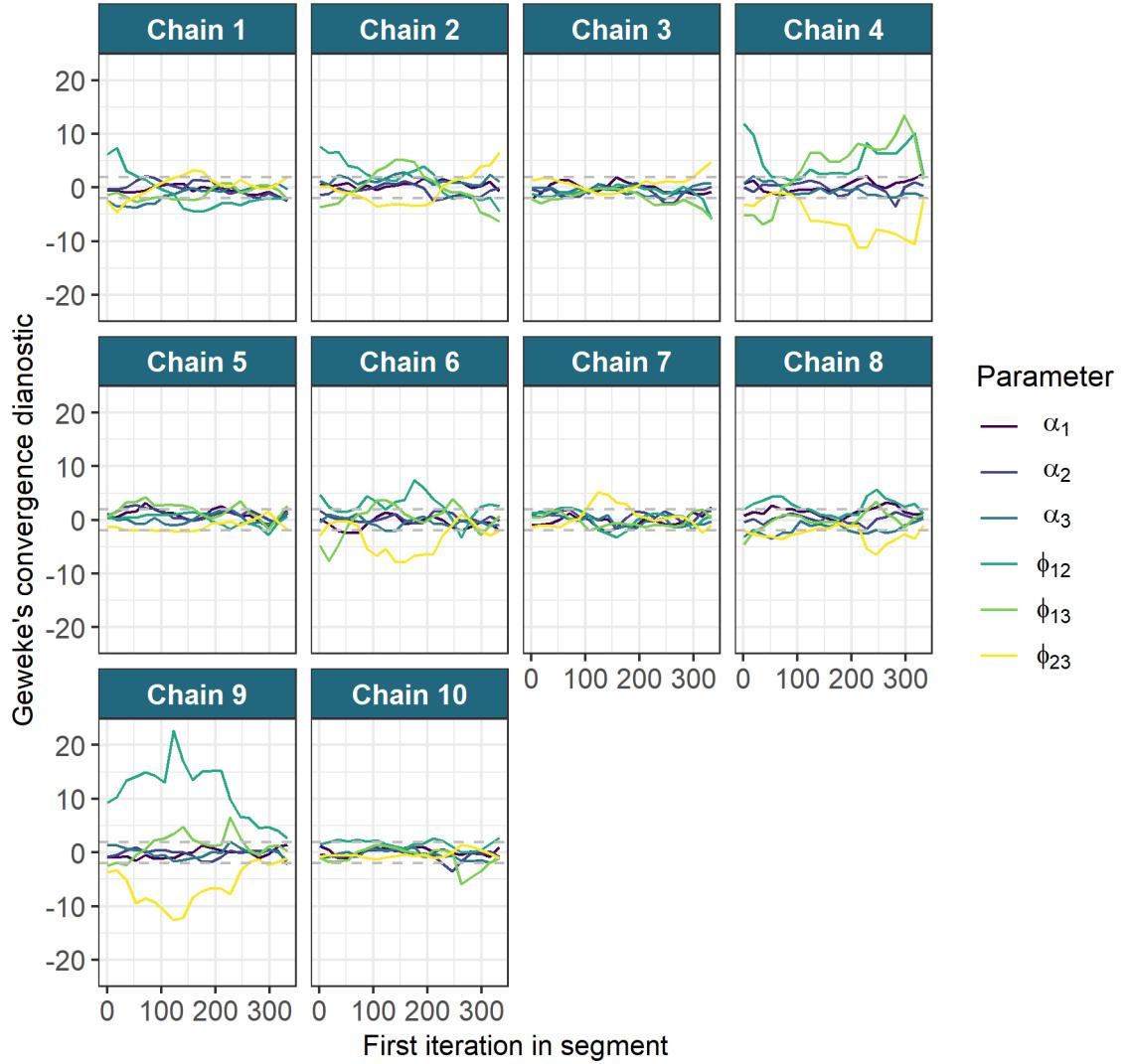


Figure 20: Chain 9 can be seen to have the most extreme behaviour in the distribution of the Geweke diagnostic for the parameters. We remove this chain from the analysis. Of the remaining chains we believe that 1, 2, 4 and 6 express the distributions furthest removed from the desired behaviour and are dropped from the analysis.

Gelman-R Rubin diagnostic plot

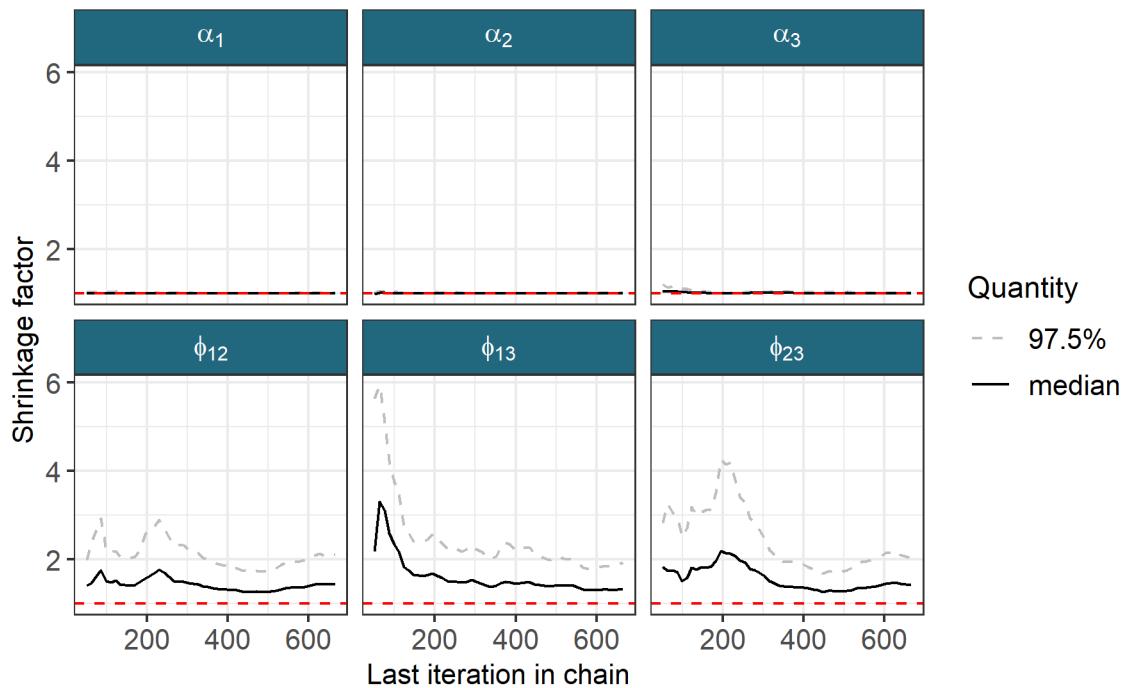


Figure 21: The chains still appear to be unconverged with \hat{R} remaining above 1.25 for the ϕ_{12}, ϕ_{13} and ϕ_{23} parameters. Stable \hat{R} is also too high with values of 1.049, 1.052 and 1.057 for ϕ_{12}, ϕ_{13} and ϕ_{23} respectively.

Parameter density

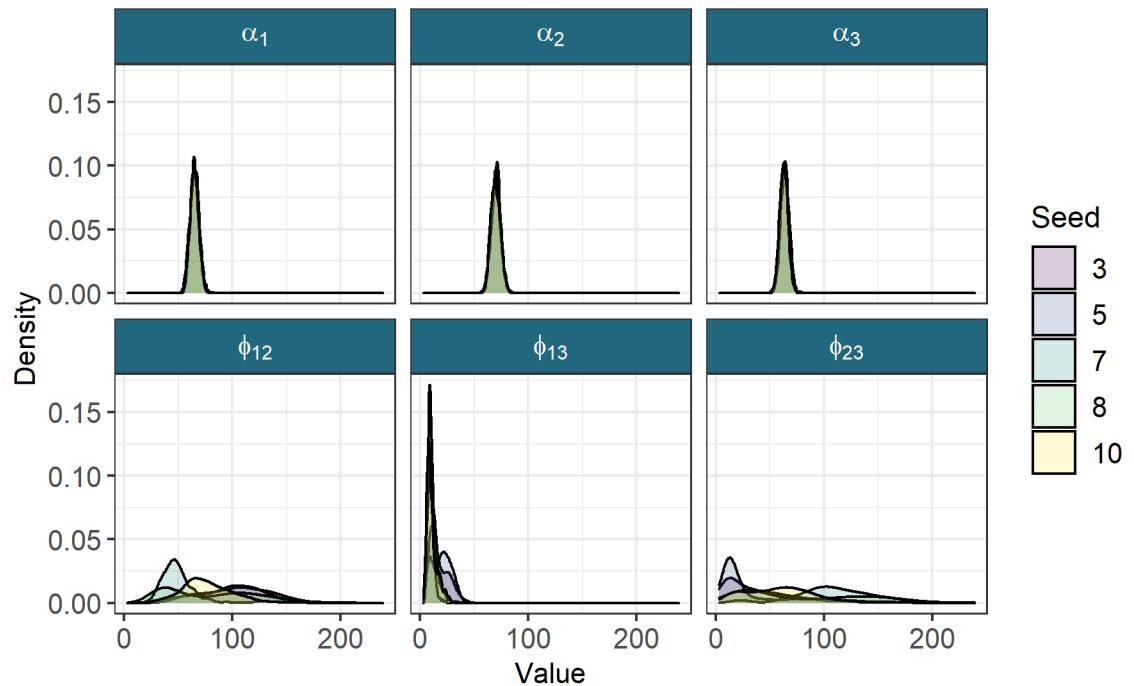


Figure 22: The densities of the continuous variables across the 5 chains kept for analysis. The mean sampled values are $\alpha_1 = 64.84$, $\alpha_2 = 69.85$, $\alpha_3 = 63.22$, $\phi_{12} = 81.76$, $\phi_{13} = 13.87$, and $\phi_{23} = 65.03$. It can be seen that different modes are being sampled for the ϕ parameters in each chain.

Yeast dataset

Posterior similarity matrices

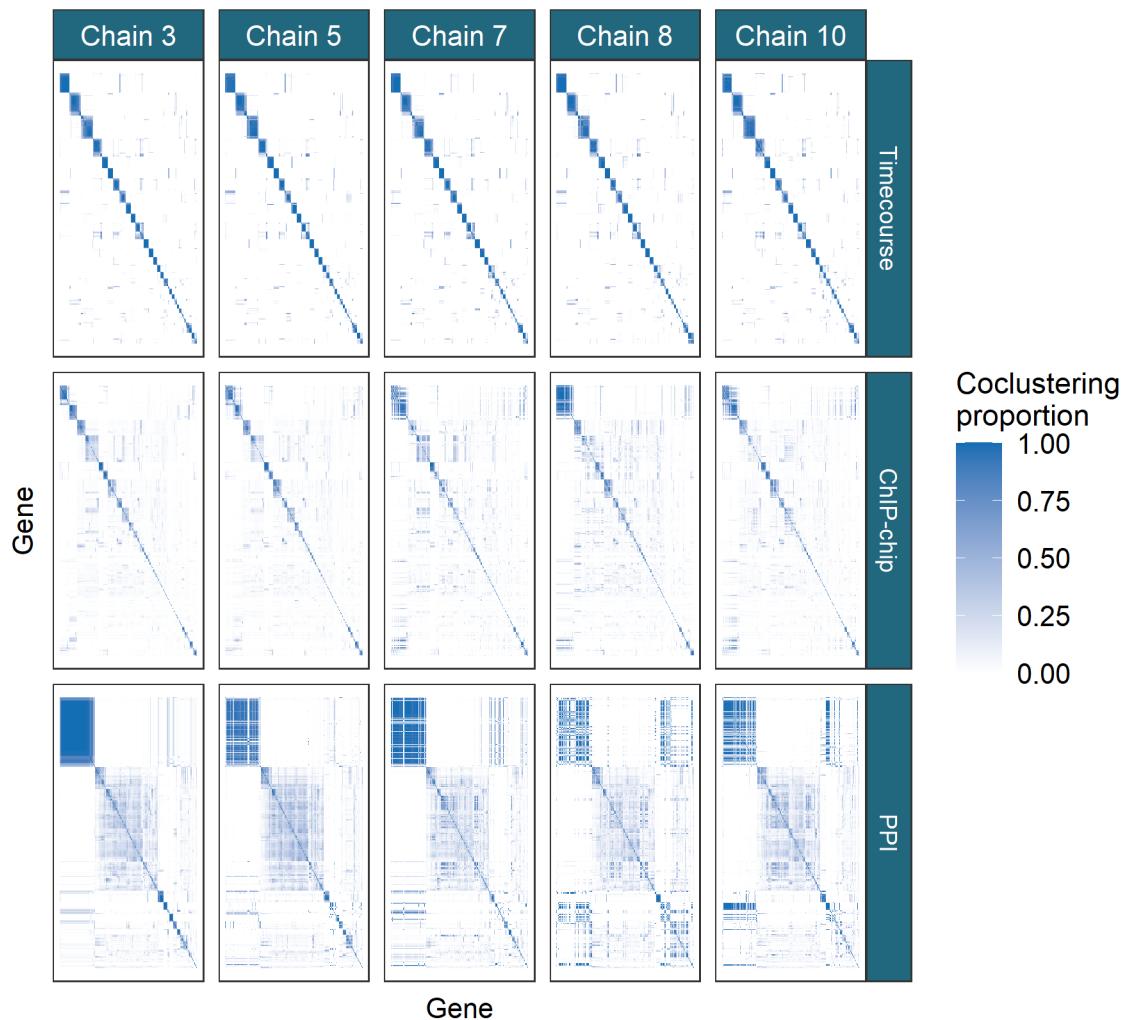


Figure 23: PSMs for each chain within each dataset. The PSMs are ordered by hierarchical clustering of the rows of the PSM for chain 3 in each dataset. There is no marked difference between the matrices for the Timecourse data with disagreement becoming more prominent in the ChIP-chip data and more so again in the PPI dataset.

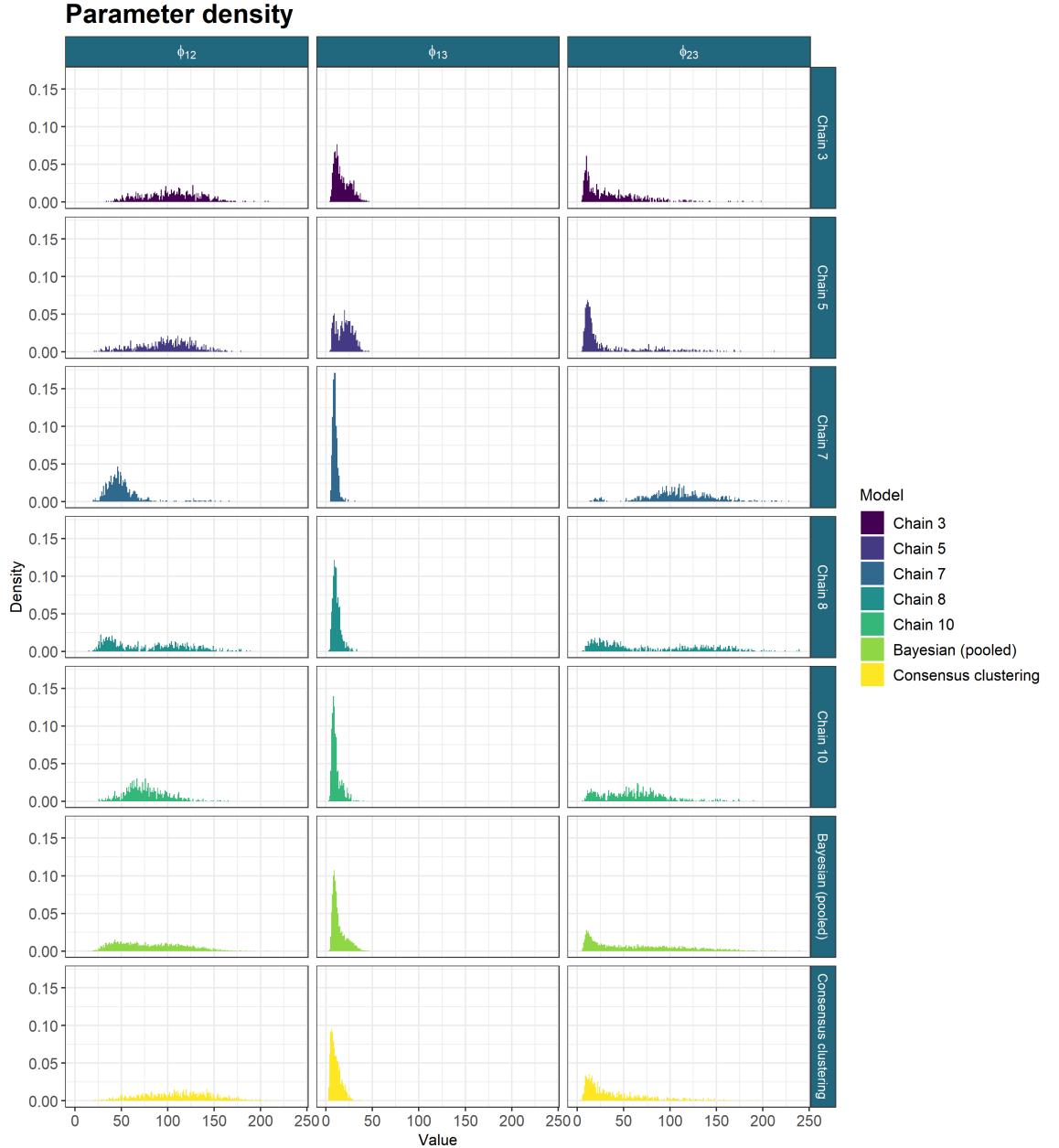


Figure 24: The sampled values for the ϕ parameters from the long chains, their pooled samples and the consensus using 1000 chains of depth 10,001. The long chains display a variety of behaviours. Across chains there is no clear consensus on the nature of the posterior distribution. The samples from any single chain are not particularly close to the behaviour of the pooled samples across all three parameters. It is the Consensus clustering that most approaches this pooled behaviour.

5.4 GO term over-representation

To validate the predicted clusters we tested if they contained a higher concentration of specific Gene Ontology (GO) terms than would be expected by chance. We estimated clusterings from the PSMs of the chains kept from section 5.3 visualised in figure 23 and the Consensus matrix of the largest ensemble run (i.e. $CC(10001, 1000)$) using the `maxpear` function from the R package `mcclust` Fritsch (2012) using default settings except for `k.max` which was set to 275 (the rounding down of $N/2$). To perform the GO term over-representation analysis we used the Bioconductor packages `clusterProfiler` (Yu et al., 2012), `biomaRt` (Durinck et al., 2009) and the annotation package `org.Sc.sgd.db` (Carlson et al., 2014).

We conditioned the test on the background set of the 551 yeast genes in the data. The gene labelled YIL167W was not found in the annotation database and was dropped from the analysis leaving a background universe of 550 genes. A hypergeometric test was used to check if the number of genes associated with specific GO terms within a cluster was greater than expected by random chance. We corrected the p -values using the Benjamini-Hochberg correction (Benjamini and Hochberg, 1995) and defined significance by a threshold of 0.01. We plotted the over-represented GO terms for the different clusterings within each dataset using the three different ontologies of “Molecular function” (**MF**), “Biological process” (**BP**) and “Cellular component” (**CC**) (figures 25, 26 and 27 respectively).

We find that the Consensus clustering finds terms common to all of the long chains. It also finds some terms with low p -values common to a majority of chains (such as DNA helicase activity in the MF ontology for the Timecourse dataset) and a small number of GO terms unique to itself. These terms that no long chain find are normally related to other terms already over-represented within either the Consensus clustering or a number of the long chains. For example, the transmembrane transporter activity and transporter activity terms uncovered by the ensemble in the Timecourse dataset are related to terms found across 3 of the chains and by Consensus clustering (specifically transferase activity and phosphotransferase).

Furthermore, we also note that the Bayesian chains have very significant disagreements between eachother; there is no consensus on the results with many terms enriched in one or two chains (see the behaviour in any ontology for the ChIP-chip and PPI datasets). We argue that the final partition from Consensus clustering is more consistent than any of the individual long chains, agreeing where the chains agree and providing sensible differences to any given chain. As the chains are not converged and there is no clear overlap, a full analysis would be difficult to defend using any one of these long chains.

ASIDE: I THINK I NEED A STATEMENT LIKE THIS, BUT FEEL IT IS A LITTLE HEAVY-HANDED

We believe that Consensus clustering does offer a solution to problems preventing the use of complex models such as MDI in their currently implemented forms, finding meaningful structure in a reproducible analysis.

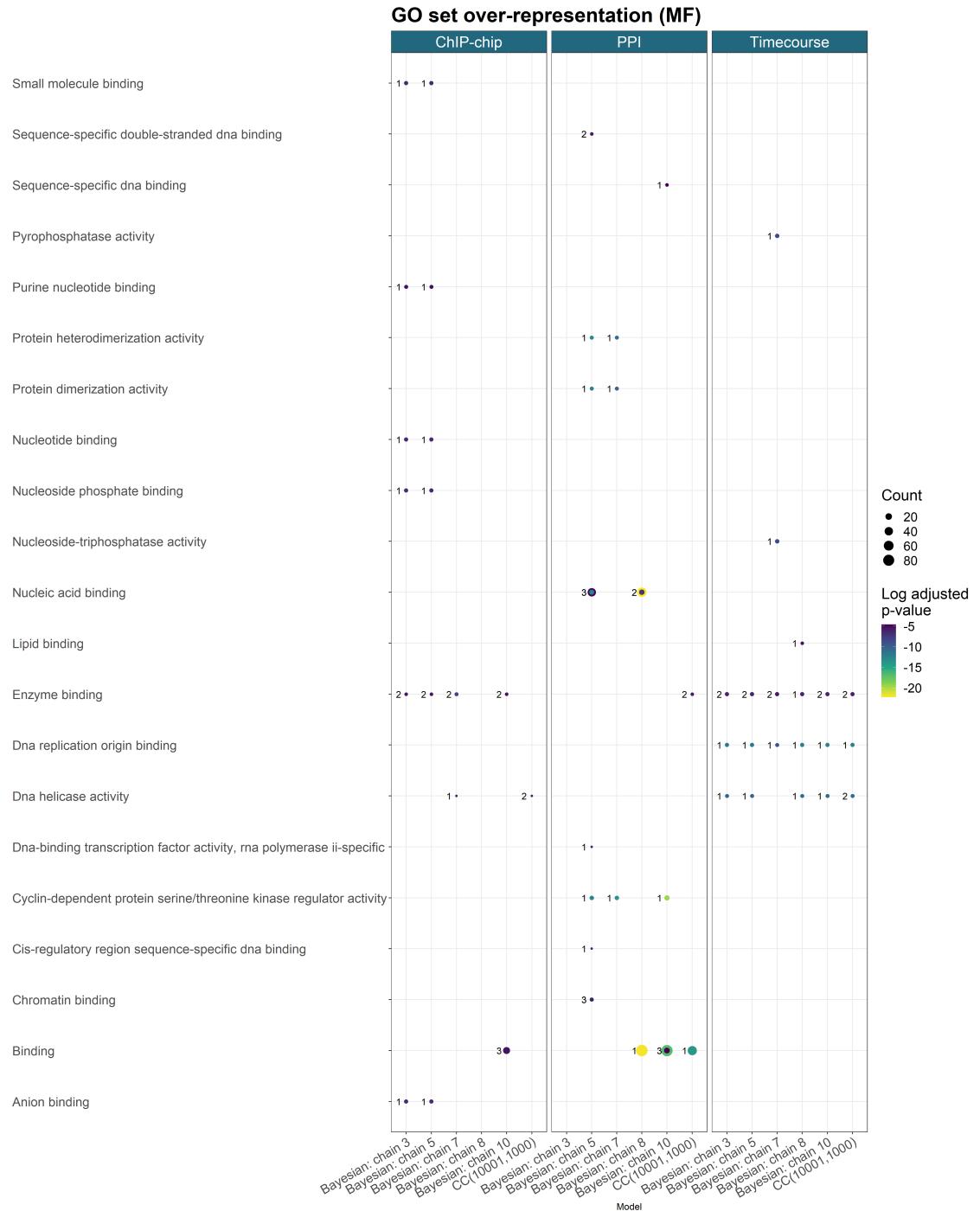


Figure 25: GO term over-representation for the Molecular function ontology for each dataset from the final clustering of each method.

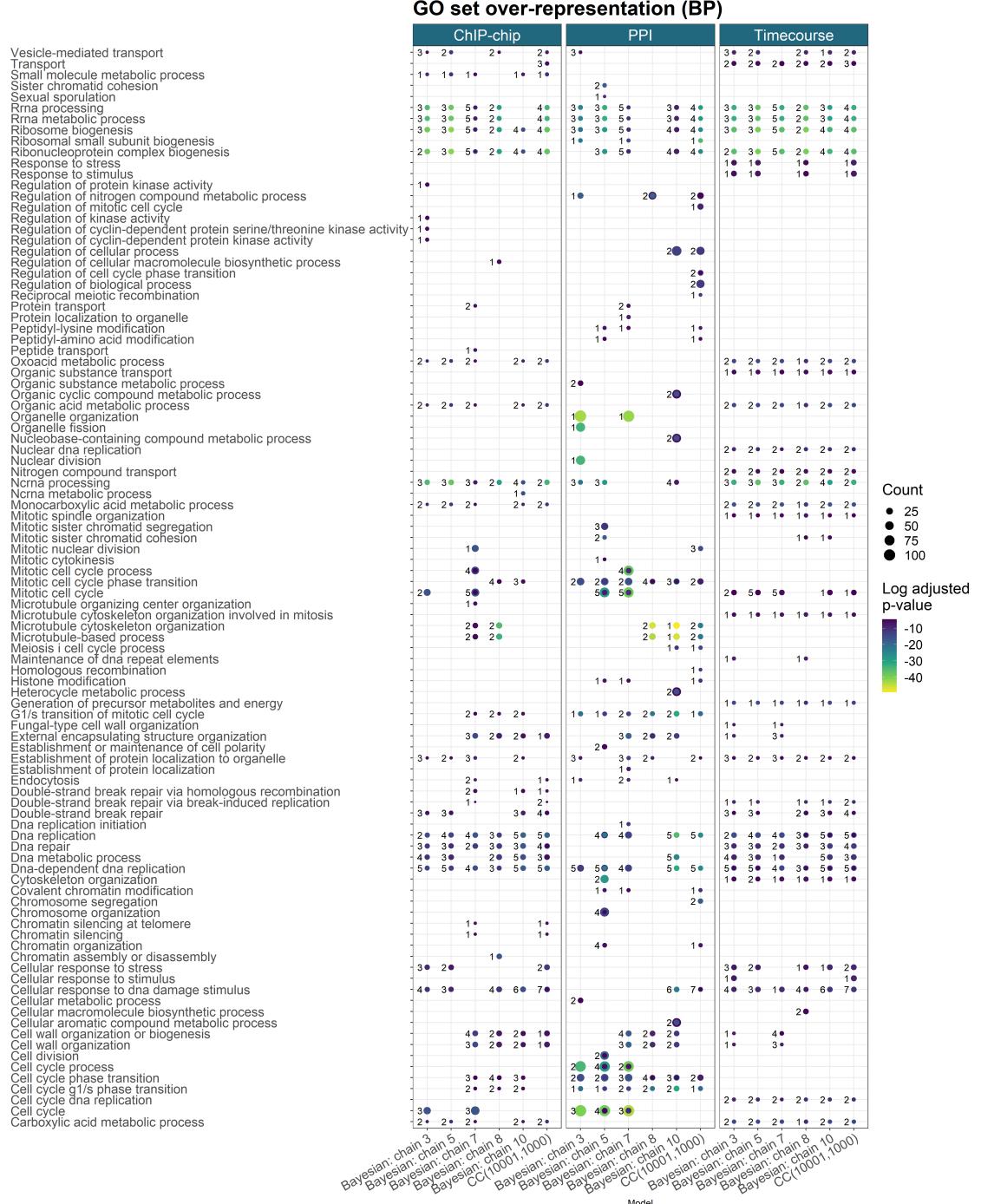


Figure 26: GO term over-representation for the Biological process ontology for each dataset from the final clustering of each method.

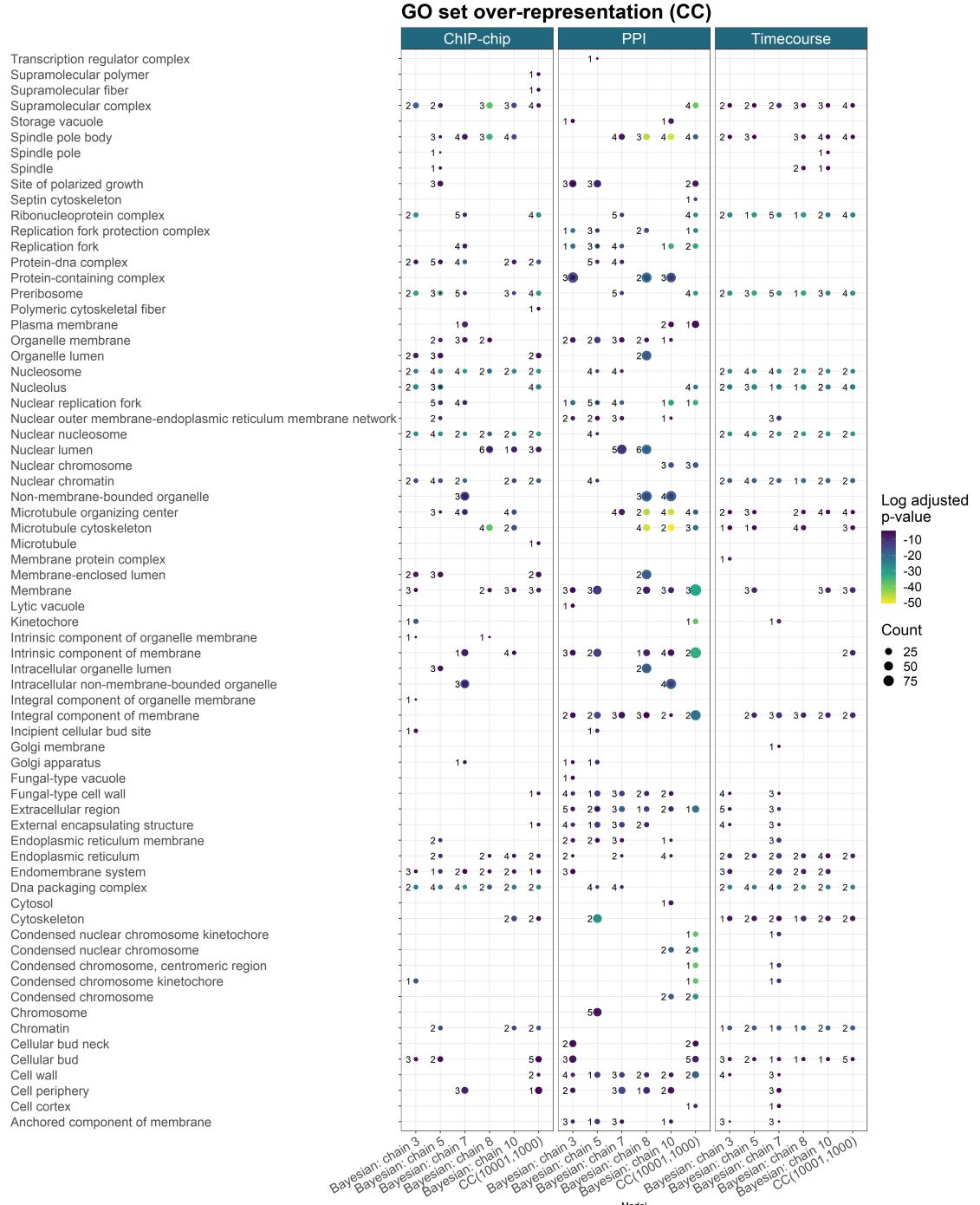


Figure 27: GO term over-representation for the Cellular component ontology for each dataset from the final clustering of each method.

References

- Bruce Alberts, Alexander Johnson, Julian Lewis, David Morgan, Martin Raff, and Dennis Bray James Watson Keith Roberts, Peter Walter. The cell cycle and programmed cell death. In Werner Dubitzky, Olaf Wolkenhauer, Kwang-Hyun Cho, and Hiroki Yokota, editors, *Molecular biology of the cell*, chapter 17. Garland Science, Taylor and Francis Group, New York, NY, 6 edition, 2018.
- Sofia Aligiani, Daniel H Lackner, Steffi Klier, Gabriella Rustici, Brian T Wilhelm, Samuel Marguerat, Sandra Codlin, Alvis Brazma, Robertus AM de Bruin, and Jürg Bähler. The fission yeast homeodomain protein yox1p binds to mbf and confines mbf-dependent cell-cycle transcription to g1-s via negative feedback. *PLoS Genet*, 5(8):e1000626, 2009.
- Yoav Benjamini and Yosef Hochberg. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological)*, 57(1):289–300, 1995.
- Linda L Breedon. Cyclin transcription: Timing is everything. *Current Biology*, 10(16):R586–R588, 2000.
- M Carlson, S Falcon, H Pages, and N Li. Org. sc. sgd. db: Genome wide annotation for yeast. *R package version*, 2(1), 2014.
- Katherine C Chen, Laurence Calzone, Attila Csikasz-Nagy, Frederick R Cross, Bela Novak, and John J Tyson. Integrative analysis of cell cycle control in budding yeast. *Molecular biology of the cell*, 15(8):3841–3862, 2004.
- Raymond J Cho, Michael J Campbell, Elizabeth A Winzeler, Lars Steinmetz, Andrew Conway, Lisa Wodicka, Tyra G Wolfsberg, Andrei E Gabrielian, David Landsman, David J Lockhart, et al. A genome-wide transcriptional analysis of the mitotic cell cycle. *Molecular cell*, 2(1):65–73, 1998.
- Rafal Ciosk, Wolfgang Zachariae, Christine Michaelis, Andrej Shevchenko, Matthias Mann, and Kim Nasmyth. An esp1/pds1 complex regulates loss of sister chromatid cohesion at the metaphase to anaphase transition in yeast. *Cell*, 93(6):1067–1076, 1998.
- RAM De Bruin, TI Kalashnikova, A Aslanian, J Wohlschlegel, C Chahwan, JR Yates, P Russell, and C Wittenberg. Dna replication checkpoint promotes g1-s transcription by inactivating the mbf repressor nrm1. *Proceedings of the National Academy of Sciences*, 105(32):11230–11235, 2008.
- Robertus AM de Bruin, Tatyana I Kalashnikova, Charly Chahwan, W Hayes McDonald, James Wohlschlegel, John Yates III, Paul Russell, and Curt Wittenberg. Constraining g1-specific transcription to late g1 phase: the mbf-associated corepressor nrm1 acts via negative feedback. *Molecular cell*, 23(4):483–496, 2006.

- Steffen Durinck, Paul T Spellman, Ewan Birney, and Wolfgang Huber. Mapping identifiers for the integration of genomic datasets with the r/bioconductor package biomart. *Nature protocols*, 4(8):1184, 2009.
- Yasin Şenbabaoğlu, George Michailidis, and Jun Z Li. A reassessment of consensus clustering for class discovery. *bioRxiv*, page 002642, 2014a.
- Yasin Şenbabaoğlu, George Michailidis, and Jun Z Li. Critical limitations of consensus clustering in class discovery. *Scientific reports*, 4(1):1–13, 2014b.
- ROSEMARY Foster, GLEN E Mikesell, and LINDA Breedon. Multiple swi6-dependent cis-acting elements control swi4 transcription through the cell cycle. *Molecular and cellular biology*, 13(6):3792–3801, 1993.
- Arno Fritsch. *mcclust: Process an MCMC Sample of Clusterings*, 2012. URL <https://CRAN.R-project.org/package=mcclust>. R package version 1.0.
- Arno Fritsch, Katja Ickstadt, et al. Improved criteria for clustering based on the posterior similarity matrix. *Bayesian analysis*, 4(2):367–391, 2009.
- Evelina Gabasova, John Reid, and Lorenz Wernisch. Clusternomics: Integrative context-dependent clustering for heterogeneous datasets. *PLoS computational biology*, 13(10):e1005781, 2017.
- Andrew Gelman, Donald B Rubin, et al. Inference from iterative simulation using multiple sequences. *Statistical science*, 7(4):457–472, 1992.
- Andrew Gelman, John B Carlin, Hal S Stern, David B Dunson, Aki Vehtari, and Donald B Rubin. *Bayesian data analysis*. CRC press, 2013.
- John Geweke et al. *Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments*, volume 196. Federal Reserve Bank of Minneapolis, Research Department Minneapolis, MN, 1991.
- Reza Ghaemi, Md Nasir Sulaiman, Hamidah Ibrahim, Norwati Mustapha, et al. A survey: clustering ensembles techniques. *World Academy of Science, Engineering and Technology*, 50:636–645, 2009.
- Reza Ghaemi, Nasir bin Sulaiman, Hamidah Ibrahim, and Norwati Mustapha. A review: accuracy optimization in clustering ensembles using genetic algorithms. *Artificial Intelligence Review*, 35(4):287–318, 2011.
- Marina V Granovskaia, Lars J Jensen, Matthew E Ritchie, Joern Toedling, Ye Ning, Peer Bork, Wolfgang Huber, and Lars M Steinmetz. High-resolution transcription atlas of the mitotic cell cycle in budding yeast. *Genome biology*, 11(3):1–11, 2010.
- Christopher T Harbison, D Benjamin Gordon, Tong Ihn Lee, Nicola J Rinaldi, Kenzie D Macisaac, Timothy W Danford, Nancy M Hannett, Jean-Bosco Tagne, David B Reynolds, Jane Yoo, et al. Transcriptional regulatory code of a eukaryotic genome. *Nature*, 431(7004):99–104, 2004.

- BP Ingalls, BP Duncker, DR Kim, and BJ McConkey. Systems level modeling of the cell cycle using budding yeast. *Cancer informatics*, 3: 117693510700300020, 2007.
- Vishwanath R Iyer, Christine E Horak, Charles S Scafe, David Botstein, Michael Snyder, and Patrick O Brown. Genomic binding sites of the yeast cell-cycle transcription factors sbf and mbf. *Nature*, 409(6819):533–538, 2001.
- Javier Jiménez, Samuel Bru, Mariana Ribeiro, and Josep Clotet. Live fast, die soon: cell cycle progression and lifespan in yeast cells. *Microbial Cell*, 2(3): 62, 2015.
- M Angeles Juanes. Methods of synchronization of yeast cells for the analysis of cell cycle progression. In *The Mitotic Exit Network*, pages 19–34. Springer, 2017.
- Paul Kirk, Jim E Griffin, Richard S Savage, Zoubin Ghahramani, and David L Wild. Bayesian correlated clustering to integrate multiple datasets. *Bioinformatics*, 28(24):3290–3297, 2012.
- Vladimir Yu Kiselev, Kristina Kirschner, Michael T Schaub, Tallulah Andrews, Andrew Yiu, Tamir Chandra, Kedar N Natarajan, Wolf Reik, Mauricio Barahona, Anthony R Green, et al. Sc3: consensus clustering of single-cell rna-seq data. *Nature methods*, 14(5):483–486, 2017.
- Christina Knudson and Dootika Vats. *stableGR: A Stable Gelman-Rubin Diagnostic for Markov Chain Monte Carlo*, 2020. URL <https://CRAN.R-project.org/package=stableGR>. R package version 1.0.
- Manfred Koranda, Alexander Schleiffer, Lukas Endler, and Gustav Ammerer. Forkhead-like transcription factors recruit ndd1 to the chromatin of g2/m-specific promoters. *Nature*, 406(6791):94–98, 2000.
- Raman Kumar, David M Reynolds, Andrej Shevchenko, Anna Shevchenko, Sherilyn D Goldstone, and Stephen Dalton. Forkhead transcription factors, fkh1p and fkh2p, collaborate with mcm1p to control transcription required for m-phase. *Current Biology*, 10(15):896–906, 2000.
- Brian D Lehmann, Joshua A Bauer, Xi Chen, Melinda E Sanders, A Bapsi Chakravarthy, Yu Shyr, Jennifer A Pietenpol, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *The Journal of clinical investigation*, 121(7):2750–2767, 2011.
- Samuel A Mason, Faiz Sayyid, Paul DW Kirk, Colin Starr, and David L Wild. Mdi-gpu: accelerating integrative modelling for genomic-scale data using gpu computing. *Statistical Applications in Genetics and Molecular Biology*, 15(1):83–86, 2016.

- Helen J McBride, Yixin Yu, and David J Stillman. Distinct regions of the swi5 and ace2 transcription factors are required for specific gene activation. *Journal of Biological Chemistry*, 274(30):21029–21036, 1999.
- Christopher J McInerny, Janet F Partridge, Glen E Mikesell, Davis P Creemer, and Linda L Breeden. A novel mcm1-dependent element in the swi4, cln3, cdc6, and cdc47 promoters activates m/g1-specific transcription. *Genes & development*, 11(10):1277–1288, 1997.
- Nicolai Meinshausen and Peter Bühlmann. Stability selection. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 72(4):417–473, 2010.
- Stefano Monti, Pablo Tamayo, Jill Mesirov, and Todd Golub. Consensus clustering: a resampling-based method for class discovery and visualization of gene expression microarray data. *Machine learning*, 52(1-2):91–118, 2003.
- Tata Pramila, Shawna Miles, Debraj GuhaThakurta, Dave Jemielo, and Linda L Breeden. Conserved homeodomain proteins interact with mads box protein mcm1 to restrict ecb-dependent transcription to the m/g1 phase of the cell cycle. *Genes & development*, 16(23):3034–3045, 2002.
- Richard S Savage, Zoubin Ghahramani, Jim E Griffin, Bernard J De la Cruz, and David L Wild. Discovering transcriptional modules by bayesian data integration. *Bioinformatics*, 26(12):i158–i167, 2010.
- Gideon Schwarz et al. Estimating the dimension of a model. *The annals of statistics*, 6(2):461–464, 1978.
- Samuel Sanford Shapiro and Martin B Wilk. An analysis of variance test for normality (complete samples). *Biometrika*, 52(3/4):591–611, 1965.
- Itamar Simon, John Barnett, Nancy Hannett, Christopher T Harbison, Nicola J Rinaldi, Thomas L Volkert, John J Wyrick, Julia Zeitlinger, David K Gifford, Tommi S Jaakkola, et al. Serial regulation of transcriptional regulators in the yeast cell cycle. *Cell*, 106(6):697–708, 2001.
- Paul T Spellman, Gavin Sherlock, Michael Q Zhang, Vishwanath R Iyer, Kirk Anders, Michael B Eisen, Patrick O Brown, David Botstein, and Bruce Futcher. Comprehensive identification of cell cycle-regulated genes of the yeast saccharomyces cerevisiae by microarray hybridization. *Molecular biology of the cell*, 9(12):3273–3297, 1998.
- Chris Stark, Bobby-Joe Breitkreutz, Teresa Reguly, Lorrie Boucher, Ashton Breitkreutz, and Mike Tyers. Biogrid: a general repository for interaction datasets. *Nucleic acids research*, 34(suppl.1):D535–D539, 2006.
- John J. Tyson, Katherine C. Chen, and Béla Novák. Cell cycle, budding yeast. In Werner Dubitzky, Olaf Wolkenhauer, Kwang-Hyun Cho, and Hiroki Yokota, editors, *Encyclopedia of Systems Biology*, pages 337–341. Springer New York, New York, NY, 2013.

- Dootika Vats and Christina Knudson. Revisiting the gelman-rubin diagnostic. *arXiv preprint arXiv:1812.09384*, 2018.
- Roel GW Verhaak, Katherine A Hoadley, Elizabeth Purdom, Victoria Wang, Yuan Qi, Matthew D Wilkerson, C Ryan Miller, Li Ding, Todd Golub, Jill P Mesirov, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in pdgfra, idh1, egfr, and nf1. *Cancer cell*, 17(1):98–110, 2010.
- Ulrike Von Luxburg and Shai Ben-David. Towards a statistical theory of clustering. In *Pascal workshop on statistics and optimization of clustering*, pages 20–26. Citeseer, 2005.
- Hong Wang, Dou Liu, Yanchang Wang, Jun Qin, and Stephen J Elledge. Pds1 phosphorylation in response to dna damage is essential for its dna damage checkpoint function. *Genes & development*, 15(11):1361–1372, 2001.
- Wilkerson, Matthew D., Hayes, and D. Neil. Consensusclusterplus: a class discovery tool with confidence assessments and item tracking. *Bioinformatics*, 26(12):1572–1573, 2010.
- Jun-Yu Xu, Chunchao Zhang, Xiang Wang, Linhui Zhai, Yiming Ma, Yousheng Mao, Kun Qian, Changqing Sun, Zhiwei Liu, Shangwen Jiang, et al. Integrative proteomic characterization of human lung adenocarcinoma. *Cell*, 182(1):245–261, 2020.
- Ayumu Yamamoto, Vincent Guacci, and Douglas Koshland. Pds1p, an inhibitor of anaphase in budding yeast, plays a critical role in the apc and checkpoint pathway (s). *The Journal of cell biology*, 133(1):99–110, 1996.
- Guangchuang Yu, Li-Gen Wang, Yanyan Han, and Qing-Yu He. clusterprofiler: an r package for comparing biological themes among gene clusters. *OMICS: A Journal of Integrative Biology*, 16(5):284–287, 2012. doi: 10.1089/omi.2011.0118.
- Gefeng Zhu, Paul T Spellman, Tom Volpe, Patrick O Brown, David Botstein, Trisha N Davis, and Bruce Futcher. Two yeast forkhead genes regulate the cell cycle and pseudohyphal growth. *Nature*, 406(6791):90–94, 2000.