Plink Report (with EpiGEN)

Ways of evaluating epistasis detection algorithm performance:

1. Number of interacting pairs (true positives) identified.
2. Number of false positives.
3. Position of true positive(s) (averaged if multiple) when ranked by p-value. If any true positives are missing their position is considered to be the “last” in the list.
   1. The above definition will be referred to as penalized true positive position.
   2. Alternatively, average true positive position can be computed only using the detected true positives. This will be referred to as unpenalized true positive position.
4. Runtime (~1second for 1000 SNPs, ~14 minutes for 100000 SNPs)
   1. Need to specify how the plink was executed on the HPC.
   2. Regardless Plink’s epistasis seems well optimized and may be usable on > 1000000 SNPs.

Compare these performance parameters across:

1. Multiplicative vs Dominant vs Recessive vs XOR Interaction.
2. Interaction Alpha: 1.25, 1.5, 2, 3, 8, 16.
3. Pure vs Impure.

Each EpiGEN dataset is named as follows: PURE/IMPURE (indicates presence of marginal effects) \_ MULTIPLICATIVE/DOMINANT/RECESSIVE/XOR (indicates type of interaction) \_ ONEPAIR / TWOPAIRS / EIGHTPAIRS (indicates number of interacting disease snp pairs) \_ BASELINEALPHA10 (indicates quantitative phenotype value in absence of marginal and interaction effects) \_ InteractionAlpha 1.25/1.5/2/3/8/16 (indicates strength of interaction effect)

**RESULTS (pages 1-11)**

Impure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha2

Number of true positives: 0

Number of false positives: 22

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha3

Number of true positives: 1

Number of false positives: 74

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 1

Impure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha1.5

Number of true positives: 0

Number of false positives: 160

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha1.25

Number of true positives: 0

Number of false positives: 44

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha2

Number of true positives: 1

Number of false positives: 526

Average true positive position (unpenalized) ranked by p-value: 30

Average true positive position (penalized) ranked by p-value: 279

Impure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha3

Number of true positives: 0

Number of false positives: 165

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha1.5

Number of true positives: 0

Number of false positives: 187

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha1.25

Number of true positives: 0

Number of false positives: 25

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Pure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha2

Number of true positives: 1

Number of false positives: 137

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 1

Pure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha3

Number of true positives: 1

Number of false positives: 15

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 1

Pure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha1.5

Number of true positives: 0

Number of false positives: 15

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Pure\_Multiplicative\_OnePair\_BaselineAlpha10\_InteractionAlpha1.25

Number of true positives: 0

Number of false positives: 0

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Pure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha2

Number of true positives: 1

Number of false positives: 100

Average true positive position (unpenalized) ranked by p-value: 4

Average true positive position (penalized) ranked by p-value: 53

Pure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha3

Number of true positives: 1

Number of false positives: 517

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 260

Pure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha1.5

Number of true positives: 1

Number of false positives: 8

Average true positive position (unpenalized) ranked by p-value: 3

Average true positive position (penalized) ranked by p-value: 6.5

Pure\_Multiplicative\_TwoPairs\_BaselineAlpha10\_InteractionAlpha1.25

Number of true positives: 0

Number of false positives: 1

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

**DOMINANT DATASETS**

Impure\_Dominant\_OnePair\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 1

Number of false positives: 247

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 1

Impure\_Dominant\_OnePair\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 1

Number of false positives: 529

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 1

Impure\_Dominant\_TwoPairs\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 2

Number of false positives: 210

Average true positive position (unpenalized) ranked by p-value: 1.5

Average true positive position (penalized) ranked by p-value: 1.5

Impure\_Dominant\_TwoPairs\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 2

Number of false positives: 232

Average true positive position (unpenalized) ranked by p-value: 1.5

Average true positive position (penalized) ranked by p-value: 1.5

Pure\_Dominant\_OnePair\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 1

Number of false positives: 298

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 1

Pure\_Dominant\_OnePair\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 1

Number of false positives: 300

Average true positive position (unpenalized) ranked by p-value: 1

Average true positive position (penalized) ranked by p-value: 1

Pure\_Dominant\_TwoPairs\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 2

Number of false positives: 271

Average true positive position (unpenalized) ranked by p-value: 1.5

Average true positive position (penalized) ranked by p-value: 1.5

Pure\_Dominant\_TwoPairs\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 2

Number of false positives: 284

Average true positive position (unpenalized) ranked by p-value: 1.5

Average true positive position (penalized) ranked by p-value: 1.5

**RECESSIVE DATASETS**

Impure\_Recessive\_OnePair\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 0

Number of false positives: 0

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Recessive\_OnePair\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 0

Number of false positives: 2

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Recessive\_TwoPairs\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 1

Number of false positives: 1369

Average true positive position (unpenalized) ranked by p-value: 57

Average true positive position (penalized) ranked by p-value: 714

Impure\_Recessive\_TwoPairs\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 1

Number of false positives: 1348

Average true positive position (unpenalized) ranked by p-value: 42

Average true positive position (penalized) ranked by p-value: 696

Pure\_Recessive\_OnePair\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 1

Number of false positives: 1692

Average true positive position (unpenalized) ranked by p-value: 191

Average true positive position (penalized) ranked by p-value: 191

Pure\_Recessive\_OnePair\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 1

Number of false positives: 1613

Average true positive position (unpenalized) ranked by p-value: 149

Average true positive position (penalized) ranked by p-value: 149

Pure\_Recessive\_TwoPairs\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 1

Number of false positives: 546

Average true positive position (unpenalized) ranked by p-value: 100

Average true positive position (penalized) ranked by p-value: 324

Pure\_Recessive\_TwoPairs\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 1

Number of false positives: 561

Average true positive position (unpenalized) ranked by p-value: 9

Average true positive position (penalized) ranked by p-value: 286

**CONTROL DATASETS**

Pure\_Control\_TwoPairs\_BaselineAlpha10

Number of true positives: 0

Number of false positives: 0

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Pure\_Control\_OnePair\_BaselineAlpha10

Number of true positives: 0

Number of false positives: 0

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Pure\_Control\_EightPairs\_BaselineAlpha10

Number of true positives: 0

Number of false positives: 0

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Control\_TwoPairs\_BaselineAlpha10

Number of true positives: 0

Number of false positives: 99

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Control\_OnePair\_BaselineAlpha10

Number of true positives: 0

Number of false positives: 30

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Control\_EightPairs\_BaselineAlpha10

Number of true positives: 0

Number of false positives: 1

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

**ADDITIONAL DATASETS:**

Pure\_XOR\_EightPairs\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 0

Number of false positives: 258

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Pure\_XOR\_EightPairs\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 0

Number of false positives: 986

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Pure\_Multiplicative\_EightPairs\_BaselineAlpha10\_InteractionAlpha3

Number of true positives: 2

Number of false positives: 742

Average true positive position (unpenalized) ranked by p-value: 324

Average true positive position (penalized) ranked by p-value: 639.75

Pure\_Multiplicative\_EightPairs\_BaselineAlpha10\_InteractionAlpha2

Number of true positives: 1

Number of false positives: 1020

Average true positive position (unpenalized) ranked by p-value: 6

Average true positive position (penalized) ranked by p-value: 895

Impure\_XOR\_EightPairs\_BaselineAlpha10\_InteractionAlpha16

Number of true positives: 0

Number of false positives: 1158

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_XOR\_EightPairs\_BaselineAlpha10\_InteractionAlpha8

Number of true positives: 0

Number of false positives: 743

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Multiplicative\_EightPairs\_BaselineAlpha10\_InteractionAlpha3

Number of true positives: 0

Number of false positives: 724

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

Impure\_Multiplicative\_EightPairs\_BaselineAlpha10\_InteractionAlpha2

Number of true positives: 0

Number of false positives: 908

Average true positive position (unpenalized) ranked by p-value: 0

Average true positive position (penalized) ranked by p-value: 0

**DISCUSSION (Page 12-13)**

Unpenalized true positive positions by interaction type.

Multiplicative: 0,1,0,0,30,0,0,0,1,1,0,0,4,1,3,0,324,6,0,0

Dominant: 1, 1, 1,5, 1.5, 1, 1, 1.5, 1.5

Recessive: 0,0, 57, 42, 191, 149, 100, 9

Control: 0, 0, 0, 0, 0, 0

XOR: 0,0,0,0

From this point onward assume all true positive positions are penalized.

Multiplicative Interaction Average True Positive Positions (note that 0 means no true positives were detected): 0,1,0,0,279,0,0,0,1,1,0,0,53,260,6.5,0,693.75,895,0,0

Dominant Interaction Average True Positive Positions: 1, 1, 1,5, 1.5, 1, 1, 1.5, 1.5

Recessive Interaction Average True Positive Positions: 0, 0, 714, 696, 191, 149, 324, 286

Control Interaction Average True Positive Positions: 0,0,0,0,0,0

XOR Interaction Average True Positive Positions: 0,0,0,0

Plink’s epistasis could not detect XOR interaction. Multiplicative and recessive interactions were frequently detected.

Pairs Detected (# of SNP pairs correctly detected / total # of interacting disease SNP pairs) – only count if at least one pair was detected: 1/1, 1/2, 1/1, 1/1, 1/2, 1/2, 1/2, 1/2, 1/2, 1/1, 1/1, 1/2, 1/2, 2/8, 1/8, 1/1, 1/1, 2/2, 2/2, 1/1, 1/1, 2/2, 2/2

The number of detected pairs was usually 1-2.

Now let us examine when Plink’s epistasis could detect multiplicative interaction.

Multiplicative Interaction Average True Positive Position Clustered by Interaction Alpha:

Interaction Alpha 1.25: 0,0,0,0

Interaction Alpha 1.5: 0,0,0,6.5

Interaction Alpha 2.0: 0,279,1,53,895,0

Interaction Alpha 3.0: 1,0,1,260,639.75,0

Clear trend here that interactions with larger effect were more easily detectable.

Let us also compare average true positive position for Pure vs Impure Epistasis in case of multiplicative interaction only.

Multiplicative Interaction Average True Positive Position Clustered by Pure Status:

Pure: 1,1,0,0,53,260,6.5,0,639.75,895

Impure: 0,1,0,0,279,0,0,0,0,0,0

Pure epistasis is easier to detect as expected.

Notably, all multiplicative pure interactions with alpha >= 2 were detected.

Notably, Plink’s epistasis rarely found more than one pair even when multiple pairs were present.