

Supplementary Materials for Tilting the Lasso by Knowledge Based Post Processing

Kukatharmini Tharmaratnam , Matt Sperrin, Thomas Jaki, Sjur Reppe and Arnoldo Frigessi

The supplementary material contains Experiment 2 for correlation structure of the covariates and four tables with results from different simulation experiments.

1 Appendix A

In this case correlations are less than the correlation structure for simulation study 1.

Table 1: Correlation structure for simulation study 2

| Covariates in True model | Biologically relevant variables | correlation |
|--|---------------------------------|---------------|
| x_1, x_2, x_3, x_4, x_5 | $x_{21}, x_{22}, \dots, x_{30}$ | $\rho = 0.5$ |
| $x_6, x_7, x_8, x_9, x_{10}$ | $x_{31}, x_{32}, \dots, x_{40}$ | $\rho = 0.4$ |
| $x_{11}, x_{12}, x_{13}, x_{14}, x_{15}$ | $x_{41}, x_{42}, \dots, x_{50}$ | $\rho = 0.35$ |
| $x_{16}, x_{17}, x_{18}, x_{19}, x_{20}$ | $x_{51}, x_{52}, \dots, x_{60}$ | $\rho = 0.3$ |

2 Appendix B

We generate covariates with a $SNR = 0.5$ and $(\beta_j = 0.1, j = 1, 2, \dots, 20)$ to generate response variables using model (3) and correlation structure for simulation study 2 as in Table1. We investigate to what extend our replacement method allows to propose models with more biologically relevant variables.

Table 2 shows that selecting bags with methods B1 and B2 select more biologically relevant variables than bag type B3 method. Lasso select only 15% biologically relevant covariates from 100 simulation runs. Our proposed bag type B1 selects around 85% biologically relevant covariates, while other bag types B2 and B3 select 73% and 67% respectively. Table 2 gives similar results to the correlation structure for simulation study 1.

To compare the performance of different type of bags, we computed percentage of ratio between PMSE for each type of bag (B1, B2 and B3) for 100 simulation runs. The average of PRPMSE is given in Table 2. It shows that generating the model from bag types B1 and B2 perform better than bag type B3. We calculated the 95% confidence interval for

Table 2: Average number and percentage of biologically relevant variables in the model with $SNR = 0.5$ and $(\beta_j = 0.1, j = 1, 2, \dots, 20)$. Percentage and standard deviations are over 100 runs from data \mathcal{D}_2 . The average of the PRPMSE over 100 runs and the percentage of such runs for which the bootstrap 95% CI includes 1 or less than 1, with $SNR = 0.5$ and $(\beta_j = 0.1, j = 1, 2, \dots, 20)$ from data \mathcal{D}_3 using correlation structure for simulation study 2

| Over 100 runs | Adaptive Lasso | B1 | B2 | B3 |
|---|----------------|--------|--------|--------|
| Average number of selected variables | 39 | 39 | 39 | 39 |
| Average number of Biologically relevant variables | 8 | 35 | 32 | 30 |
| Averageof Biologically relevant variables (%) | 20.5% | 89.7% | 82.1% | 76.9% |
| Standard deviation | 9.8 | 1.02 | 1.69 | 4.38 |
| PMSE (absolute) | 1.289 | 1.272 | 1.262 | 1.304 |
| PRPMSE % | 100% | 98.7% | 97.9% | 101.2% |
| (St.dev) | | (1.05) | (1.29) | (3.12) |
| Favorable substitution% | | 87% | 72% | 66% |
| (St.dev) | | (1.01) | (0.92) | (4.34) |
| MISE | 1.687 | 1.699 | 1.731 | 1.782 |
| Over 100 runs | Lasso | B1 | B2 | B3 |
| Average number of selected variables | 52 | 52 | 52 | 52 |
| Average number of Biologically relevant variables | 8 | 44 | 38 | 35 |
| Averageof Biologically relevant variables (%) | 14.8% | 84.6% | 73.1% | 67.3% |
| Standard deviation | 11.1 | 1.46 | 2.09 | 5.81 |
| PMSE (absolute) | 1.697 | 1.665 | 1.656 | 1.733 |
| PRPMSE % | 100% | 98.1% | 97.6% | 102.1% |
| (St.dev) | | (1.11) | (1.41) | (3.66) |
| Favorable substitution% | | 84% | 69% | 61% |
| (St.dev) | | (1.06) | (0.97) | (5.01) |
| MISE | 1.995 | 2.049 | 2.076 | 2.983 |

the percentage of ratio between PMSE (PRPMSE) for each of the 100 simulation runs by bootstrap as described in the main manuscript. Table 2 shows that bag types B1 and B2 are selecting the biologically relevant covariates around 85% and 70% favorable replacement respectively. Bag type B3 selects around 60% favorable substitution.

The results from the adaptive lasso is given in the bottom of Table 2. It shows that less number of variable selected from adaptive lasso as we expected. We get higher percentage of biologically relevant variables on average over 100 simulation runs than lasso selection case. We also get slightly higher percentage of favorable replacements from adaptive lasso than lasso.

We present mean integrated square error in Table 2 and it shows that, MISE are slightly larger than lasso selected variables with our proposed bag types variables. But we can get more biologically relevant variables from our proposed bag types. We can see similar results with adaptive lasso as well.

We use $SNR = 0.5$ and $(\beta_j = 0.2, j = 1, 2, \dots, 20)$ values for 20 variables $x_j, j = 1, 2, \dots, 20$ to generate response variable using (3) and experiment 1 as described in the

main manuscript. Table 3 shows that selecting bags with methods B1 and B2 selects

Table 3: Average number and percentage of biologically relevant variables in the model with $SNR = 0.5$ and $(\beta_j = 0.2, j = 1, 2, \dots, 20)$. Percentage and standard deviations are over 100 runs from data \mathcal{D}_2 . The average of the PRPMSE over 100 runs and the percentage of such runs for which the bootstrap 95% CI includes 1 or less than 1, with $SNR = 0.5$ and $(\beta_j = 0.2, j = 1, 2, \dots, 20)$ from data \mathcal{D}_3 using correlation structure for simulation study 1

| Over 100 runs | Adaptive Lasso | B1 | B2 | B3 |
|---|----------------|--------|--------|--------|
| Average number of selected variables | 40 | 40 | 40 | 40 |
| Average number of Biologically relevant variables | 13 | 38 | 35 | 31 |
| Averageof Biologically relevant variables (%) | 32.5% | 95.0% | 87.5% | 77.5% |
| Standard deviation | 9.73 | 0.89 | 1.24 | 3.89 |
| PMSE (absolute) | 1.102 | 1.099 | 1.095 | 1.116 |
| PRPMSE % | 100% | 99.7% | 99.4% | 101.3% |
| (St.dev) | | (1.34) | (2.15) | (6.72) |
| Favorable substitution% | | 89% | 71% | 69% |
| (St.dev) | | (1.67) | (2.07) | (7.54) |
| MISE | 2.432 | 2.486 | 2.519 | 2.538 |
| Over 100 runs | Lasso | B1 | B2 | B3 |
| Average number of selected variables | 54 | 54 | 54 | 54 |
| Average number of Biologically relevant variables | 13 | 47 | 43 | 37 |
| Averageof Biologically relevant variables (%) | 23.4% | 87.0% | 79.1% | 68.5% |
| Standard deviation | 10.8 | 0.96 | 1.80 | 4.56 |
| PMSE (absolute) | 1.528 | 1.522 | 1.514 | 1.572 |
| PRPMSE % | 100% | 99.6% | 99.1% | 102.9% |
| (St.dev) | | (1.62) | (2.82) | (7.56) |
| Favorable substitution% | | 85% | 67% | 64% |
| (St.dev) | | (2.13) | (2.52) | (8.12) |
| MISE | 2.867 | 2.906 | 2.954 | 2.981 |

more biologically relevant variables than B3. To compare the performance of different type of bags, we computed PRPMSE for each type of bag (B1, B2 and B3) and lasso selected model for 100 simulation runs. The average of the PRPMSE is given in Table 3. It shows that generating the model from bag types B1 and B2 perform better than bag type B3 in terms of prediction performance.

We use $SNR = 0.5$ and $(\beta_j = 0.8, j = 1, 2, \dots, 20)$ values for 20 variables $x_j, j = 1, 2, \dots, 20$ to generate response variable using (3) and experiment 1 as described in the main manuscript. Table 4 shows that selecting bags with methods B1 and B2 selects more biologically relevant variables than B3. To compare the performance of different type of bags, we computed PRPMSE for each type of bag (B1, B2 and B3) and lasso selected model for 100 simulation runs. The average of the PRPMSE is given in Table 4. It shows that generating the model from bag types B1 and B2 perform better than bag type B3 in terms of prediction performance.

We calculated the 95% confidence interval for the PRPMSE for each 100 simulation

Table 4: Average number and percentage of biologically relevant variables in the model with $SNR = 0.5$ and $(\beta_j = 0.8, j = 1, 2, \dots, 20)$. Percentage and standard deviations are over 100 runs from data \mathcal{D}_2 . The average of the PRPMSE over 100 runs and the percentage of such runs for which the bootstrap 95% CI includes 1 or less than 1, with $SNR = 0.5$ and $(\beta_j = 0.8, j = 1, 2, \dots, 20)$ from data \mathcal{D}_3 using correlation structure for simulation study 1

| Over 100 runs | Adaptive Lasso | B1 | B2 | B3 |
|---|----------------|--------|--------|--------|
| Average number of selected variables | 42 | 42 | 42 | 42 |
| Average number of Biologically relevant variables | 13 | 39 | 36 | 32 |
| Averageof Biologically relevant variables (%) | 31.0% | 92.9% | 85.7% | 76.2% |
| Standard deviation | 9.54 | 0.82 | 1.19 | 3.58 |
| PMSE (absolute) | 1.143 | 1.140 | 1.134 | 1.164 |
| PRPMSE % | 100% | 99.7% | 99.2% | 101.8% |
| (St.dev) | | (1.29) | (2.01) | (6.46) |
| Favorable substitution% | | 88% | 70% | 67% |
| (St.dev) | | (1.73) | (2.16) | (7.41) |
| MISE | 2.583 | 2.589 | 2.594 | 2.608 |
| Over 100 runs | Lasso | B1 | B2 | B3 |
| Average number of selected variables | 56 | 56 | 56 | 56 |
| Average number of Biologically relevant variables | 13 | 48 | 44 | 38 |
| Averageof Biologically relevant variables (%) | 23.2% | 85.7% | 78.6% | 67.9% |
| Standard deviation | 11.9 | 0.99 | 1.860 | 5.04 |
| PMSE (absolute) | 1.485 | 1.482 | 1.475 | 1.522 |
| PRPMSE % | 100% | 99.8% | 99.3% | 102.5% |
| (St.dev) | | (1.51) | (2.67) | (7.03) |
| Favorable substitution% | | 87% | 69% | 62% |
| (St.dev) | | (2.00) | (2.23) | (7.62) |
| MISE | 2.916 | 2.935 | 2.973 | 2.996 |

runs by bootstrap as described in the main manuscript. Table 3 confirms that bag types B1 and B2 performs better than B3. The adaptive lasso results show simillar pattenen as well.

Table 5: Selection of genes from lasso and corresponding bags from bag type B1, percentage of ratio between PMSE

| Genes from Lasso | Genes in the Bags | | | | | | | | | |
|---------------------|-------------------|---------------------|-----------|--------|----------|----------|-----------|--------|---------|----------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| AK3L1 | FLJ39051 | ADAMTS2 | RRP12 | PSMB2 | SUN5 | PKLR | SFN | RBL1 | C19orf6 | PGAP3 |
| PRPMSE % | 157 | 99 | 163 | 163 | 161 | 99 | 174 | 169 | 154 | 154 |
| CCHCR1 | CCHCR1 | KLHL22 | STARD10 | SERHL2 | B3GNT6 | KBTBD4 | DGCR14 | LACTB | EHD1 | ERCC6 |
| PRPMSE % | 115 | 108 | 105 | 129 | 107 | 113 | 141 | 110 | 123 | 104 |
| CRYGS | LACTB | CD5 | FAM115A | SEC16B | USP46 | CRIM1 | SYNRG | PPARA | CPEB3 | UBR5 |
| PRPMSE % | 69 | 88 | 69 | 70 | 70 | 74 | 63 | 94 | 68 | 57 |
| CSRNP3 | RUNX2 | UNC5B | UNC13D | BMP2 | FAM20C | TRIM2 | CDK13 | MMP16 | ZFHX4 | BMP7 |
| PRPMSE % | 158 | 120 | 133 | 125 | 126 | 124 | 122 | 98 | 145 | 88 |
| FAF1 | CAMSAP1 | ZNF75A | EXOG | RFFL | ABLM2 | ARPC5L | CRCP | EIF5B | NLGN2 | TNRC18 |
| PRPMSE % | 129 | 118 | 103 | 102 | 90 | 119 | 114 | 103 | 118 | 113 |
| FKBP14 | C12orf47 | SS18 | TACC1 | SPAG9 | THBD | GTF2H2B | FNDC5 | CRYGS | ZBTB43 | SPTBN1 |
| PRPMSE % | 91 | 224 | 227 | 151 | 206 | 182 | 189 | 171 | 112 | 228 |
| FLRT2 | PDGFA | EDNRA | ITGBL1 | LMO7 | ITGBL1 | NRP2 | LOC728190 | MYO6 | LAMA4 | SEPT11 |
| PRPMSE % | 63 | 55 | 86 | 79 | 57 | 57 | 63 | 54 | 45 | 64 |
| KDM4A | SLC44A1 | FUT7 | ING3 | GRB10 | TBX2 | PPI2 | SDCCAG8 | CPPED1 | PPARA | EIF5B |
| PRPMSE % | 107 | 117 | 104 | 113 | 108 | 118 | 101 | 126 | 124 | 77 |
| LOC642852 | ADAMTSL1 | PRKAG2 | CEP164 | ABAT | ZNF45 | OGFRL1 | CTU2 | THEM4 | SARM1 | ATP5S |
| PRPMSE % | 88 | 105 | 80 | 75 | 66 | 88 | 85 | 72 | 82 | 111 |
| MAPK8 | PFKFB2 | RIT1 | CASZ1 | F7 | BMP7 | SLA2 | FTCD | CHDH | SNAPC4 | CAMK2D |
| PRPMSE % | 97 | 91 | 157 | 111 | 99 | 99 | 91 | 73 | 98 | 112 |
| NF1 | MYH14 | ZNF20 /// ZNF625 | ASXL3 | LTBP4 | KLK4 | ZFHX4 | FOXN4 | TLE4 | GTF3C4 | IL17RC |
| PRPMSE % | 145 | 142 | 124 | 116 | 150 | 144 | 156 | 139 | 129 | 163 |
| PIAS4 | GFPT1 | CEP152 | SH3RF1 | SP3 | B3GNT6 | DHX30 | TTC28 | TCEA2 | PLAC2 | DIO2 |
| PRPMSE % | 38 | 45 | 48 | 59 | 68 | 46 | 44 | 52 | 75 | 53 |
| PLIN5 | NOX1 | SFTPC | MESP2 | MUC5AC | SETDB2 | NPR3 | IL1RL1 | PROM2 | VAV2 | TMEM161B |
| PRPMSE % | 80 | 83 | 92 | 92 | 75 | 88 | 115 | 98 | 86 | 56 |
| PPIL2 | ACTG1 | ACTG1 | BMP5 | ARSK | ITGBL1 | C9orf167 | PCIF1 | KLHL18 | ITGBL1 | SIN3A |
| PRPMSE % | 108 | 105 | 118 | 103 | 101 | 106 | 115 | 104 | 104 | 91 |
| RNF31 | SEPT8 | SENP2 | CMAH | B3GAT3 | MLLT10 | KIAA0415 | FLJ44342 | GFPT1 | BCL3 | GALNT5 |
| PRPMSE % | 97 | 94 | 96 | 130 | 95 | 100 | 99 | 82 | 94 | 100 |
| SRR | C1orf163 | FAM38B | TNFRSF10A | ERCC6 | THBD | PDCD2 | SMAD3 | RRN3P1 | EGFR | PDE4A |
| PRPMSE % | 53 | 67 | 58 | 73 | 55 | 47 | 76 | 60 | 61 | 56 |
| TRPS1 | FLRT2 | LMO7 | WWC2 | EDNRA | ITPRIPL2 | PDGFA | ZHX3 | TRPC6 | SFRP1 | SEPT11 |
| PRPMSE % | NA | 187 | 192 | 199 | 157 | 176 | 205 | 202 | 114 | 161 |
| ZMAT3 | CNOT3 | MARK4 | WDR74 | ERCC1 | HSPA1L | FBXO9 | WDR27 | FOSL2 | GOSR2 | C15orf39 |
| PRPMSE % | 155 | 150 | 150 | 160 | 146 | 152 | 106 | 153 | 157 | 169 |

(// between two genes indicates that transcripts from both genes are detected by the relevant Affymetrix probe set)

Table 6: Selection of genes from lasso and corresponding bags from bag type B2 (correlation > 0.55), percentage of ratio between PMSE

| Genes from Lasso | | | Genes in the Bags | | | | | | | | | |
|------------------|----------|---------|-------------------|----------|---------|----------|-----------|---------|-------|----------|--|--|
| AK3L1 | FLJ39051 | ADAMTS2 | | | | | | | | | | |
| PRPMSE % | 157 | 99 | | | | | | | | | | |
| CCHCR1 | CCHCR1 | KLHL22 | STARD10 | | | | | | | | | |
| PRPMSE % | 115 | 108 | 105 | | | | | | | | | |
| CRYGS | LACTB | CD5 | FAM115A | SEC16B | USP46 | CRIM1 | SYNRG | PPARA | CPEB3 | UBR5 | | |
| PRPMSE % | 69 | 88 | 69 | 70 | 70 | 74 | 63 | 94 | 68 | 57 | | |
| CRYGS | NAA25 | TARSL2 | EPHB4 | FANCA | C7orf50 | GNAS | PEX13 | ZNF385B | | | | |
| PRPMSE % | 70 | 89 | 75 | 109 | 94 | 75 | 67 | 64 | | | | |
| CSRNP3 | RUNX2 | UNC5B | UNC13D | BMP2 | FAM20C | TRIM2 | CDK13 | MMP16 | ZFHX4 | | | |
| PRPMSE % | 158 | 120 | 133 | 125 | 126 | 124 | 122 | 98 | 145 | | | |
| FAF1 | CAMSAP1 | ZNF75A | EXOG | RFPL | ABLIM2 | ARPC5L | CRCP | EIF5B | NLGN2 | TNRC18 | | |
| PRPMSE % | 129 | 118 | 103 | 102 | 90 | 119 | 114 | 103 | 118 | 113 | | |
| FKBP14 | C12orf47 | SS18 | TACC1 | SPAG9 | | | | | | | | |
| PRPMSE % | 91 | 224 | 227 | 151 | | | | | | | | |
| FLRT2 | PDGFA | EDNRA | ITGBL1 | LMO7 | ITGBL1 | NRP2 | LOC728190 | MYO6 | LAMA4 | SEPT11 | | |
| PRPMSE % | 63 | 55 | 86 | 79 | 57 | 57 | 63 | 54 | 45 | 64 | | |
| FLRT2 | TRPS1 | TMTG2 | PTPRG | COL11A1 | SSH3 | PCIF1 | CHAF1A | ZNF341 | UNC5B | SMAD4 | | |
| PRPMSE % | 60 | 50 | 60 | 56 | 57 | 55 | 55 | 65 | 57 | 90 | | |
| FLRT2 | ITGB4 | | | | | | | | | | | |
| PRPMSE % | 78 | | | | | | | | | | | |
| KDM4A | | | | | | | | | | | | |
| LOC642852 | ADAMTS1 | PRKAG2 | CEP164 | | | | | | | | | |
| PRPMSE % | 88 | 105 | 80 | | | | | | | | | |
| MAPK8 | PFKFB2 | | | | | | | | | | | |
| PRPMSE % | 97 | | | | | | | | | | | |
| NF1 | | | | | | | | | | | | |
| PIAS4 | GFPT1 | CEP152 | | | | | | | | | | |
| PRPMSE % | 38 | 45 | | | | | | | | | | |
| PLIN5 | NOX1 | SFTPC | MESP2 | MUC5AC | SETDB2 | NPR3 | IL1RL1 | PROM2 | VAV2 | TMEM161B | | |
| PRPMSE % | 80 | 83 | 92 | 92 | 75 | 88 | 115 | 98 | 86 | 56 | | |
| PLIN5 | ABHD11 | NFYC | ZNF780A | FLJ38717 | ADPRHL1 | CELF4 | | | | | | |
| PRPMSE % | 87 | 87 | 85 | 92 | 44 | 87 | | | | | | |
| PPIL2 | ACTG1 | ACTG1 | BMP5 | ARSK | ITGBL1 | | | | | | | |
| PRPMSE % | 108 | 105 | 118 | 103 | 101 | | | | | | | |
| RNF31 | SEPT8 | SENP2 | CMAH | B3GAT3 | MLLT10 | KIAA0415 | FLJ44342 | GFPT1 | BCL3 | | | |
| PRPMSE % | 97 | 94 | 96 | 130 | 95 | 100 | 99 | 82 | 94 | | | |
| SRR | Clorf163 | | | | | | | | | | | |
| PRPMSE % | 53 | | | | | | | | | | | |
| TRPS1 | FLRT2 | LMO7 | WWC2 | | | | | | | | | |
| PRPMSE % | NA | 187 | 192 | | | | | | | | | |
| ZMAT3 | | | | | | | | | | | | |

Some genes are denoted as follows,(SAA1 // SAA2)=SAA1/2 , (ZNF20 // ZNF625)=ZNF20/625, (D4S234E // FOXP1)=D4S234E1, RAB11FIP4 =RAB1 (/// between two genes indicates that transcripts from both genes are detected by the relevant Affymetrix probe set)

Table 7: Selection of genes from lasso and corresponding bags from bag type B3, percentage of ratio between PMSE

| Genes from Lasso | Genes in the Bags | | | | | | | | | |
|---------------------|-------------------|----------|--------|--------|---------|----------|---------|---------|---------|---------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| AK3L1 | WWP2 | ETV5 | SRGAP3 | ECE2 | SRCIN1 | RARA | MFI2 | CLDN11 | OSBPL10 | HPX |
| PRPMSE % | 147 | 130 | 231 | 156 | 180 | 173 | 163 | 175 | 119 | 109 |
| CCHCR1 | GLP1R | SRGAP3 | ECE2 | KCTD1 | WHA1/2 | IL28RA | HPX | CSNK | C16o | NTRK3 |
| PRPMSE % | 124 | 140 | 119 | 121 | 120 | 132 | 93 | 136 | 104 | 99 |
| CRYGS | ECE2 | WHA1/2 | NTRK3 | SRGAP3 | HPX | IL28RA | GLP1R | KCTD1 | CSNK | WWP2 |
| PRPMSE % | 65 | 71 | 58 | 79 | 56 | 100 | 70 | 76 | 77 | 72 |
| CSRNP3 | GLP1R | ECE2 | CSNK | KCTD1 | HFE | C15orf42 | NTRK3 | INF2 | NUP188 | EHMT2 |
| PRPMSE % | 152 | 139 | 160 | 160 | 107 | 136 | 125 | 104 | 137 | 104 |
| FAF1 | ECE2 | CSNK | KCTD1 | BMPR2 | CROCC | WHA1/2 | PSAT1 | NCLN | RNF157 | GLP1R |
| PRPMSE % | 118 | 141 | 147 | 142 | 66 | 122 | 117 | 135 | 75 | 132 |
| FKBP14 | SRGAP3 | IGF2BP1 | ECE2 | WWP2 | KCTD1 | PPP2R3B | C16o | LOC4 | TUB | SRCIN1 |
| PRPMSE % | 252 | 235 | 195 | 186 | 237 | 190 | 182 | 172 | 135 | 204 |
| FLRT2 | GLP1R | ECE2 | WHA1/2 | CSNK | HPX | MFI2 | NTRK3 | IL28RA | C16o | ZNF561 |
| PRPMSE % | 69 | 58 | 64 | 84 | 38 | 64 | 50 | 71 | 53 | 65 |
| KDM4A | GLP1R | ECE2 | SRGAP3 | HPX | MFI2 | IL28RA | KCTD1 | WHA1/2 | NTRK3 | CSNK |
| PRPMSE % | 128 | 115 | 149 | 96 | 124 | 144 | 139 | 117 | 105 | 132 |
| LOC642852 | GLP1R | SRGAP3 | ECE2 | IL1RL1 | PRKAR1B | TRPC4 | CLDN19 | C7orf63 | NLGN2 | CADM3 |
| PRPMSE % | 108 | 127 | 90 | 110 | 69 | 63 | 91 | 78 | 107 | 108 |
| MAPK8 | WHA1/2 | CSNK | ECE2 | C16o | MFI2 | ALG10B | WWP2 | LOC3 | HPX | ZNF780A |
| PRPMSE % | 107 | 131 | 103 | 96 | 112 | 124 | 99 | 108 | 81 | 94 |
| WHAMML2 | 1G3 | | | | | | | 39290 | | |
| NF1 | CSNK | C15orf42 | PSAT1 | WHA1/2 | FUT6 | HNF1B | GLP1R | C21orf2 | TRPC6 | KCTD1 |
| PRPMSE % | 173 | 136 | 144 | 151 | 143 | 129 | 168 | 162 | 140 | 184 |
| PIAS4 | WHA1/2 | TRPC4 | FCER2 | CSNK | BICD1 | NTRK3 | ST7L | LOC4 | ALC10B | RECQL5 |
| PRPMSE % | 58 | 41 | 58 | 69 | 60 | 41 | 41 | 37 | 70 | 58 |
| PLIN5 | GLP1R | IL28RA | C16o | IL1RL1 | NTRK3 | PPP2R3B | NCS1 | HNF1B | WWP2 | FUT6 |
| PRPMSE % | 116 | 135 | 95 | 115 | 86 | 101 | 73 | 89 | 93 | 104 |
| PPIL2 | SRGAP3 | ECE2 | HPX | GLP1R | MFI2 | WHA1/2 | KCTD1 | IL28RA | CLDN11 | WWP2 |
| PRPMSE % | 140 | 109 | 84 | 123 | 113 | 111 | 135 | 139 | 116 | 104 |
| RNF31 | GLP1R | SRGAP3 | KCTD1 | ECE2 | HPX | NTRK3 | IL28RA | CLDN11 | FCRL2 | C16o |
| PRPMSE % | 111 | 129 | 128 | 93 | 81 | 89 | 135 | 111 | 104 | 99 |
| SRR | GLP1R | ECE2 | WHA1/2 | WWP2 | NTRK3 | SLC25A17 | C16o | MFI2 | FCER2 | HPX |
| PRPMSE % | 93 | 61 | 66 | 63 | 61 | 114 | 58 | 77 | 68 | 45 |
| TRPS1 | GLP1R | SRGAP3 | KCTD1 | IL1RL1 | HPX | WWP2 | C21orf2 | SRCIN1 | ECE2 | C16o |
| PRPMSE % | 195 | 222 | 212 | 193 | 117 | 185 | 182 | 192 | 200 | 183 |
| ZMAT3 | GLP1R | SRGAP3 | ECE2 | WHA1/2 | KCTD1 | MFI2 | NTRK3 | HPX | CSNK | WWP2 |
| PRPMSE % | 184 | 201 | 172 | 170 | 195 | 178 | 154 | 154 | 190 | 157 |

Some genes are denoted as follows, (WHAMML1// WHAMML2)= WHA1/2, C16orf45=C16o, CSNK1G3=CSNK, LOC401320= LOC4 (// between two genes indicates that transcripts from both genes are detected by the relevant Affymetrix probe set)

3 Appendix C

```
#code for running the bone example for the paper

#packages
library(glmnet)
library(MASS)
#read in the data
bone<-read.csv("boneT.csv") ## Need to specify the path of the directory, where data stored
dim(bone)
#split data: one set for training data + another set for test data to do validation in lasso
#THIS SECTION splits the data in 1/3 and uses 2/3 of the data used as training data

set.seed(1111)
n<-dim(bone)[1]
TRS<-sample(1:n,floor(2*n/3))
bone1<-bone[TRS,] # Training data
bone2<-bone[-TRS,] # Test data
boneX1<-as.matrix(bone[TRS,4:8652]) #predictors
boneY1<-as.vector(bone[TRS,3]) #response (Z-score)
P=dim(boneX1)[2]
nTR=dim(boneX1)[1]
colnames(boneX1)=1:P

##### Lasso fit for Training data
TRfit<-cv.glmnet(boneX1,boneY1,nfolds=5) #initial fit
plot(TRfit) #a well-defined minimum in the MSE
which.min(TRfit$lambda)
lassofit=glmnet(boneX1,boneY1,family="gaussian",lambda=TRfit$lambda.min,standardize=T)
coef=as.vector(lassofit$beta)
coef1=cbind(colnames(boneX1),coef)
nonzeroX=coef1[coef!=0][1:lassofit$df]
nonzeroX

#####Make bags with respect to correlation
corrmatrixW=matrix(NA,ncol=length(nonzeroX),nrow=(P-1))
##### select 20 highly correlated covariates
absmcororderall=matrix(NA,ncol=length(nonzeroX),nrow=(P-1))
absmcororder=matrix(NA,ncol=length(nonzeroX),nrow=20)
##### select covariates with corr > 0.5
absmcorgreaterthan05 =list()
selectabsmcorgreaterthan05 =list()
for( j in 1:length(nonzeroX)){
  corrmatrixW[,j]=abs(cor(boneX1[,as.numeric(nonzeroX[j])],
                          boneX1[,-as.numeric(nonzeroX[j])]))
  absmcororder[,j]=order(corrmatrixW[,j],decreasing=TRUE)[1:20] #indices of top 20 variables
}
for(i in 1:(P-1)){
  if(corrmatrixW[i,j]>0.5) absmcororderall[i,j]= corrmatrixW[i,j]
}
```

```

absmcorgreaterthan05[j]=list(order(absmcorderall[,j],na.last = NA,decreasing=TRUE))
}

#####Fit OLS regression with selected variables from lasso and compute MSE
lsfitlasso=lm(boneY1~1+boneX1[,c(as.numeric(nonzeroX))])
betalasso=as.matrix(lsfitlasso$coef,ncol=1,nrow=length(nonzeroX))
yhat=(boneX1[,c(as.numeric(nonzeroX))]*%*%betalasso)
lsfitlassoMSE=1/nTR*sum(boneY1-yhat)^2
lsfitlassoMSE

lsMSE=matrix(NA,ncol=length(nonzeroX),nrow=P)
lsMSEdiff=matrix(NA,ncol=length(nonzeroX),nrow=P)
colname=matrix(1:P,ncol=1,nrow=P)
lsMSEdifforder=matrix(NA,ncol=length(nonzeroX),nrow=20)
for(j in 1:length(nonzeroX)){
  for(i in 1:P){
    newX=boneX1[,replace(as.numeric(nonzeroX),j,as.numeric(colname[i]))]
    lsfitX1=lm(boneY1~-1+newX)
    betalassoX1=as.matrix(c(lsfitX1$coef),ncol=1,nrow=length(nonzeroX))
    yhat=(newX%*%betalassoX1)
    lsMSE[i,j]=1/nTR*sum(boneY1-yhat)^2
    lsMSEdiff[i,j]=((lsMSE[i,j]/lsfitlassoMSE)*100)
  }
  lsMSEdifforder[,j]=order(lsMSEdiff[,j],decreasing=TRUE)[1:20] #indices of top 20 variables
}

nonzeroX
absmcorder      ###Bag with 20 highly correlated variables
absmcorgreaterthan05 ###Bag with variables larger than 0.5
lsMSEdifforder           ### Bag with 20 small MSE

##### Identify genes with respect to renamed selected covariates
genename=read.csv("C:/Users/tharmark/Desktop/Bags Project/Arnoldo project
                   /genename.csv",sep = "\t")
dim(genename)
nonzeroXgene=genename[c(as.numeric(nonzeroX)),3]
nonzeroXgene

absmcordergene=matrix(0,ncol=length(nonzeroX),nrow=20)
absmcorgreaterthan05gene=list()
lsMSEdiffordergene=matrix(0,ncol=length(nonzeroX),nrow=20)
for(j in 1:length(nonzeroX)){
  absmcordergene[,j]=as.matrix((genename[c(absmcorder[,j]),2]))
  absmcorgreaterthan05gene[[j]]=list(genename[c(absmcorgreaterthan05[[j]]),2])
  lsMSEdiffordergene[,j]=as.matrix(genename[c(lsMSEdifforder[,j]),2])
}
t(absmcordergene)
absmcorgreaterthan05gene
t(lsMSEdiffordergene)

```

```

##### prediction mean squares error #####
testn=n-nTR
boneX2<-as.matrix(bone[-TRS,4:8652]) #predictors
boneY2<-as.vector(bone[-TRS,3]) #response (Z-score)

nonzeroX
Lasso.yhat=boneX2[,c(as.numeric(nonzeroX))]*%betlasso ##### using test data
Lasso.PMSE= 1/testn * sum(boneY2-Lasso.yhat)^2
Lasso.PMSE

Lasso.yhat1=boneX1[,c(as.numeric(nonzeroX))]*%betlasso #####using training data
Lasso.MSE= 1/nTR * sum(boneY1-Lasso.yhat1)^2
Lasso.MSE

#####
#####Compute PMSE from the model with green genes #####
greengeneX1B1=boneX1[,replace(as.numeric(nonzeroX),c(1:18),c(137,1364,5735,6366,2498,
7066,5440,6840,5284,754,4995,2432,5449,749,6261,6881,6565,8357))]
greengeneX1B2=boneX1[,replace(as.numeric(nonzeroX),c(1:18),c(137,1364,5735,6366,2498,
7066,5440,3701,5284,754,4995,2432,3565,749,6261,7105,6565,8357))]
greengeneX1B3=boneX1[,replace(as.numeric(nonzeroX),c(1:18),c(6054,1364,2433,1807,760,
8071,2768,3701,4160,4377,1798,5562,6194,5756,6261,7105,7789,8357)]]

####Bag type B1 #####
lsfitX1=lm(boneY1~-1+greengeneX1B1)
betlassoX1B1=as.matrix(c(lsfitX1$coef),ncol=1,nrow=length(nonzeroX))
newX2=boneX2[,replace(as.numeric(nonzeroX),c(1:18),c(137,1364,5735,6366,2498,
7066,5440,6840,5284,754,4995,2432,5449,749,6261,6881,6565,8357))]
yhat2=(newX2*%betlassoX1B1)
lsPMSEgreengeneX1=1/testn*sum(boneY2-yhat2)^2 ##### using test data
lsPMSEgreengeneX1

yhat1=(greengeneX1B1*%betlassoX1B1) #####using training data
lsMSEgreengeneX1=1/nTR*sum(boneY1-yhat1)^2
lsMSEgreengeneX1

####Bag type B2 #####
lsfitX1=lm(boneY1~-1+greengeneX1B2)
betlassoX1B2=as.matrix(c(lsfitX1$coef),ncol=1,nrow=length(nonzeroX))
newX2=boneX2[,replace(as.numeric(nonzeroX),c(1:18),c(137,1364,5735,6366,2498,
7066,5440,3701,5284,754,4995,2432,3565,749,6261,7105,6565,8357))]
yhat2=(newX2*%betlassoX1B2)
lsPMSEgreengeneX1=1/testn*sum(boneY2-yhat2)^2 ##### using test data
lsPMSEgreengeneX1

yhat1=(greengeneX1B2*%betlassoX1B2) #####using training data
lsMSEgreengeneX1=1/nTR*sum(boneY1-yhat1)^2
lsMSEgreengeneX1

```

```

#####Bag type B3 #####
lsfitX1=lm(boneY1~-1+greengeneX1B3)
betalassoX1B3=as.matrix(c(lsfitX1$coef),ncol=1,nrow=length(nonzeroX))
newX2=boneX2[,replace(as.numeric(nonzeroX),c(1:18),c(6054,1364,2433,1807,760,
8071,2768,3701,4160,4377,1798,5562,6194,5756,6261,7105,7789,8357))]

yhat2=(newX2%*%betalassoX1B3)
lsPMSEgreengeneX1=1/testn*sum(boneY2-yhat2)^2 ##### using test data
lsPMSEgreengeneX1

yhat1=(greengeneX1B3%*%betalassoX1B3) #####using training data
lsMSEgreengeneX1=1/nTR*sum(boneY1-yhat1)^2
lsMSEgreengeneX1

```