A Sparse Additive Model for High-Dimensional Interactions with an Exposure Variable 2 Sahir R Bhatnagar^{1,2}, Tianyuan Lu^{3,4}, Amanda Lovato⁵, David L Olds⁶, Michael S Kobor⁷, Michael J Meaney⁸, Kieran O'Donnell⁹, Yi Yang¹⁰, and Celia MT Greenwood 1,3,5 5 ¹Department of Epidemiology, Biostatistics and Occupational Health, McGill University 7 ²Department of Diagnostic Radiology, McGill University ³Quantitative Life Sciences, McGill University ⁴Lady Davis Institute, Jewish General Hospital, Montréal, QC 10 ⁵Statistics Canada, Ottawa, ON 11 ⁶Department of Pediatrics, University of Colorado School of Medicine, Denver ⁷Department of Medical Genetics, University of British Columbia, BC 13 ⁸Singapore Institute for Clinical Sciences, Singapore; McGill University 14 ⁹Department of Psychiatry, McGill University 15 ¹⁰Department of Mathematics and Statistics, McGill University 16 ¹¹Departments of Oncology and Human Genetics, McGill University 17

September 5, 2021

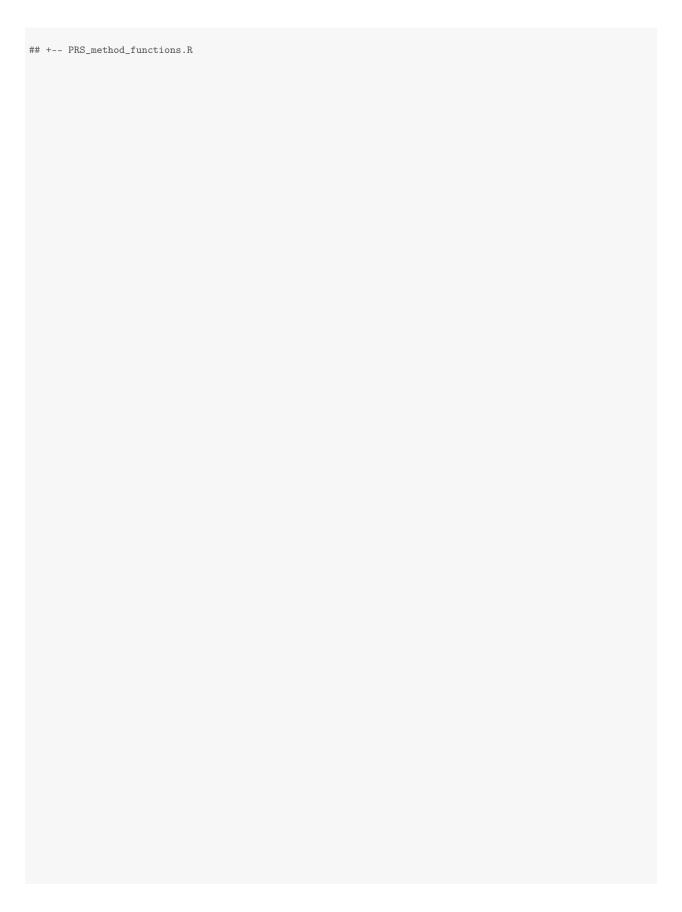
18

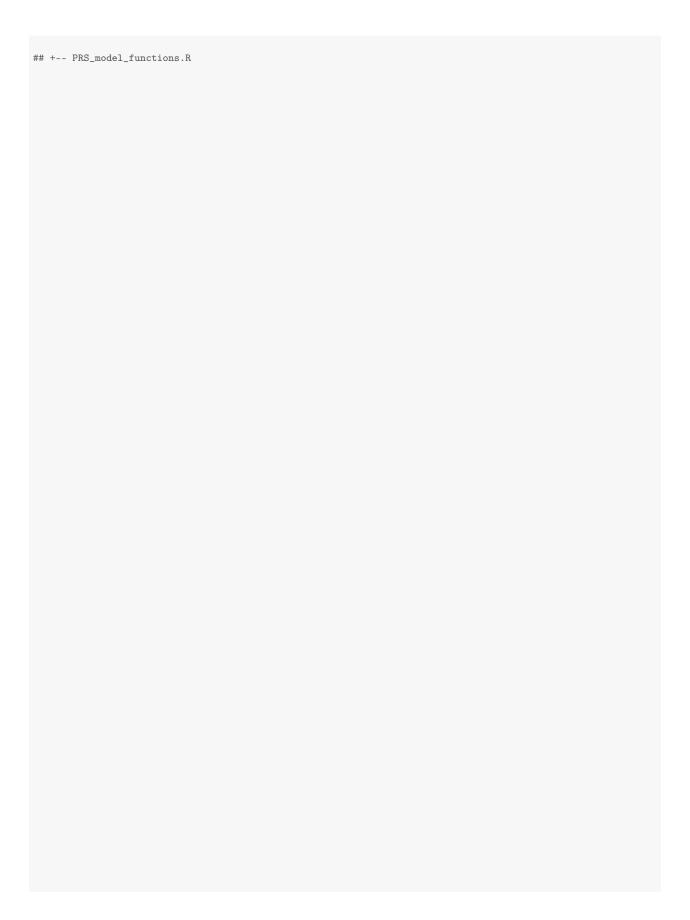
/scratch/bhatnagar-lab/sbhatnagar/git_repositories/sail/manuscript/bin

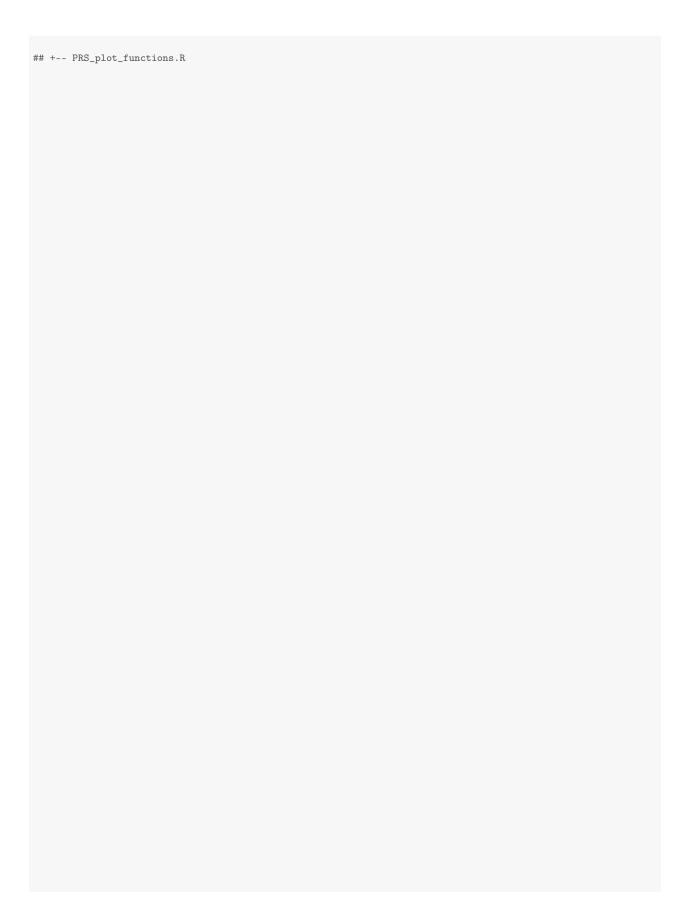
+-- ADNI.R

+-- PRS_bootstrap.R

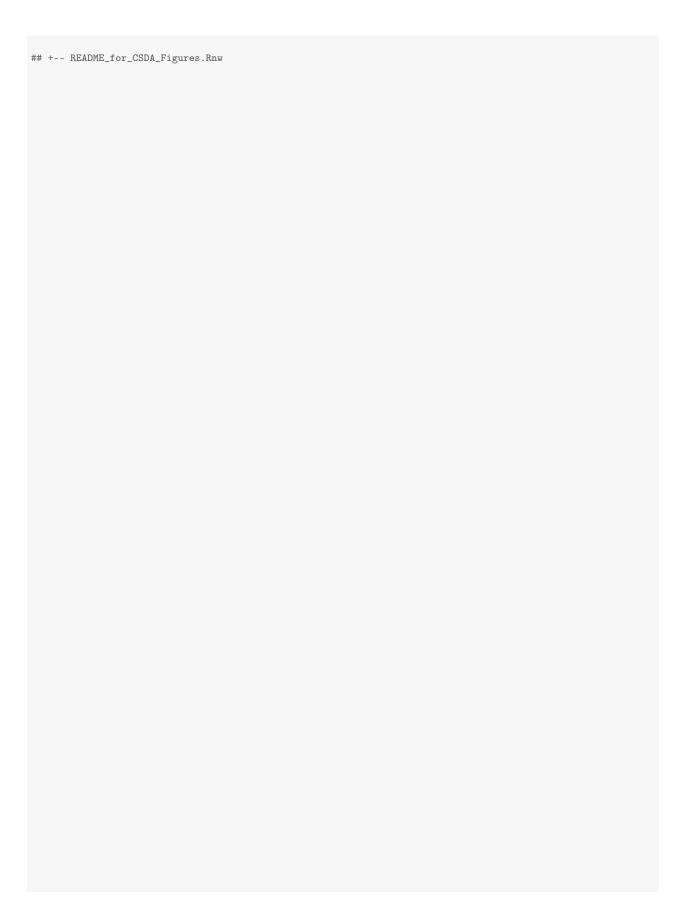
+-- PRS_eval_functions.R







+-- PRS_plots.R



```
## +-- README_for_CSDA_Figures.pdf
## +-- README_for_CSDA_Figures.tex
## +-- cache
## | +-- __packages
     +-- globals_6d1d04419b10b1a06759621e8a2eb8a6.RData
## |
      +-- globals_6d1d04419b10b1a06759621e8a2eb8a6.rdb
## |
      +-- globals_6d1d04419b10b1a06759621e8a2eb8a6.rdx
## |
      +-- packages_9258a6f76ff684c0e2fd1b9c0ebacc65.RData
## |
## |
      +-- packages_9258a6f76ff684c0e2fd1b9c0ebacc65.rdb
## |
      +-- packages_9258a6f76ff684c0e2fd1b9c0ebacc65.rdx
      +-- plot-mse-sim_9c0c9a1ddefc6e0131421d7b889a78cc.RData
       +-- plot-mse-sim_9c0c9a1ddefc6e0131421d7b889a78cc.rdb
       +-- plot-mse-sim_9c0c9a1ddefc6e0131421d7b889a78cc.rdx
      +-- setup2_900cd6b26f4a65ef22443e3819f71205.RData
      +-- setup2_900cd6b26f4a65ef22443e3819f71205.rdb
## |
## |
      +-- setup2_900cd6b26f4a65ef22443e3819f71205.rdx
      +-- simulation-results_05ea566347202b9db8e06fd8152aac10.RData
## |
      +-- simulation-results_05ea566347202b9db8e06fd8152aac10.rdb
## |
      +-- simulation-results_05ea566347202b9db8e06fd8152aac10.rdx
## |
      +-- toy-effects_601ac4af2c99af20848947802c3de27d.RData
## |
      +-- toy-effects_601ac4af2c99af20848947802c3de27d.rdb
## |
## |
      +-- toy-effects_601ac4af2c99af20848947802c3de27d.rdx
      +-- toy-example_a90f8c38d0355dd05704afeb06d0c2c6.RData
## |
      +-- toy-example_a90f8c38d0355dd05704afeb06d0c2c6.rdb
      +-- toy-example_a90f8c38d0355dd05704afeb06d0c2c6.rdx
      +-- toy-solution-path_991c1813a5d6d78869c629849579836d.RData
      +-- toy-solution-path_991c1813a5d6d78869c629849579836d.rdb
## |
      +-- toy-solution-path_991c1813a5d6d78869c629849579836d.rdx
## |
      +-- unnamed-chunk-1_9950a44ce550dc548513d2b840367e35.RData
## |
      +-- unnamed-chunk-1_9950a44ce550dc548513d2b840367e35.rdb
## |
      \-- unnamed-chunk-1_9950a44ce550dc548513d2b840367e35.rdx
## +-- figure
## | +-- plot-mse-sim-1.pdf
## | +-- toy-effects-1.pdf
## | \-- toy-solution-path-1.pdf
## +-- intro.R
## +-- setup.R
## +-- simulation.R
## +-- support_bootstrap.R
## \-- support_plots.R
```

1 Figure 1 - Toy example solution path and effects

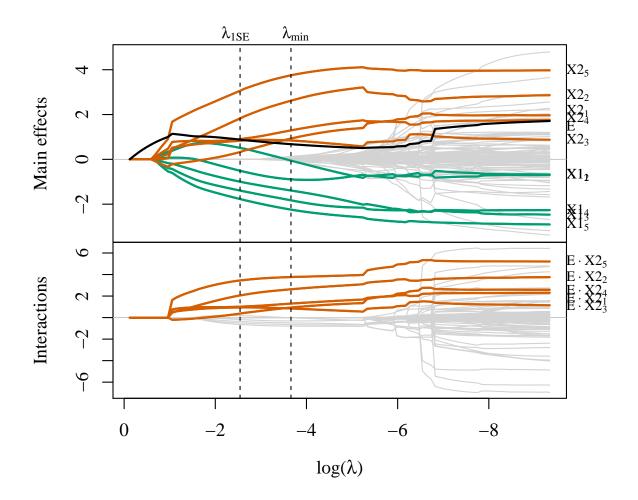


Figure 1: Toy example solution path for main effects (top) and interactions (bottom). $\{X1_1, X1_2, X1_3\}$ and $\{X2_1, X2_2, X2_3\}$ are the three basis coefficients for X_1 and X_2 , respectively. λ_{1SE} is the largest value of penalization for which the CV error is within one standard error of the minimizing value λ_{min} .

In Figure 2, we plot the true and estimated component functions $\hat{f}_1(X_1)$ and $E \cdot \hat{f}_2(X_2)$, and their estimates from this analysis with sail. We are able to capture the shape of the correct functional form, but the means are not well aligned with the data. Lack-of-fit for $f_1(X_1)$ can be partially explained by acknowledging that sail is trying to fit a cubic spline to a linear function. Nevertheless, this example demonstrates that sail can still identify trends reasonably well.

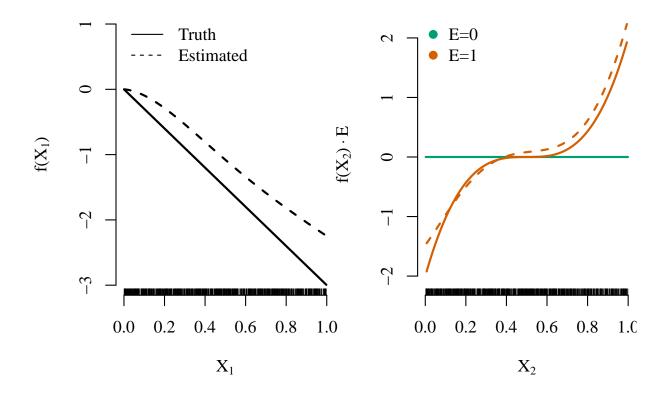


Figure 2: Estimated smooth functions for X_1 and the $X_2 \cdot E$ interaction by the sail method based on λ_{min} .

$_{26}$ 2 Figure 2 - Test set MSE

```
## Error in ':='(scenario, as.numeric(as.character(stringr::str_extract_all(parameterIndex, : Check that is.data.table(DT)
== TRUE. Otherwise, := and ':='(...) are defined for use in j, once only and in particular ways. See help(":=").

## Error in ':='(scen, ifelse(scenario == 1, "Strong Hierarchy", ifelse(scenario == : Check that is.data.table(DT))
== TRUE. Otherwise, := and ':='(...) are defined for use in j, once only and in particular ways. See help(":=").

## Error in ':='(scen, factor(scen, levels = c("Strong Hierarchy", "Weak Hierarchy", : Check that is.data.table(DT))
== TRUE. Otherwise, := and ':='(...) are defined for use in j, once only and in particular ways. See help(":=").
```

$_{27}$ 3 Table 1

Table 1: Mean (standard deviation) of the number of selected variables $(|\hat{\mathcal{J}}|)$, true positive rate (TPR) and false positive rate (FPR) as a percentage from 200 simulations for each of the five scenarios. $|\mathcal{J}|$ is the number of truly associated variables.

			(6			_	<u>-1</u>				6				6				1)	
	sail weak	(6)	21 (3) $82.1 (10 9)$	0.8 (0.1		14(10)	55.0(13.7)	0.6(0.5)		26(30)	22.9 (36.9)	1.3(1.5)		20 (4)	68.1 (14.9)	0.7 (0.2)		22(2)	85.2 (12 1)	0.9 (0.1
Non-linear Interactions	adaptive sail	(6)	8 (3) 81.4 (13.0)	0.1 (0.1)		5 (3)	46.4 (10.1)	0.2(0.1)		2 (2)	0.0(0.0)	0.1 (0.1)		11 (4)	86.0(18.5)	0.2(0.2)		9 (2)	84.1 (9.2)	0.2(0.1)
	sail	(6)	21 (3)	0.8 (0.1)		16(7)	50.5 (10.4)	0.7(0.3)		7 (7)	0.0(0.0)	0.4 (0.3)		20(4)	91.8 (10.5)	0.7(0.2)		22(2)	88.3 (10.3)	0.9(0.1)
Non-linear Main Effects	gamsel	(10)	46 (21) $56.9 (7.7)$	2.1 (1.1)		21 (15)	42.7(6.8)	1.0 (0.7)		12 (12)	0.0 (0.0)	0.6(0.6)		37 (16)	70.4(3.7)	1.6 (0.8)		56(20)	81.3(9.5)	2.6(1.0)
	$_{ m SPAM}$	(0,1)	42 (19) $60.9 (8.5)$	1.9(0.9)		28 (16)	53.9(9.4)	1.2(0.8)		13 (12)	0.0(0.0)	$(0.0) \ 7.0$		42 (19)	65.0(8.1)	1.9(0.9)		46 (21)	93.1 (10.7)	2.1(1.0)
	HierBasis	(07)	133 (48) 65.2 (8.1)	6.5(2.4)		24(23)	42.2 (6.3)	1.1 (1.1)		12 (13)	0.0(0.0)	0.6(0.7)		37(19)	70.3(3.8)	1.6(0.9)		154 (17)	97.5 (6.6)	7.5(0.9)
ear ctions	GLinternet	(00) 07	40 (20) $66.4 (14.0)$	1.8 (1.0)		38 (23)	64.1 (14.9)	1.7(1.1)		38 (21)	81.4 (27.0)	1.8(1.0)		51 (23)	93.4 (8.5)	2.2(1.2)		34 (18)	77.0(9.5)	1.5(0.9)
Linear Interactions	lassoBT	7	35 (18) $61.7 (11.5)$	1.5 (0.9)		20(13)	40.8(3.8)	(7.0) 6.0		14 (13)	0.0(0.0)	0.7 (0.7)		48 (19)	72.3(6.3)	2.2(1.0)		31 (15)	76.0(10.9)	1.3(0.8)
Linear Main Effects	adaptive lasso	$(\mathcal{J} = 7)$	8 (4) $49.3 (10.1)$	0.2 (0.2)	$(\mathcal{J} = 5)$	4 (2)	40.1 (1.4)	0.1 (0.1)	$ y (\mathcal{J} =2)$	3 (2)	0.0(0.0)	(6.9) 9.0	$\mathcal{I} =7$	8 (3)	67.2 (6.7)	0.2(0.2)	$y(\mathcal{J} = 5)$	7 (4)	66.5 (15.3)	0.2(0.2)
	lasso	1a) Strong heredity $(\mathcal{J} = 7)$	28 (15) $53.9 (8.4)$	1.2 (0.7)	1b) Weak heredity $(\mathcal{J} = 5)$	19 (12)	40.7(3.6)	$(9.0) \ 6.0$	1c) Interactions Only $(\mathcal{J} = 2)$	12 (12)	0.0(0.0)	(9.0) 9.0	2) Linear Effects $(\mathcal{J} = 7)$	37(17)	70.4(3.7)	1.6(0.8)	3) Main Effects Only $(\mathcal{J} = 5)$	29 (14)	75.9(10.9)	1.3(0.7)
		$\frac{1a}{ \widehat{\beta} }$ Str	\sum_{ \text{\subset}/ \text{TPR}}	FPR	$\frac{1}{1}$ We	$\overline{\mathcal{L}}$	TPR	FPR	1c) Int	$\overline{\mathcal{L}}$	TPR	FPR	2) Line	$\overline{\mathcal{L}}$	TPR	FPR	3) Mai	$\overline{\mathcal{L}}$	TPR	FPR

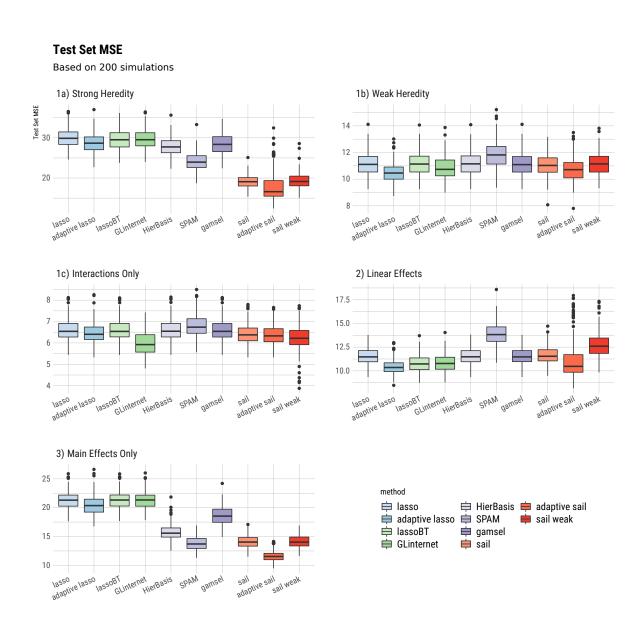


Figure 3: Boxplots of the test set mean squared error from 200 simulations for each of the five simulation scenarios.