Different Alternative Types

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Abstract

I compare SUCCOTASH to various competitors under the same alternative scenarios in Stephens (2016). SUCCOTASH generally has superior performance in terms of (1) estimating π_0, (2) having higher AUC, and (3) having lower MSE. LEAPP does better under some scenarios in terms of estimating π_0 but has far worse AUC and MSE. SUCCOTASH accurately estimates the average sign error rate, though not in as conservative manner as one might hope in some scenarios. I also look at limma-shrinking the variances in RUVASH. It doesn't change the results too much. It seems to just make the estimates of π_0 slightly more conservative.

Simulation Setup

I ran through 200 repetitions of generating data from GTEX muscle data under the following parameter conditions:

- $n \in \{10, 20, 40\}$,
- $p = 1000$.
- $\pi_0 \in \{0.5, 0.9\}$,
- The alternative distribution being either spiky, near-normal, flattop, skew, big-normal, or bimodal, where these are the same alternatives defined in Stephens (2016) and the following table. New alternatives are generated every iteration.

Scenario	Alternative Distribution
Spiky	$0.4N(0, 0.25^2) + 0.2N(0, 0.5^2) + 0.2N(0, 1^2), 0.2N(0, 2^2)$
Near Normal	$2/3N(0, 1^2) + 1/3N(0, 2^2)$
Flattop	$(1/7)N(-1.5, .5^2) + N(-1, .5^2) + N(-.5, .5^2) + N(0, .5^2) + N(0.5, .5^2) + N(1.0, .5^2) + N(1.5, .5^2)$
Skew	$(1/4)N(-2, 2^2) + (1/4)N(-1, 1.5^2) + (1/3)N(0, 1^2) + (1/6)N(1, 1^2)$
Big-normal	$N(0, 4^2)$
Bimodal	$0.5N(-2, 1^2) + 0.5N(2, 1^2)$

I extracted the most expressed p genes from the GTEX muscle data and n samples are chosen at random. Half of these samples are randomly given the "treatment" label 1, the other half given the "control" label 0. Of the p genes, $\pi_0 p$ were chosen to be non-null. Signal was added by a Poisson-thinning approach, where the log-2 fold change was sampled from one of five the alternative models above. That is

$$A_1, \ldots, A_{p/2} \sim f \tag{1}$$

$$B_i = 2^{A_i} \text{ for } i = 1, \ldots, p/2, \tag{2}$$

where f is from the table above. If $A_i > 0$ then we replace $Y_{[1:(n/2),i]}$ with $Binom(Y_{[j,i]}, 1/B_i)$ for $j = 1, \ldots, n/2$. If $A_i < 0$ then we replace $Y_{[(n/2+1):n,i]}$ with $Binom(Y_{[j,i]}, B_i)$ for $j = n/2 + 1, \ldots, n$.

I now describe the justification for this. Suppose that

$$Y_{ij} \sim Poisson(\lambda_j). \tag{3}$$

Let x_i be the indicator of treatment vs control for individual i. Let Ω be the set of non-null genes. Let Z be the new dataset derived via the steps above. That is

$$Z_{ij}|Y_{ij} = \begin{cases} Binom(Y_{ij}, 2^{A_j x_i}) & \text{if } A_j < 0 \text{ and } j \in \Omega \\ Binom(Y_{ij}, 2^{-A_j(1-x_i)}) & \text{if } A_j > 0 \text{ and } j \in \Omega \\ Y_{ij} & \text{if } j \notin \Omega. \end{cases} \tag{4}$$

Then

$$Z_{ij}|A_j, A_j < 0, j \in \Omega \sim Poisson(2^{A_j x_i}\lambda_j) \tag{5}$$
$$Z_{ij}|A_j, A_j > 0, j \in \Omega \sim Poisson(2^{-A_j(1-x_i)}\lambda_j), \tag{6}$$

and

$$E[\log_2(Z_{ij}) - \log_2(Z_{kj})|A_j, A_j < 0, j \in \Omega] \approx A_j x_i - A_j x_k, \text{ and} \tag{7}$$
$$E[\log_2(Z_{ij}) - \log_2(Z_{kj})|A_j, A_j > 0, j \in \Omega] \approx -A_j(1 - x_i) + A_j(1 - x_k). \tag{8}$$

if individual i is in the treatment group and individual k is in the control group, then this just equals A_j. I treat the A_j's as the true coefficient values when calculating the MSE below.

Methods

I first normalized the counts by $\log_2(COUNTS + 1)$. The number of hidden confounders was estimated using the methods of Buja and Eyuboglu (1992) implemented in the `num.sv()` function in the `sva` package in `R`.

The confounder adjustment methods I look at in this write-up are:

- OLS + qvalue.
- RUVols + estimate variance inflation using controls + ASH
- RUVgls + estimate variance inflation using controls + ASH
- RUVgls + estimate variance inflation using controls + MLE to UMVUE motivated scaling + ASH
- RUVgls + limma shrink variances + estimate variance inflation using conrols + MLE to UMVUE motivated scaling + ASH
- SUCCOTASH using normal mixtures and heteroscedastic PCA as the factor-analysis method.
- The robust regression version of CATE using PCA as the factor analysis method + qvalue.
- SVA + qvalue.
- Negative control version of CATE using PCA as the factor analysis method + qvalue.
- RUV2 + qvalue.
- RUV4 + qvalue.
- Sparse version of LEAPP. Since this is a sparsity-inducing procedure, I used the proportion of zeros as the estimate of π_0.
- Ridge version of LEAPP + qvalue.

RUVASH

The model for the second step in RUV4, LEAPP, CATE, and SUCCOTASH is

$$
\begin{aligned}
&Y = \beta_{p\times 1} + \hat{\alpha}_{p\times q} Z_{q\times 1} + E_{p\times 1} && (9)\\
&E \sim N_p(0, \lambda\hat{\Sigma}) && (10)\\
&\hat{\Sigma} = diag(\hat{\sigma}_1^2, \ldots, \hat{\sigma}_p^2), && (11)
\end{aligned}
$$

with $\hat{\Sigma}$ and $\hat{\alpha}$ known. λ is a variance inflation parameter that is novel to SUCCOTASH.

Let $\mathcal{C} \subseteq \{1, \ldots, p\}$ denote the indices for the negative controls. I.e. $\beta_{\mathcal{C}} = 0$. Then the model for the negative controls is

$$
Y_{\mathcal{C}} = \alpha_{\mathcal{C}} Z + E_{\mathcal{C}}. \tag{12}
$$

The maximum likelihood estimates of Z and λ are easy:

$$
\hat{Z} = (\alpha_{\mathcal{C}}^T \hat{\Sigma}^{-1} \alpha_{\mathcal{C}})^{-1} \alpha_{\mathcal{C}}^T \hat{\Sigma}^{-1} Y_{\mathcal{C}}. \tag{13}
$$

Let $R_{\mathcal{C}} = Y_{\mathcal{C}} - \hat{\alpha}_{\mathcal{C}} \hat{Z}$. Then the MLE of λ is

$$
\hat{\lambda} = \frac{1}{|\mathcal{C}|} \sum_{i \in \mathcal{C}} R_i^2 / \hat{\sigma}_i^2. \tag{14}
$$

RUVASH runs ASH with means $\hat{\beta} = Y - \hat{\alpha}\hat{Z}$ and variances $\hat{\lambda}\hat{\sigma}_i^2$.

In the same way that I made an ad-hoc correction to the SUCCOTASH variance inflation parameter, I also explore using this for RUVASH. Specifically, I set

$$
\tilde{\lambda} = \frac{n}{n - k - q} \hat{\lambda} \tag{15}
$$

and run ASH with variances $\tilde{\lambda}\hat{\sigma}_i^2$. These are called SRUVASH in the plots below.

Results

Note that in the plots below, n refers to the size of each group, not the total size.

Estimates of π_0

- RUV + ASH Works much better here than vanilla ASH at estimating π_0, but it is slightly anti-conservative.
- RUV + ad-hoc scaling + ASH has conservative FDR with high probability in almost every scenario. The only one where it isn't conservative is the Bimodal alternative scenario.

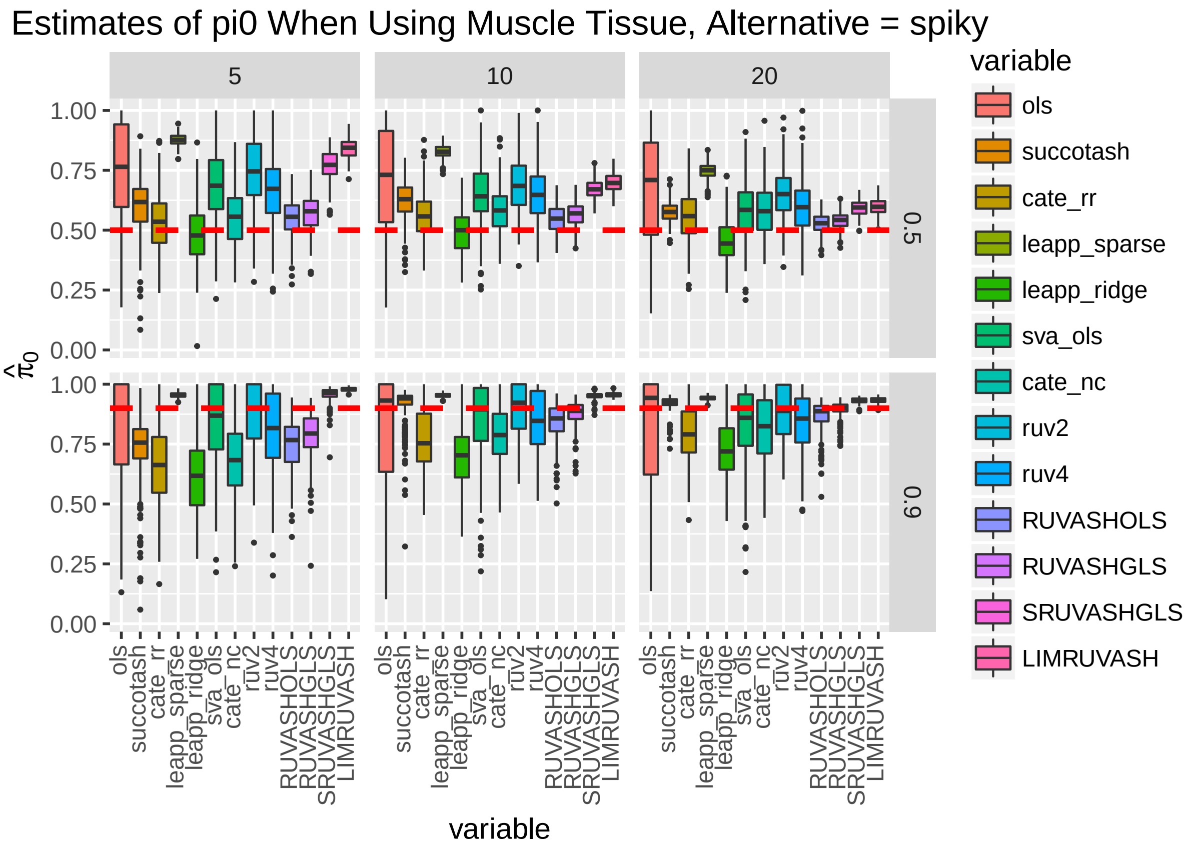
- SUCCOTASH has slightly anti-conservative estimates of π_0 in the Flattop and bimodal Scenarios. It does well for every other scenario for larger n.
- LEAPP does amazingly well in the Big-normal and bimodal scenarios, even for $n = 10$. However, it is far too conservative in every other non-null scenario. This seems to indicate that LEAPP functions best if there is a separation of the alternative signal from zero.
- No method using qvalue ever performed as well as succotash. Indeed, none exhibited this “conservative with high-probability” behavior that is desirable.
- Limma-shrinking the variances results in slightly more conservative estimates of π_0.

AUC performance.

- SUCCOTASH always has higher AUC, even in the bimodal and big-normal scenarios where LEAPP estimated π_0 more accurately.
- All of the RUV + ASH methods have about the same AUC as SUCCOTASH — including the one with the ad-hoc scaling value that works so well with estimating π_0.

MSE

- SUCCOTASH has superior performance in term of MSE compared to other methods.
- LEAPP has terrible MSE performance in all cases except the all-null setting.
- Even then, SUCCOTASH has better performance.
- RUV + ASH has pretty good MSE performance.
- The ad-hoc scaling version of RUV + ASH seems to suffer in MSE a little bit, especially at low sample sizes.


Estimates of pi0 When Using Muscle Tissue, Alternative = spiky
5
10
20
0.5
0.9
$\hat{\pi}_0$
1.00
0.75
0.50
0.25
0.00
ols
succotash
cate_rr
leapp_sparse
leapp_ridge
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH
variable
variable
ols
succotash
cate_rr
leapp_sparse
leapp_ridge
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ruv4
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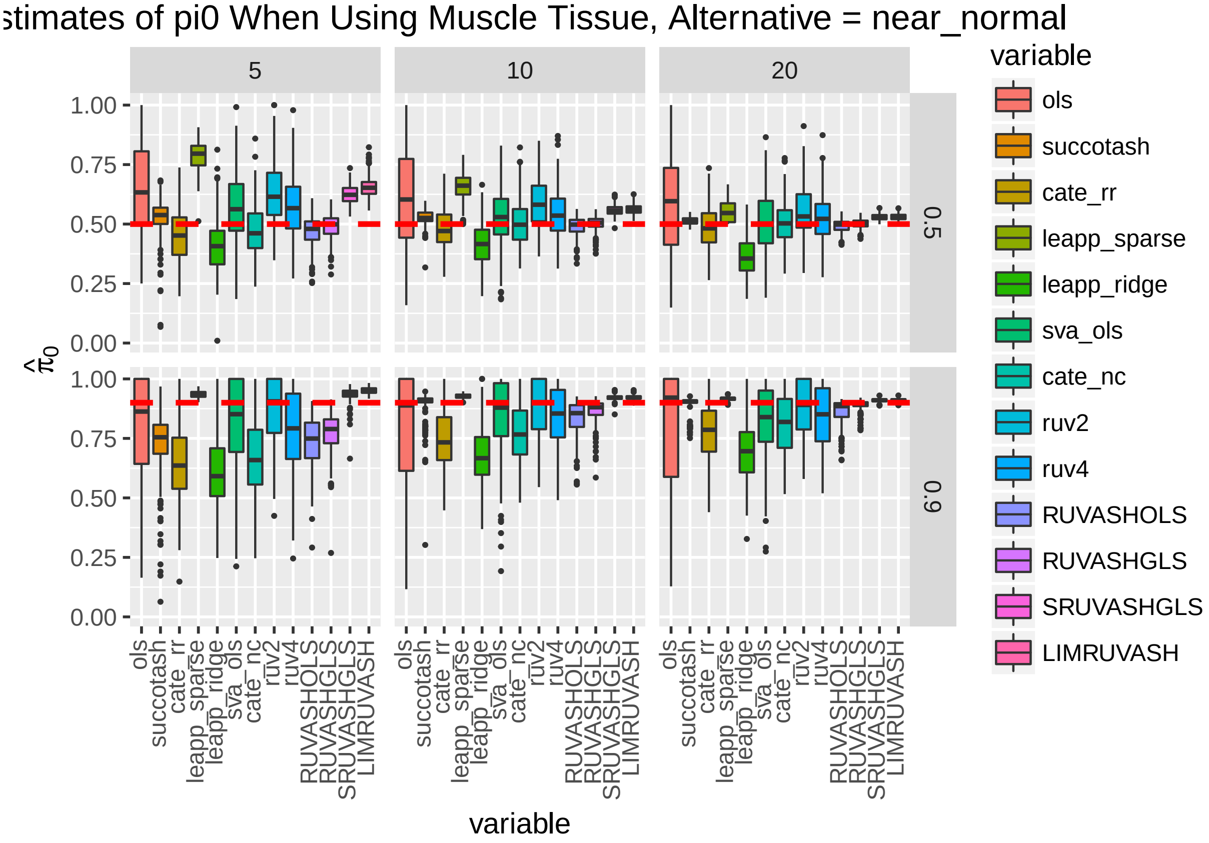
RUVASHGLS
SRUVASHGLS
LIMRUVASH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10
20
0.5
0.9
$\hat{\pi}_0$
1.00
0.75
0.50
0.25
0.00
ols
succotash
cate_rr
leapp_sparse
leapp_ridge
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH
variable
variable
ols
succotash
cate_rr
leapp_sparse
leapp_ridge
sva_ols
cate_nc
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ruv4
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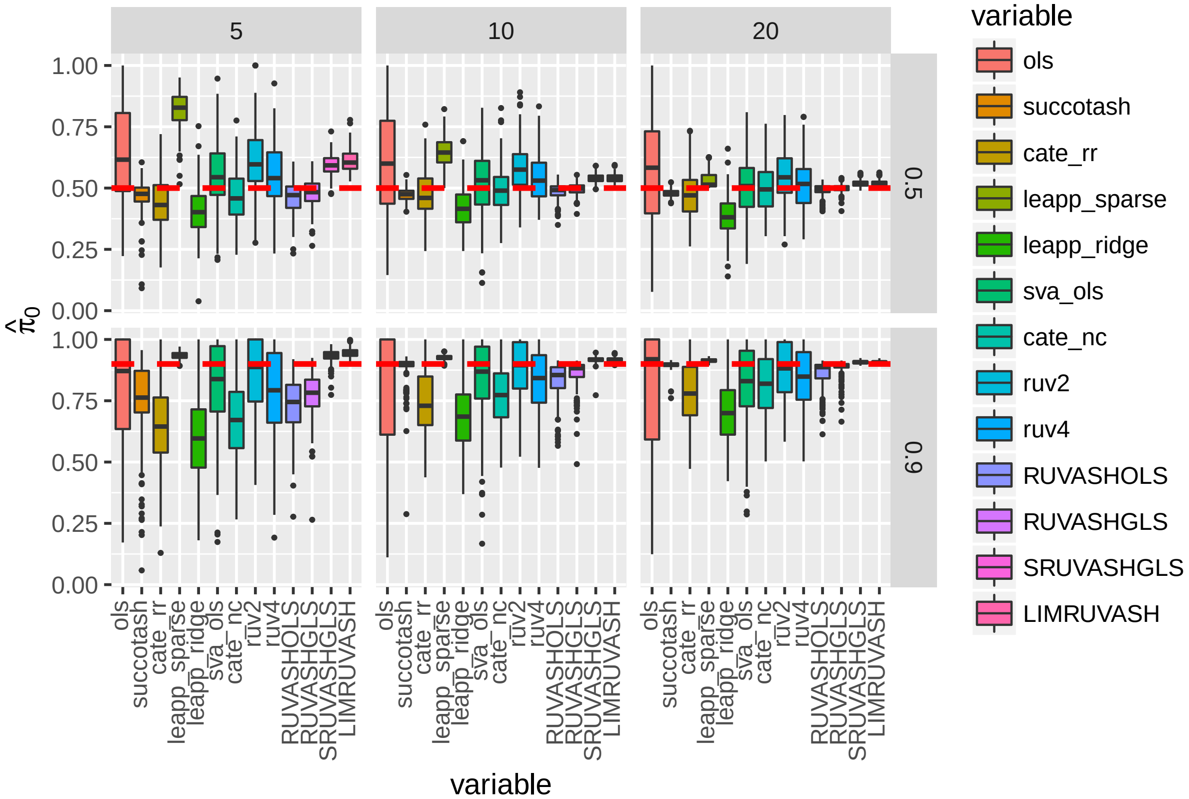
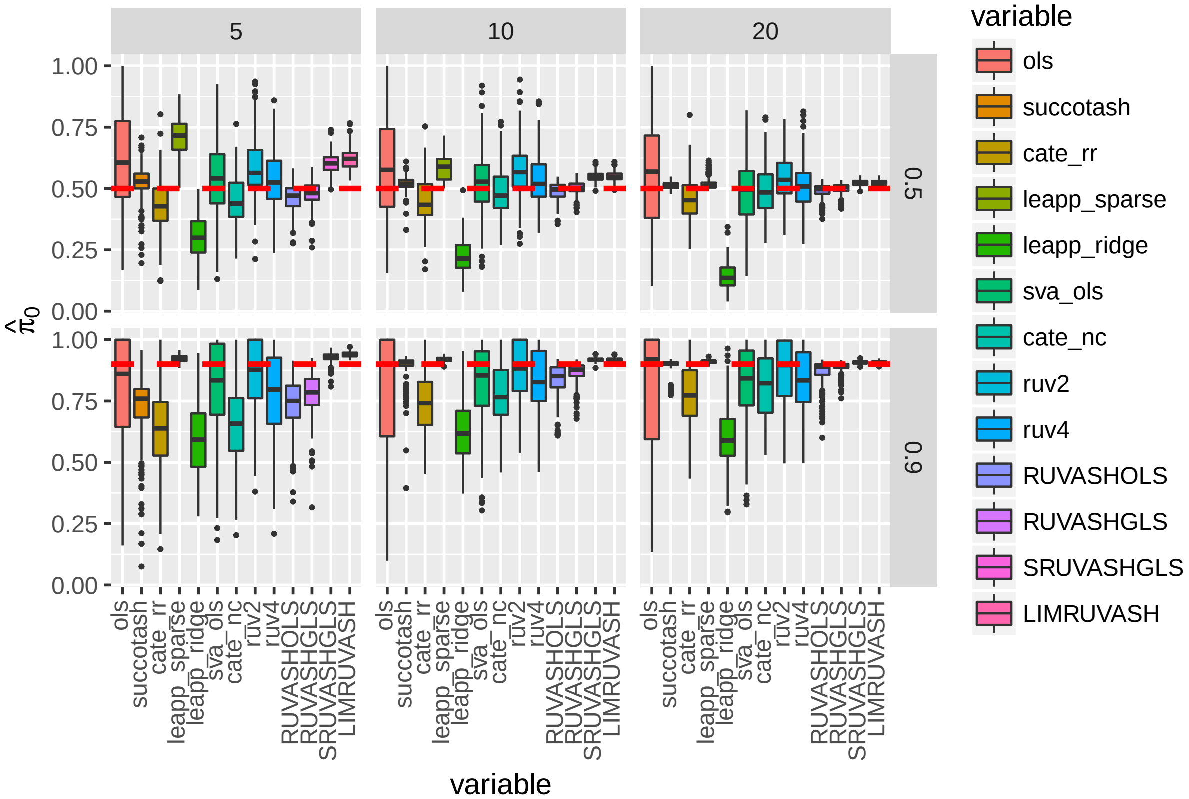
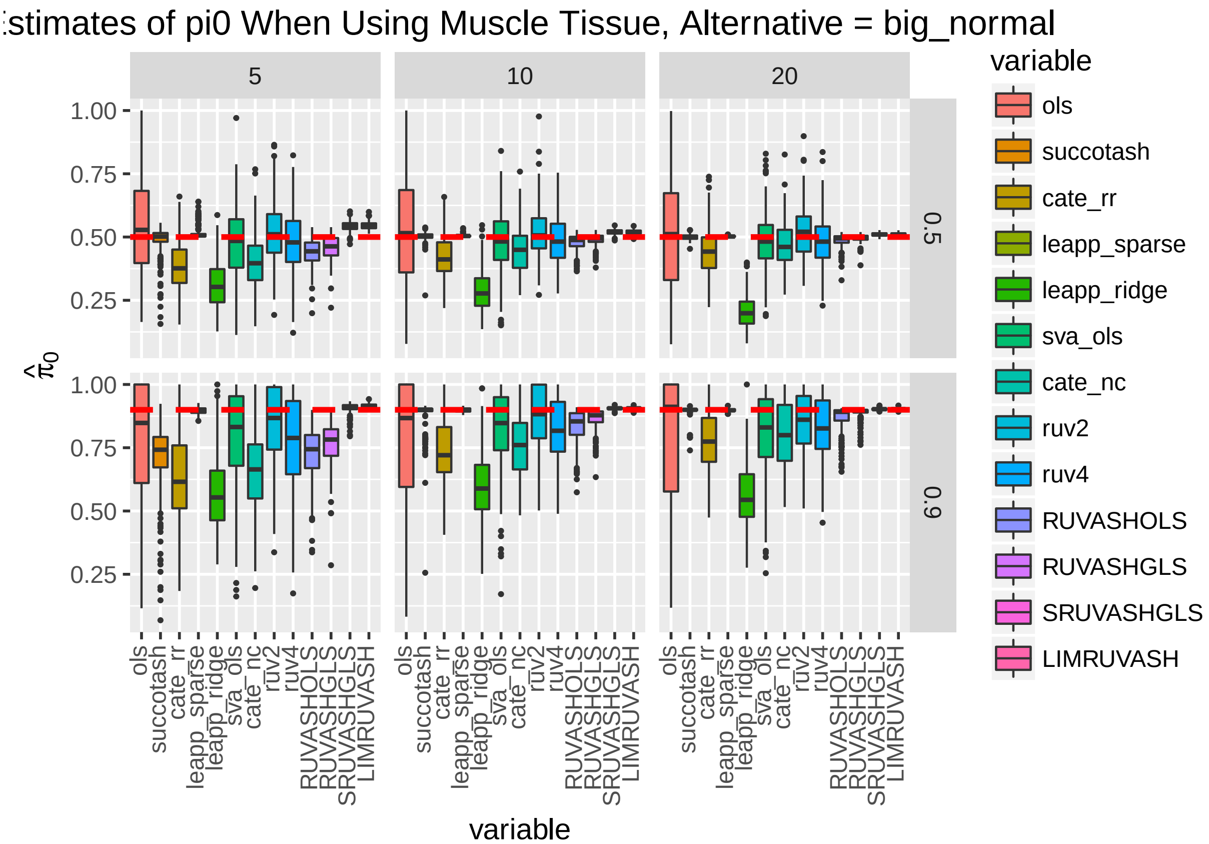
RUVASHGLS
SRUVASHGLS
LIMRUVASH

Estimates of pi0 When Using Muscle Tissue, Alternative = flattop



Estimates of pi0 When Using Muscle Tissue, Alternative = skew




stimates of pi0 When Using Muscle Tissue, Alternative = big_normal
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0.75
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variable
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succotash
cate_rr
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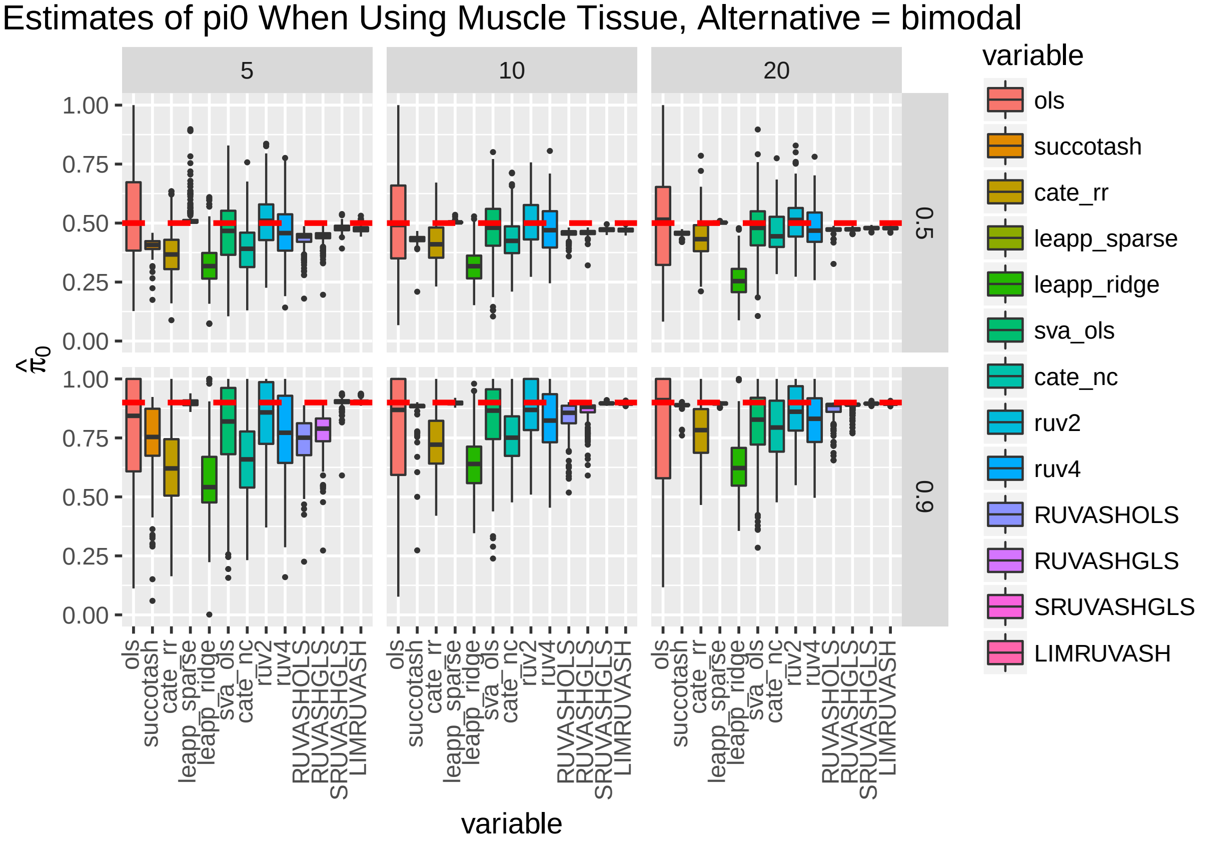
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH


Estimates of pi0 When Using Muscle Tissue, Alternative = bimodal
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10
20
0.5
0.9
$\hat{\pi}_0$
1.00
0.75
0.50
0.25
0.00
variable
ols
succotash
cate_rr
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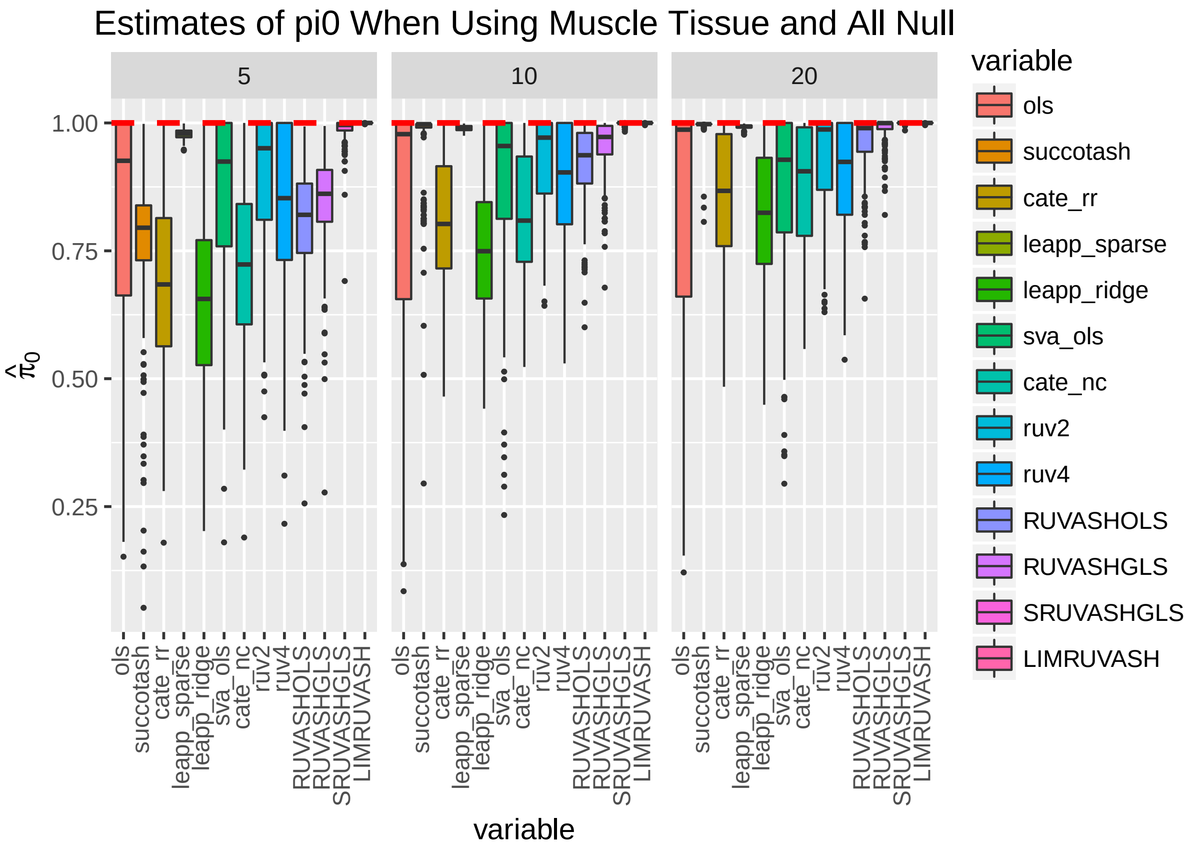
RUVASHGLS
SRUVASHGLS
LIMRUVASH


Estimates of pi0 When Using Muscle Tissue and All Null
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20
1.00
0.75
0.50
0.25
$\hat{\pi}_0$
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cate_rr
leapp_sparse
leapp_ridge
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH
variable
variable
ols
succotash
cate_rr
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leapp_ridge
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cate_nc
ruv2
ruv4
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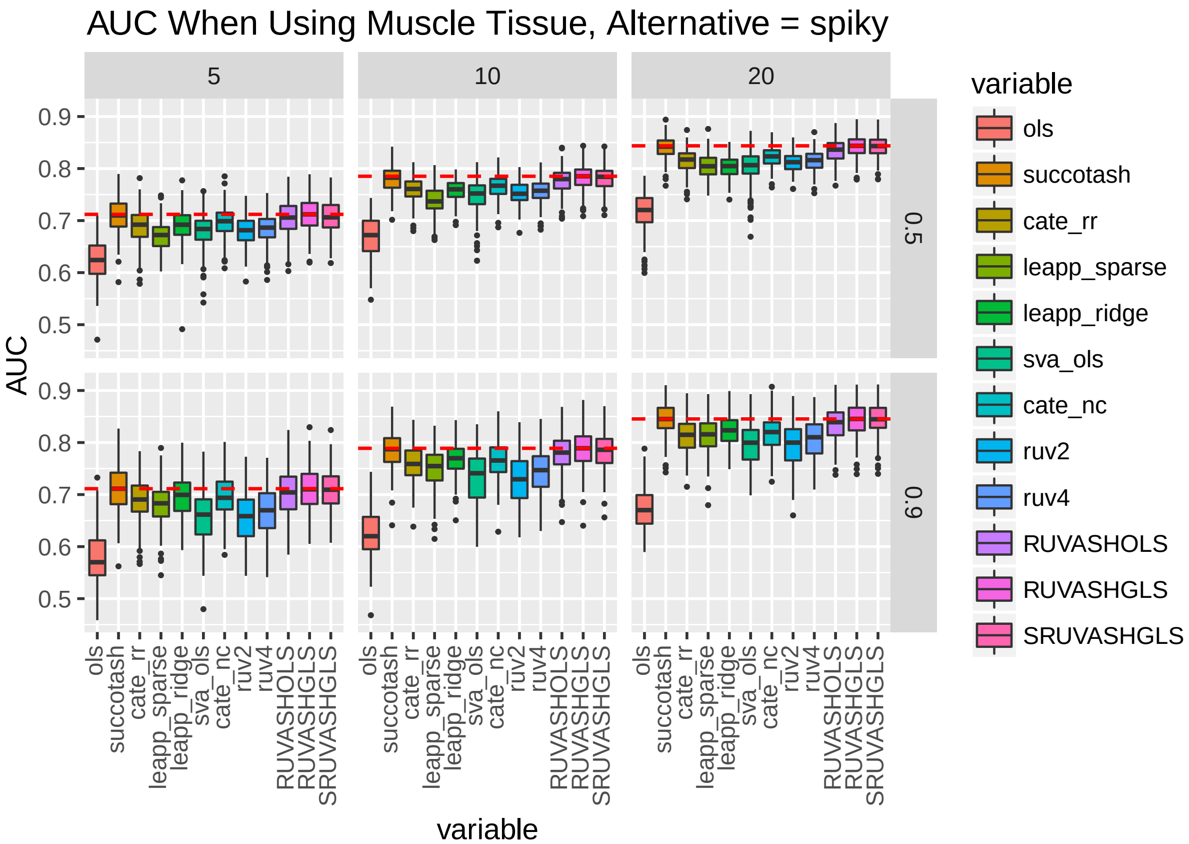
RUVASHGLS
SRUVASHGLS
LIMRUVASH


AUC When Using Muscle Tissue, Alternative = spiky
5
10
20
0.5
0.9
AUC
0.5
0.6
0.7
0.8
0.9
ols
succotash
cate_rr
leapp_sparse
leapp_ridge
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
variable
variable
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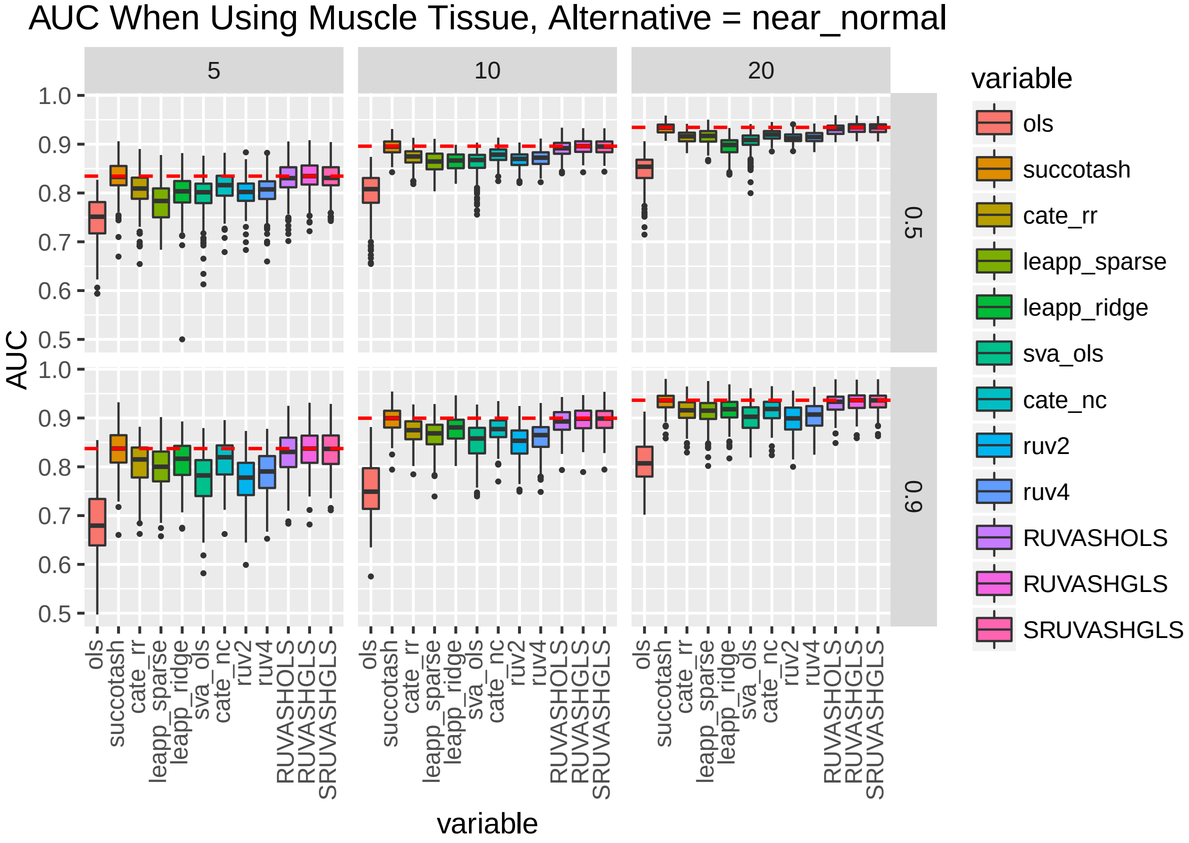
SRUVASHGLS


AUC When Using Muscle Tissue, Alternative = near_normal
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0.5
0.9
AUC
0.5
0.6
0.7
0.8
0.9
1.0
ols
succotash
cate_rr
leapp_sparse
leapp_ridge
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
variable
variable
ols
succotash
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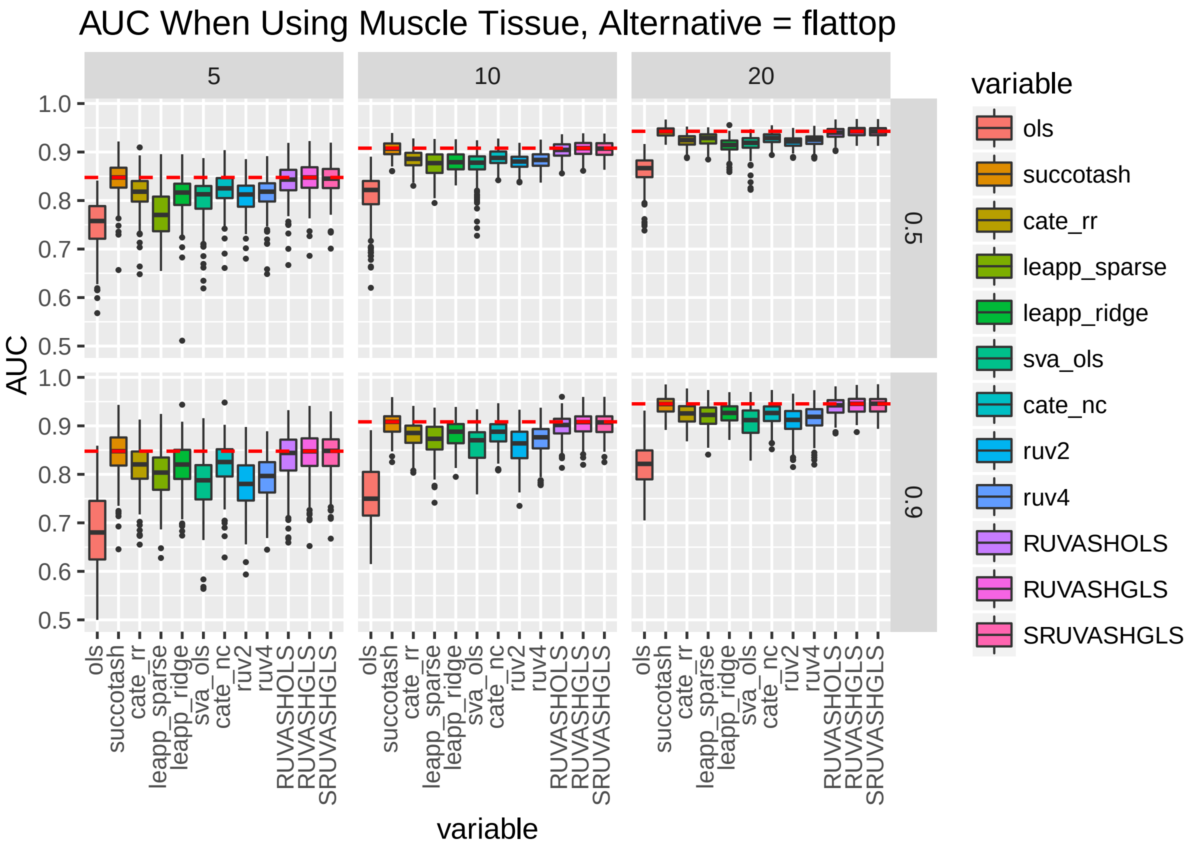
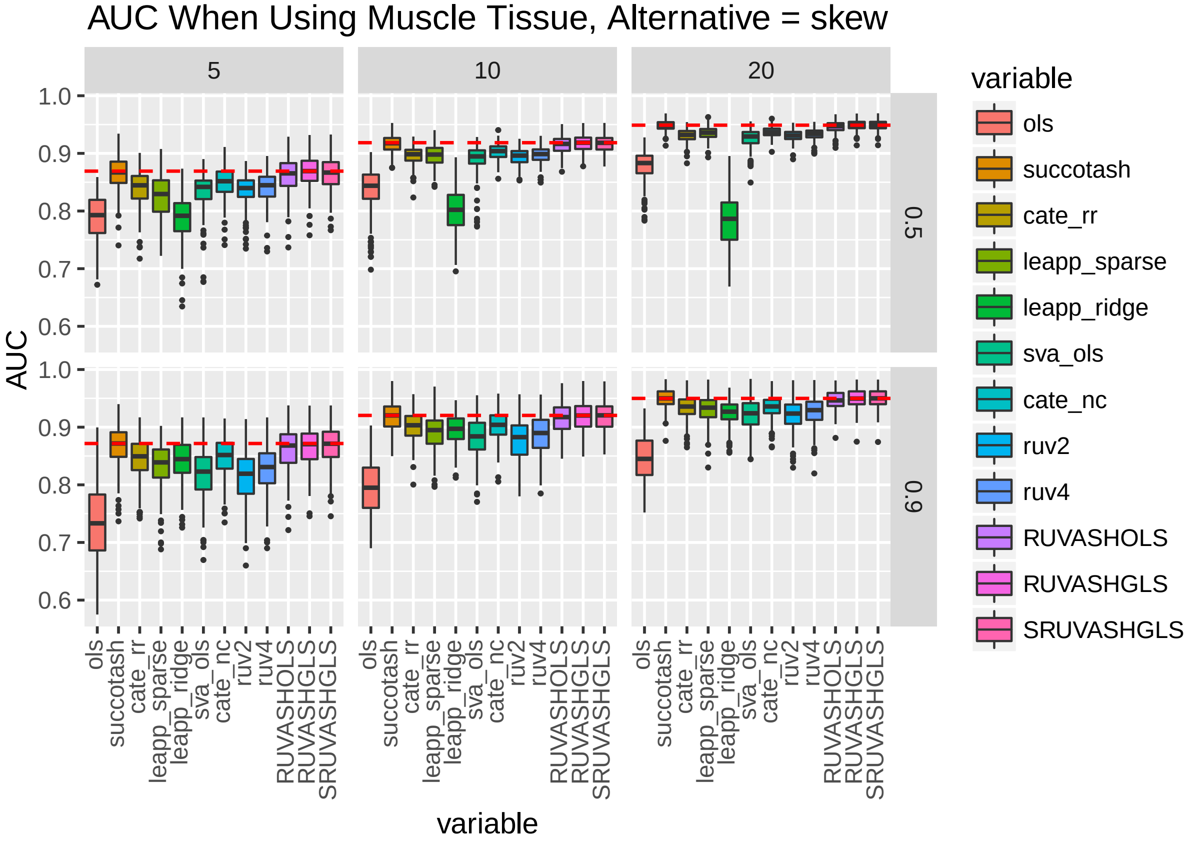
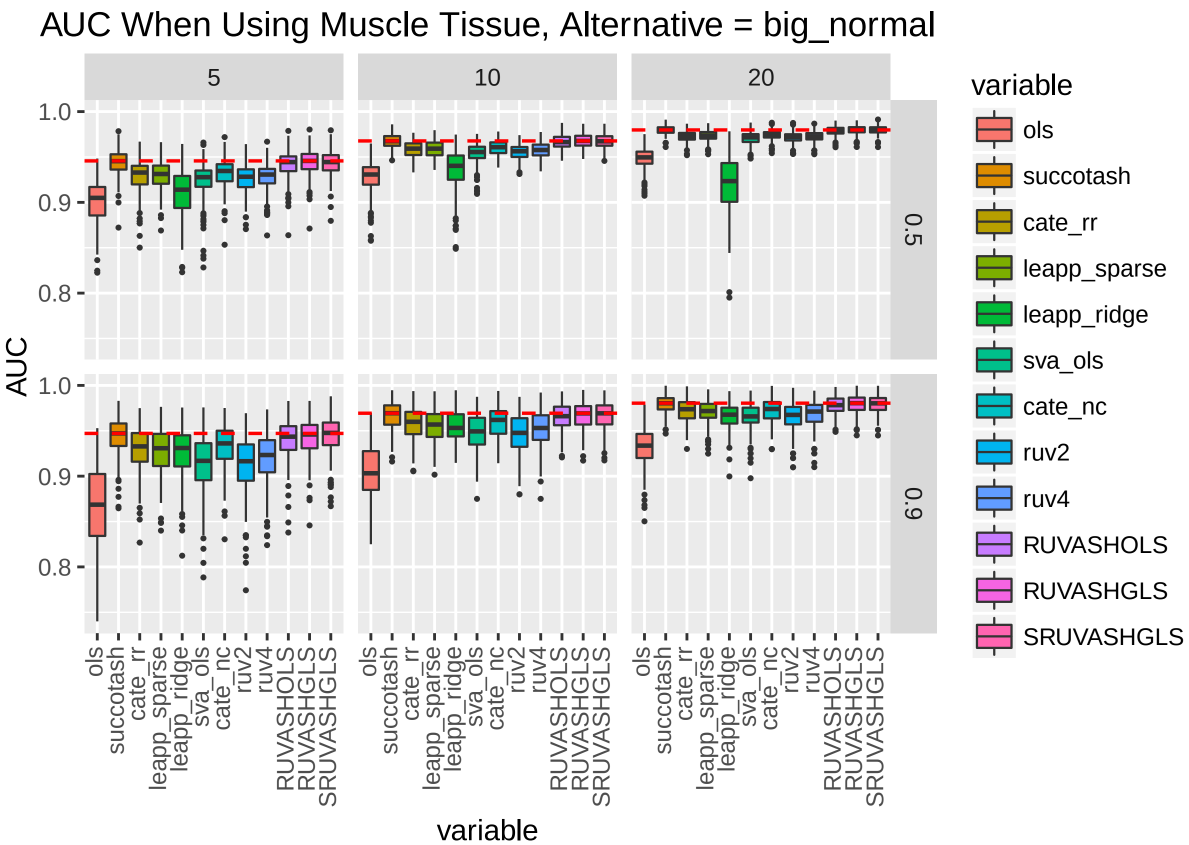
SRUVASHGLS


AUC When Using Muscle Tissue, Alternative = flattop


AUC When Using Muscle Tissue, Alternative = skew


AUC When Using Muscle Tissue, Alternative = big_normal
5
10
20
0.5
0.9
AUC
1.0
0.9
0.8
variable
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ruv4
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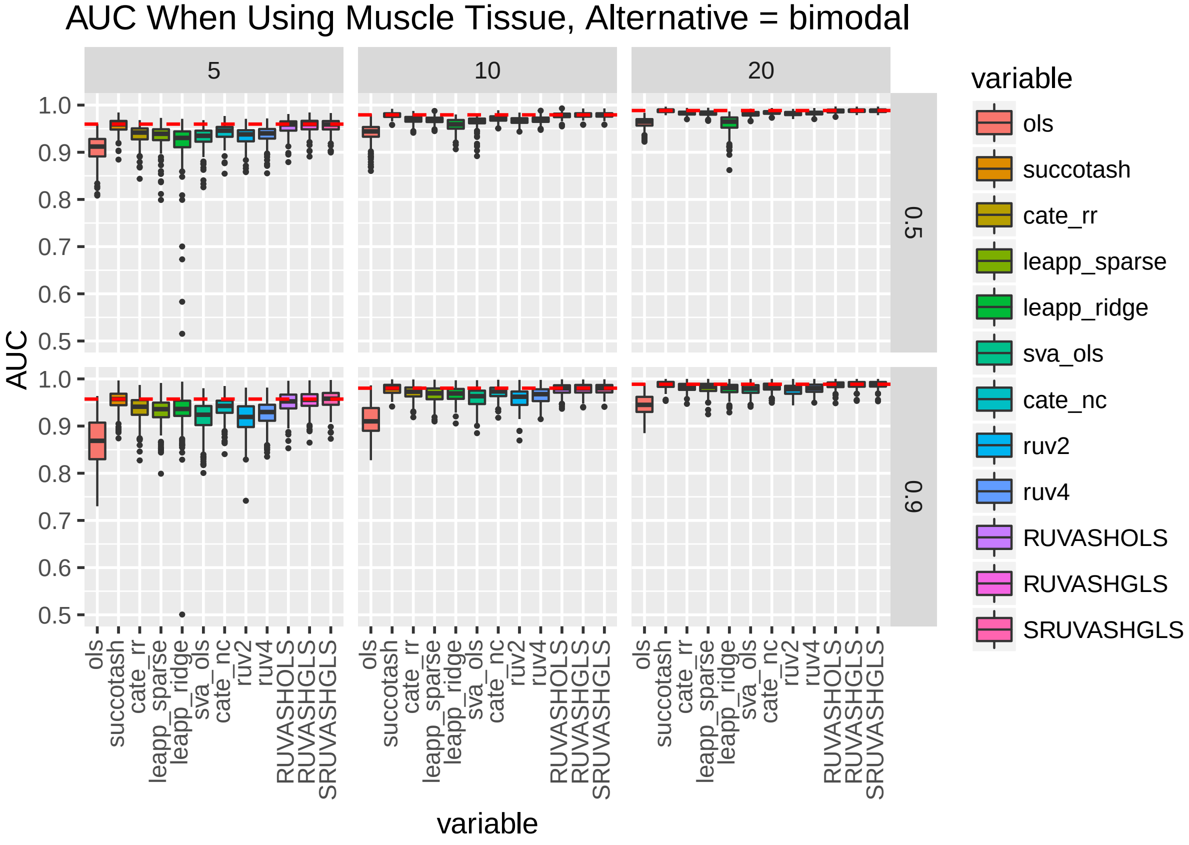
AUC When Using Muscle Tissue, Alternative = bimodal
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20
0.5
0.9
AUC
1.0
0.9
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0.7
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0.5
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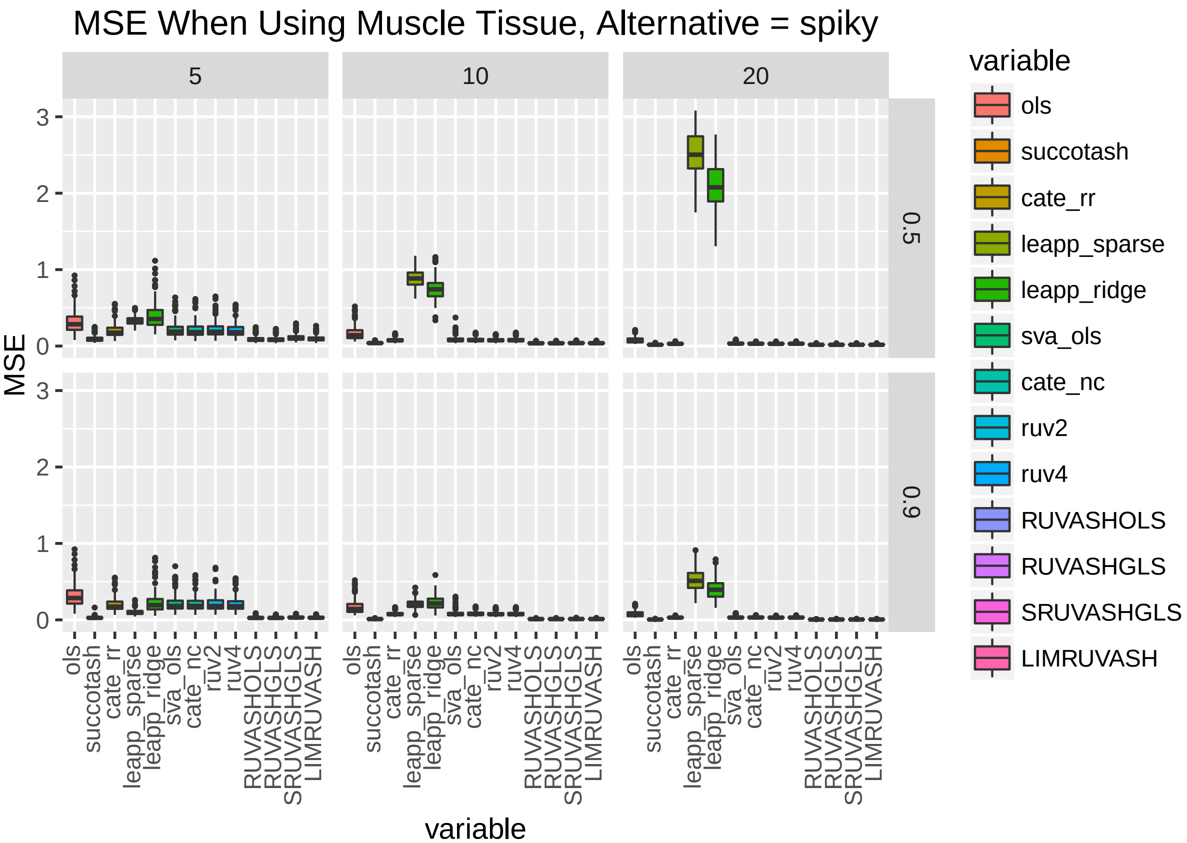
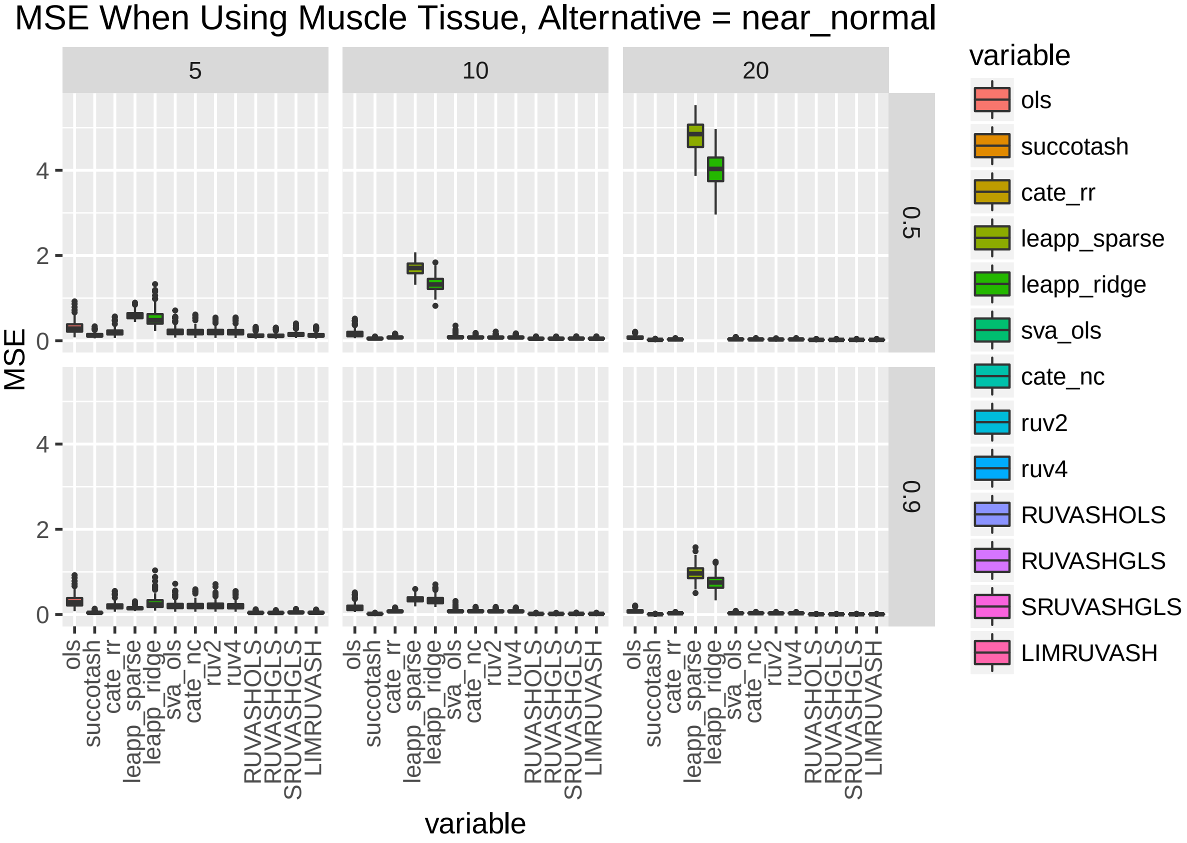
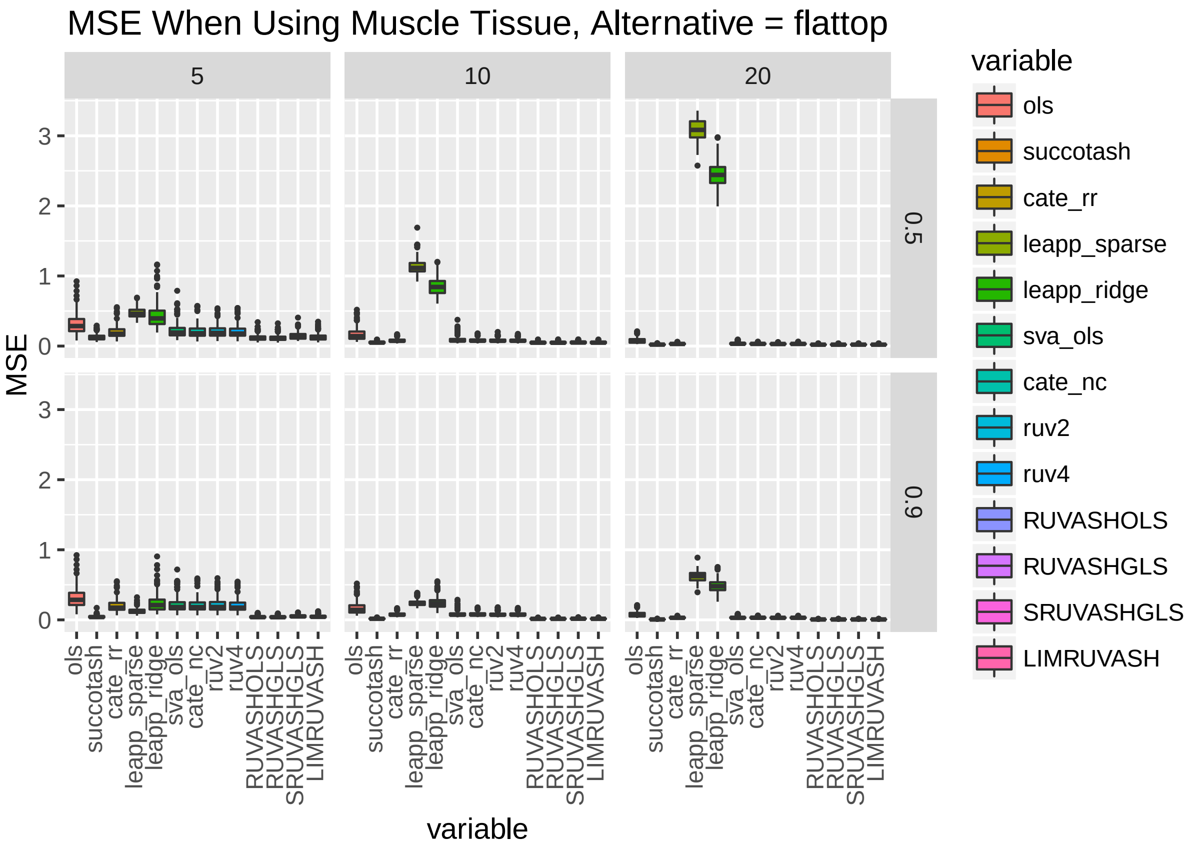

MSE When Using Muscle Tissue, Alternative = spiky


MSE When Using Muscle Tissue, Alternative = near_normal


MSE When Using Muscle Tissue, Alternative = flattop
5
10
20
0.5
0.9
MSE
0
1
2
3
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cate_rr
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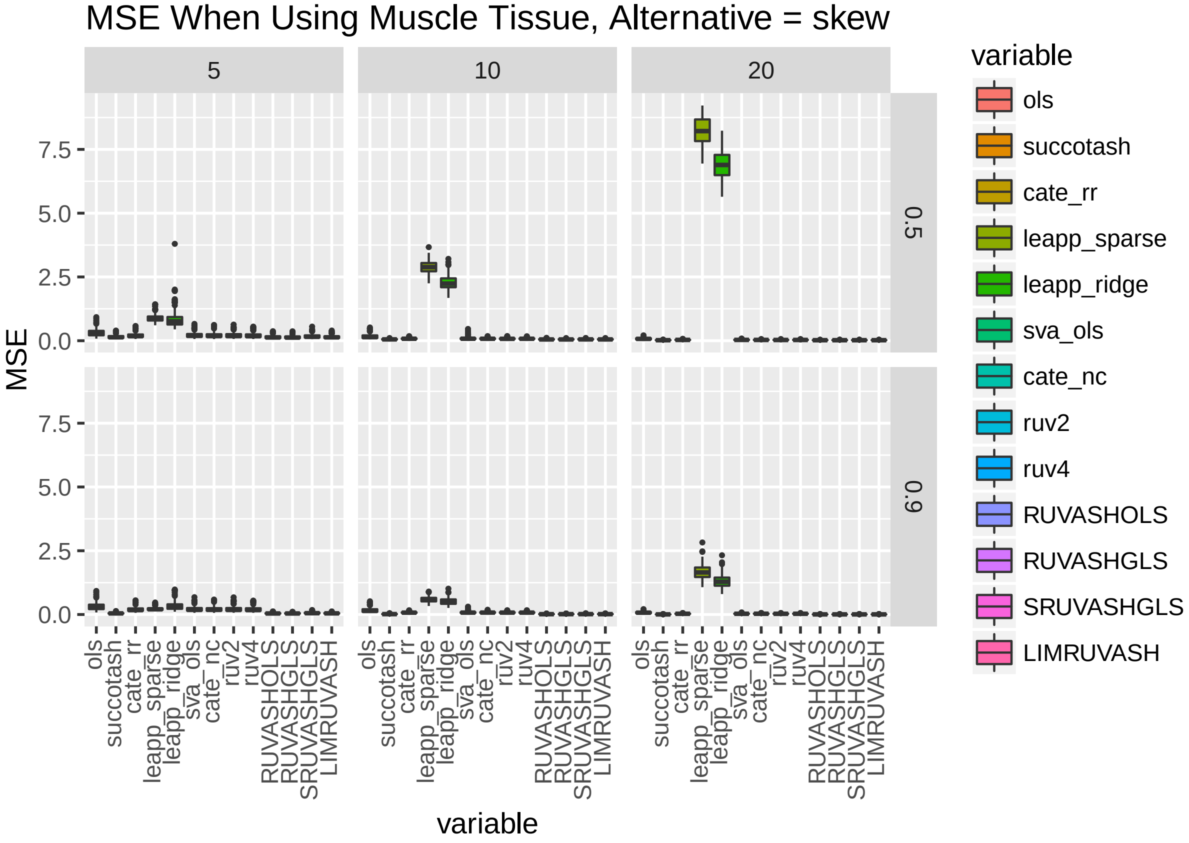
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH


MSE When Using Muscle Tissue, Alternative = skew
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0.9
MSE
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5.0
7.5
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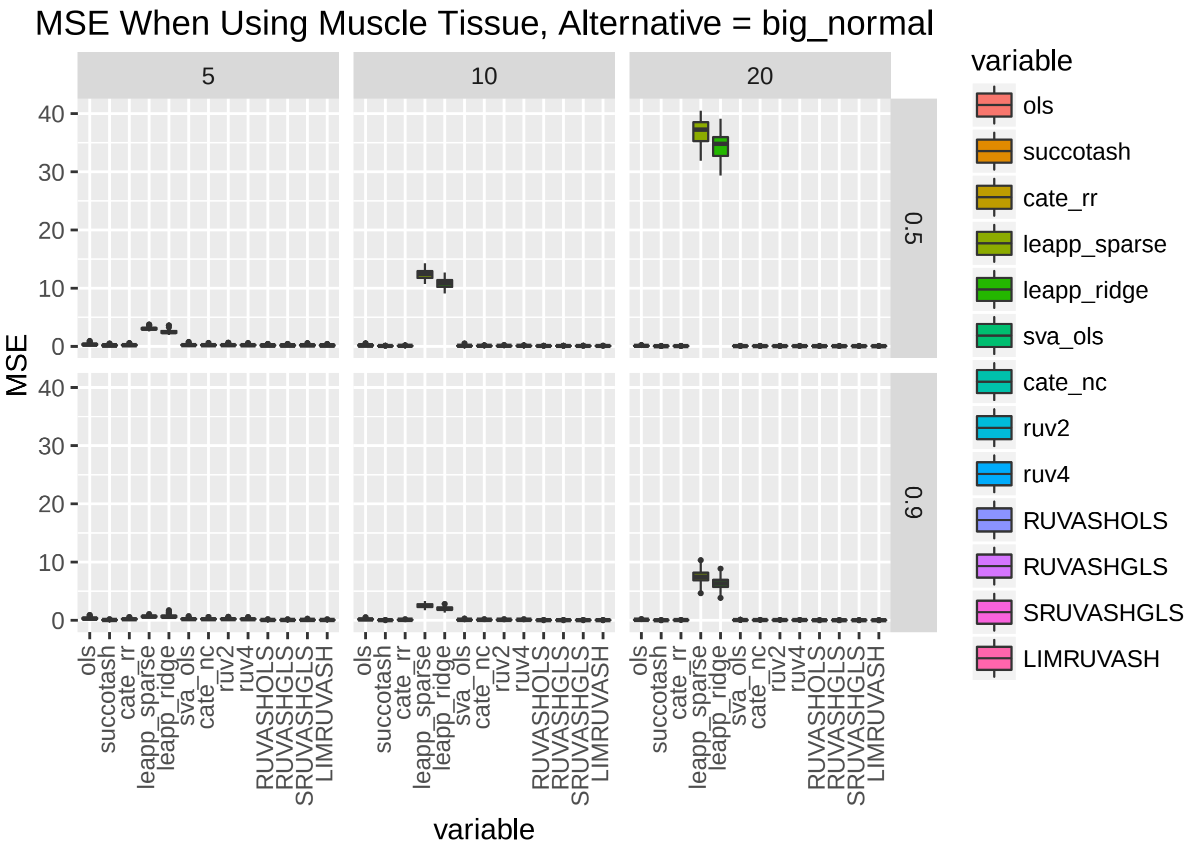
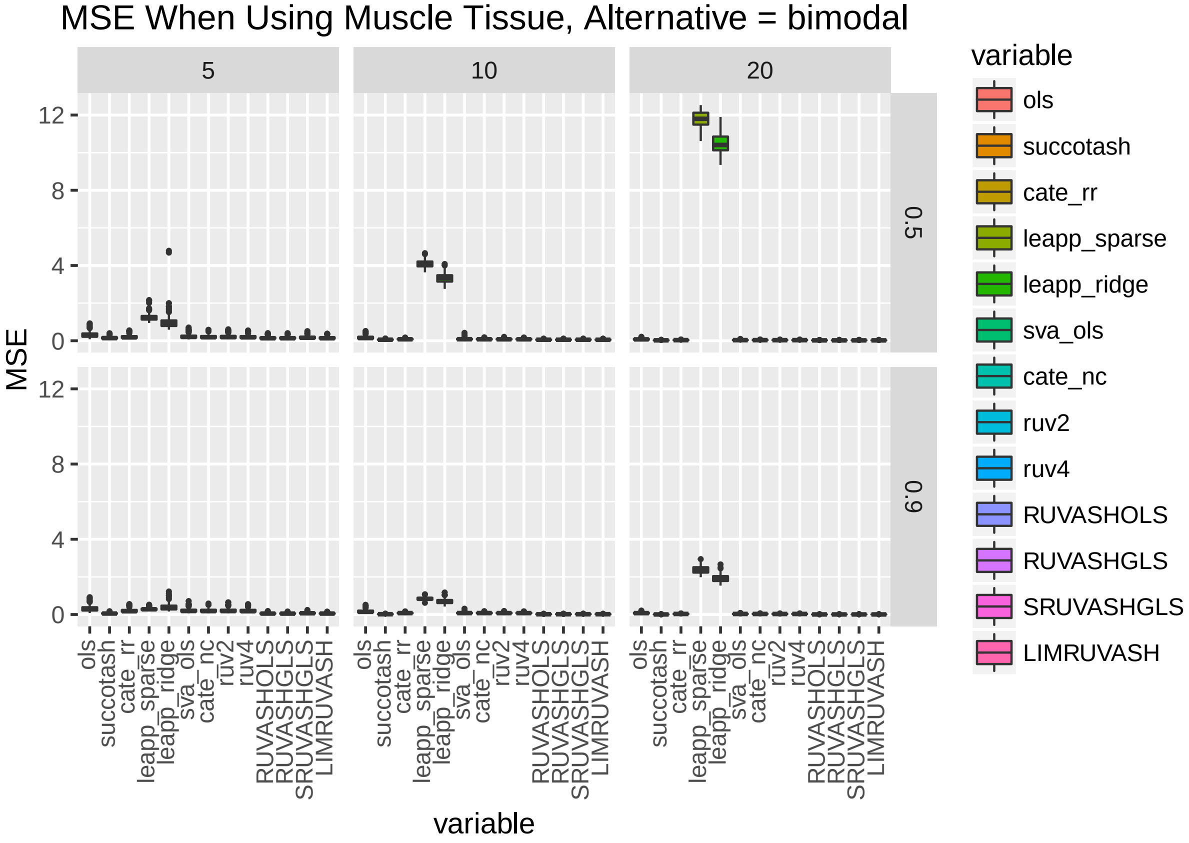
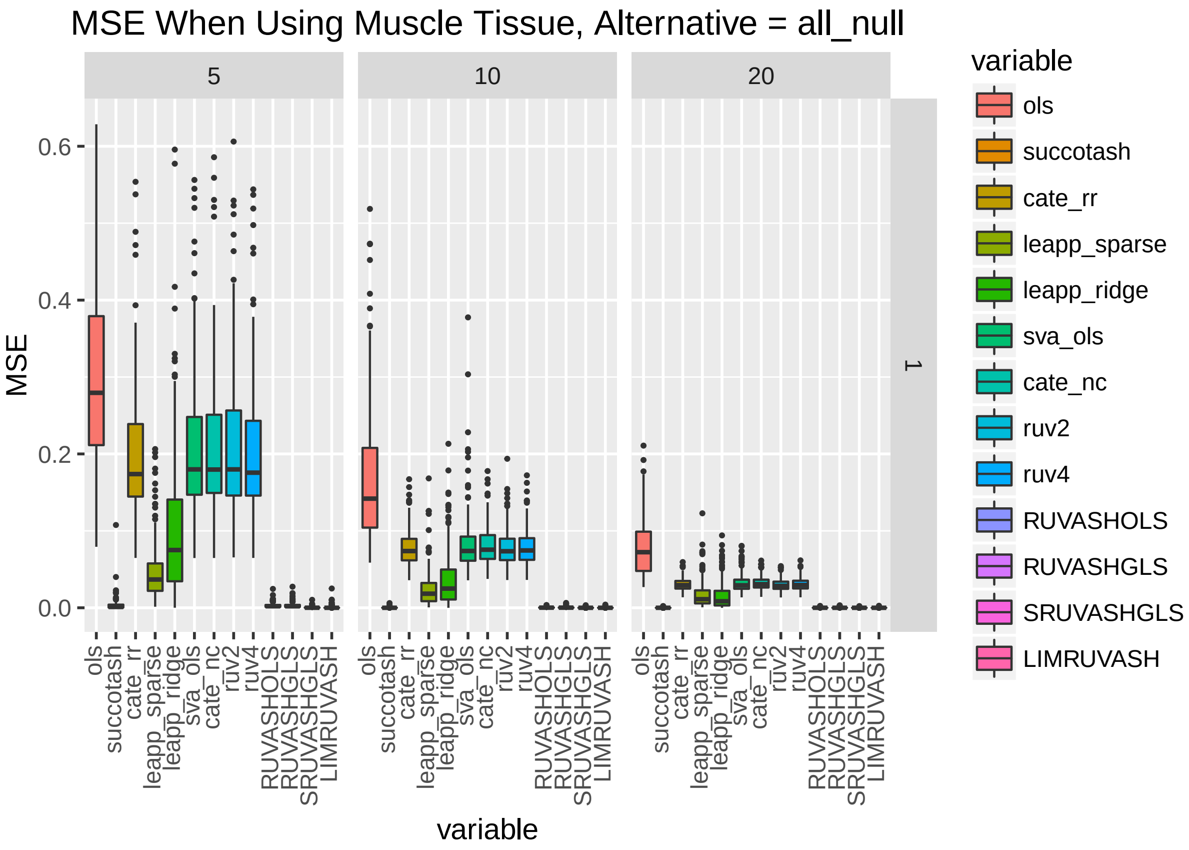
LIMRUVASH


MSE When Using Muscle Tissue, Alternative = big_normal


MSE When Using Muscle Tissue, Alternative = bimodal


MSE When Using Muscle Tissue, Alternative = all_null
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10
20
1
MSE
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0.4
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0.0
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leapp_ridge
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH
variable
variable
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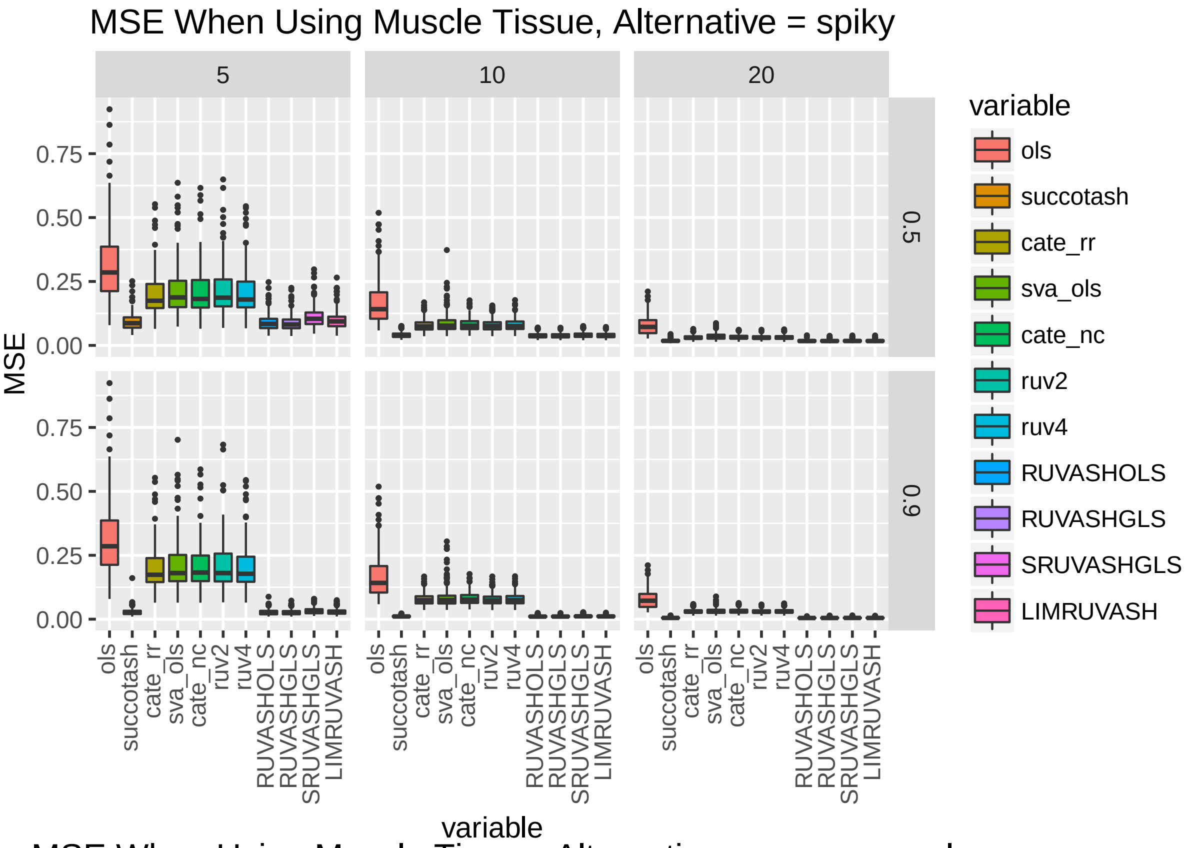
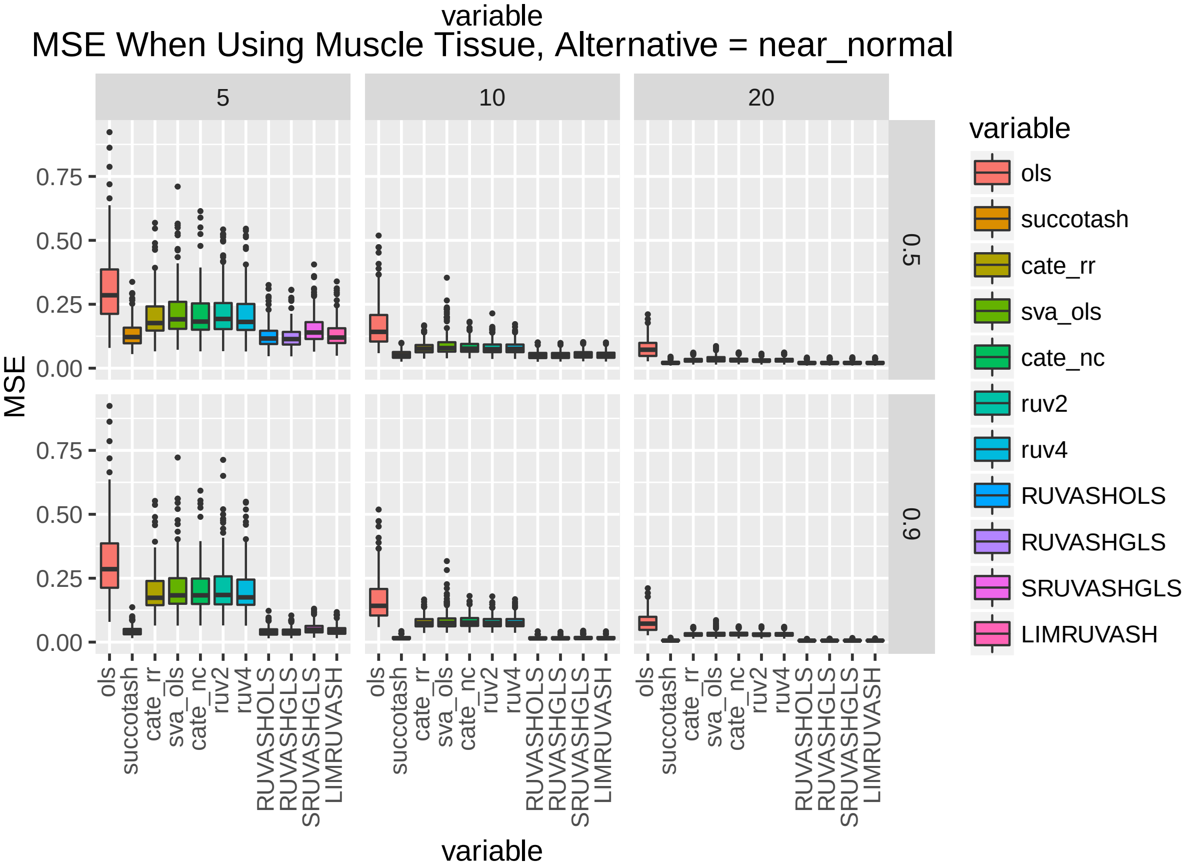
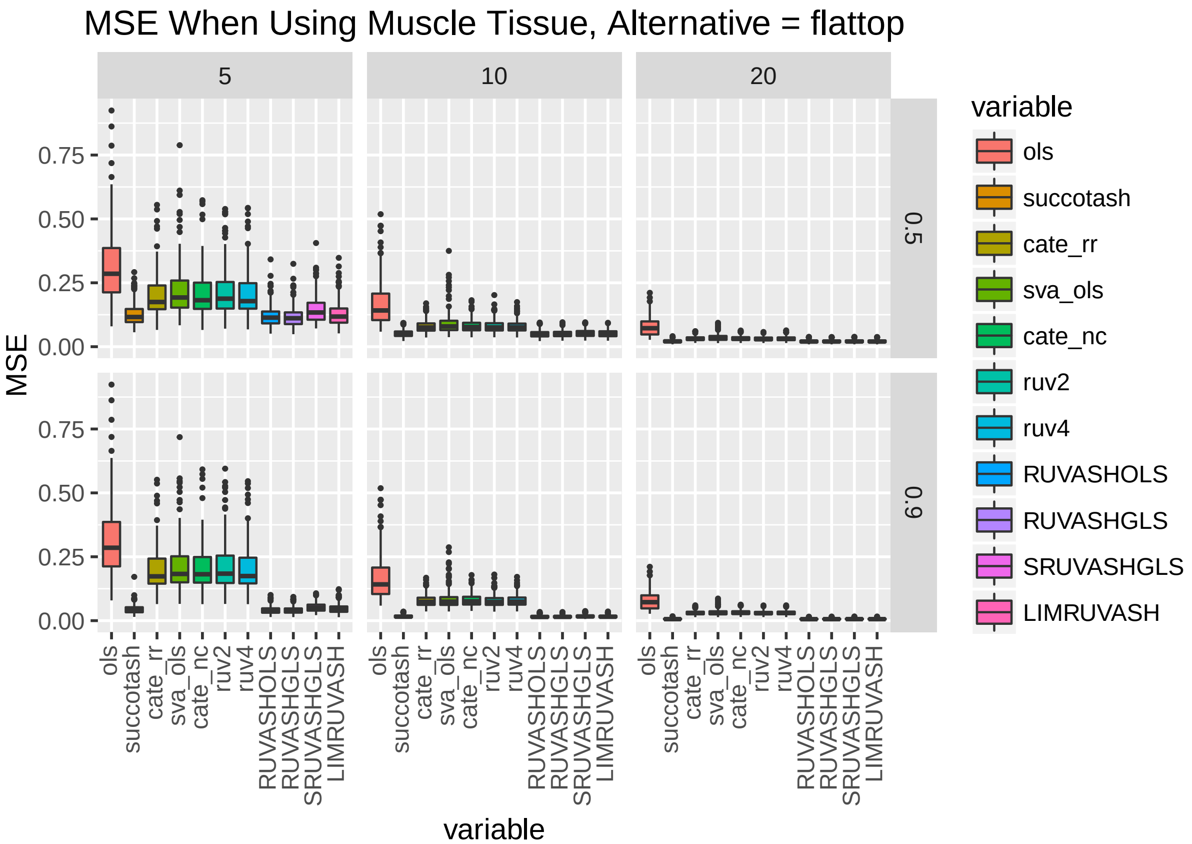
cate_rr
leapp_sparse
leapp_ridge
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH

MSE without LEAPP






MSE When Using Muscle Tissue, Alternative = flattop
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10
20
0.5
0.9
MSE
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cate_rr
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH
variable
variable
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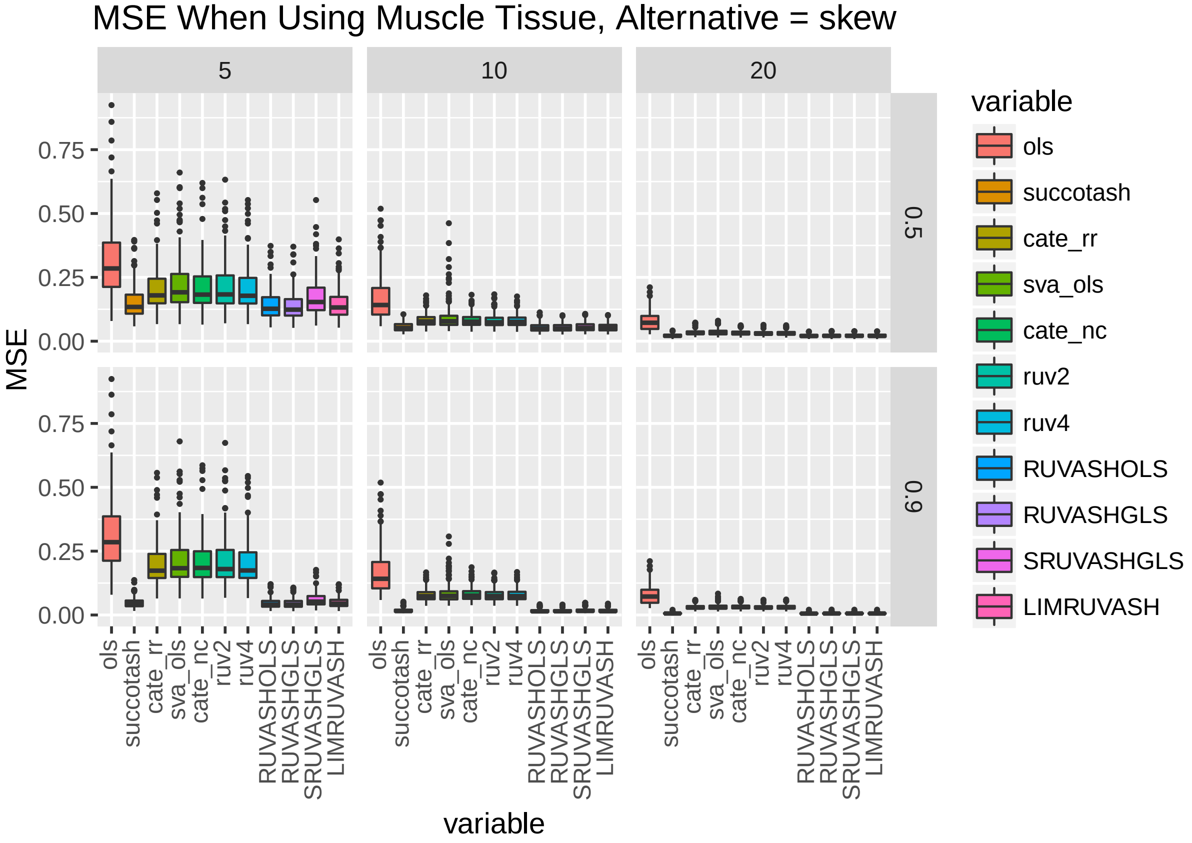
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH


MSE When Using Muscle Tissue, Alternative = skew
5
10
20
0.5
0.9
MSE
0.00
0.25
0.50
0.75
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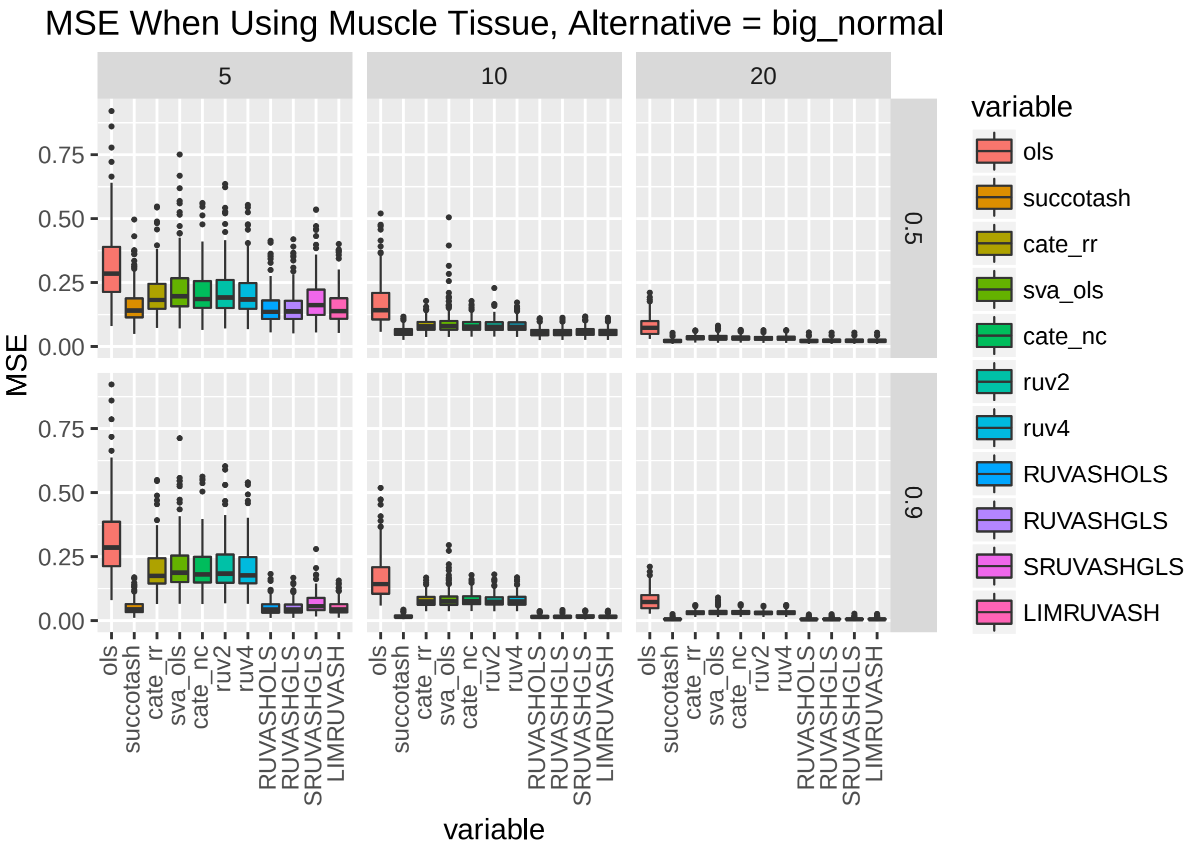
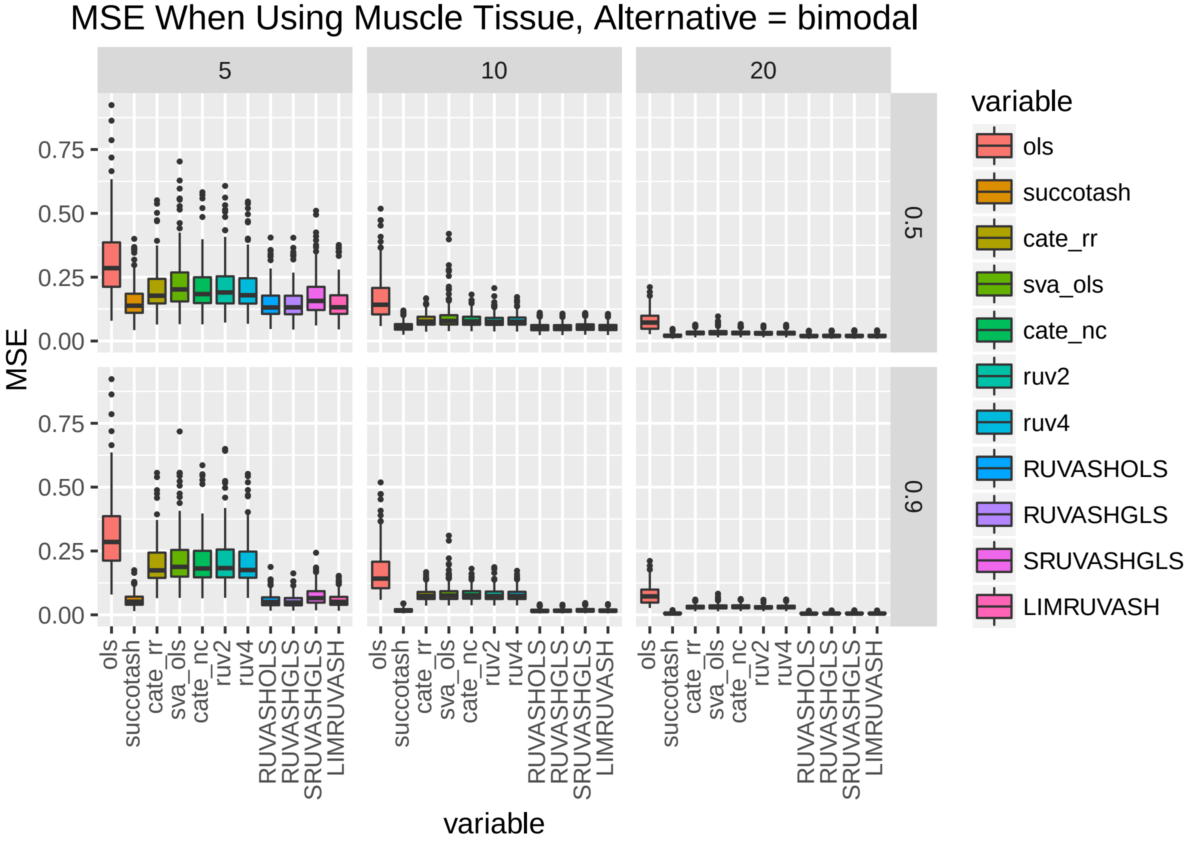
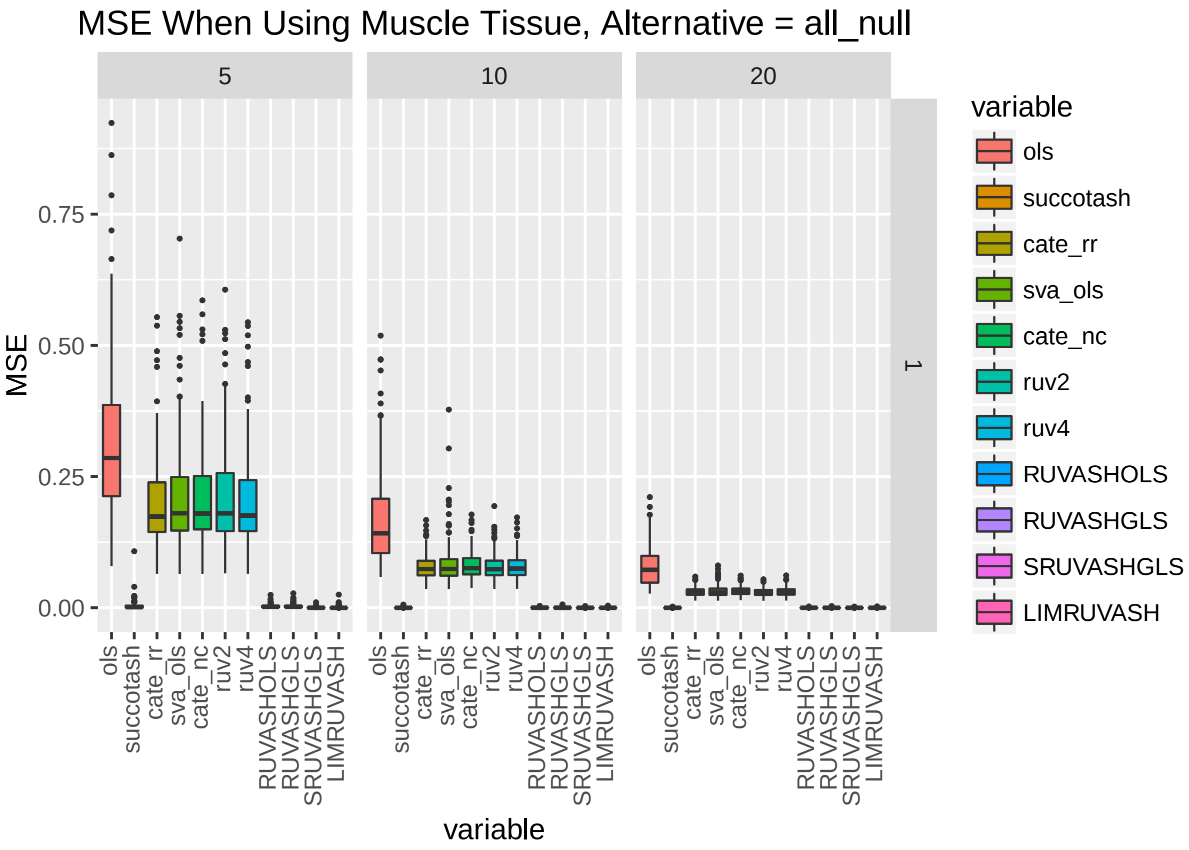
succotash
cate_rr
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH
variable
variable
ols
succotash
cate_rr
sva_ols
cate_nc
ruv2
ruv4
RUVASHOLS
RUVASHGLS
SRUVASHGLS
LIMRUVASH


MSE When Using Muscle Tissue, Alternative = big_normal


MSE When Using Muscle Tissue, Alternative = bimodal



```
sessionInfo()
```

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## R version 3.3.0 (2016-05-03)
## Platform: x86_64-pc-linux-gnu (64-bit)
## Running under: Ubuntu 14.04.4 LTS
##
## locale:
##  [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
##  [3] LC_TIME=en_US.UTF-8        LC_COLLATE=en_US.UTF-8
##  [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
##  [7] LC_PAPER=en_US.UTF-8       LC_NAME=C
##  [9] LC_ADDRESS=C               LC_TELEPHONE=C
## [11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
## [1] pROC_1.8       dplyr_0.4.3    reshape2_1.4.1 ggplot2_2.1.0
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.5      knitr_1.12.28    magrittr_1.5     munsell_0.4.3
##  [5] colorspace_1.2-6 R6_2.1.2         stringr_1.0.0    plyr_1.8.3
##  [9] tools_3.3.0      parallel_3.3.0   grid_3.3.0       gtable_0.2.0
## [13] DBI_0.4          htmltools_0.3.5  yaml_2.1.13      lazyeval_0.1.10
## [17] assertthat_0.1   digest_0.6.9     formatR_1.3      codetools_0.2-14
## [21] evaluate_0.9     rmarkdown_0.9.6  labeling_0.3     stringi_1.0-1
## [25] compiler_3.3.0   scales_0.4.0
```

Buja, Andreas, and Nermin Eyuboglu. 1992. “Remarks on Parallel Analysis.” *Multivariate Behavioral Research* 27 (4). Taylor & Francis: 509–40.

Stephens, Matthew. 2016. “False Discovery Rates: A New Deal.” *BioRxiv*. Cold Spring Harbor Labs Journals, 038216.