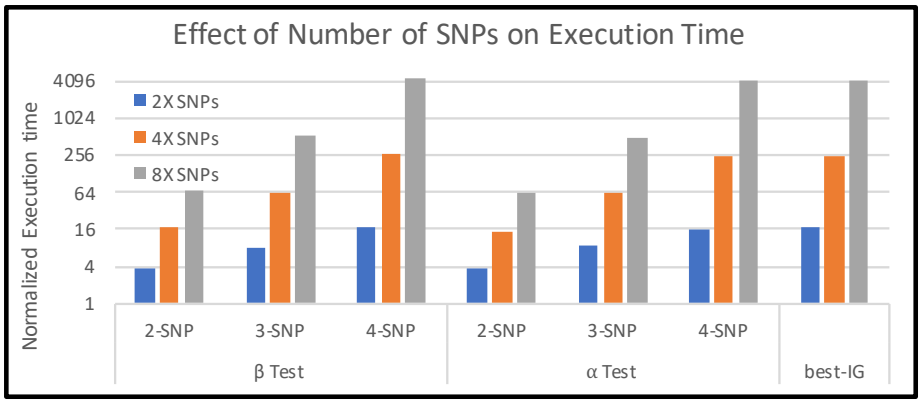
BitEpi: A Fast and Accurate Exhaustive Higher-Order Epistasis Search

Supplementary Data

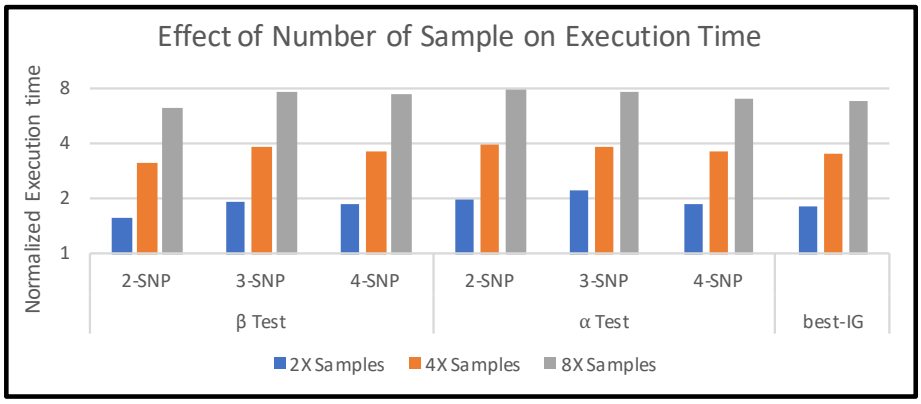
Arash Bayat*, Brendan Hosking, Yatish Jain
Cameron Hosking, Milindi Kodikara, Daniel Reti,
Natalie Twine and Denis C. Bauer*

Health and Biosecurity, CSIRO, Australia

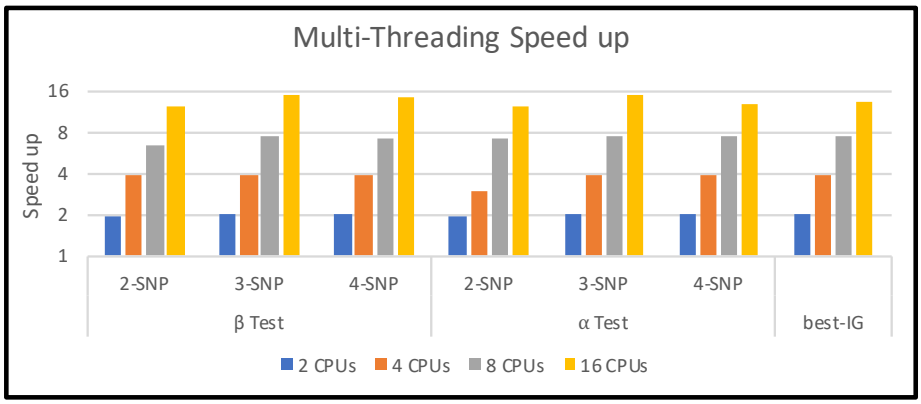
*email: Arash.Bayat@csiro.au
*email: Denis.Bauer@csiro.au



(a) The effect of number of SNPs on BitEpi execution time.



(b) The effect of number of samples on BitEpi execution time.



(c) The effect of number of threads on BitEpi execution time.

Figure 1: The effect of number of SNPs, samples and threads on BitEpi execution time.

Table 1: BitEpi execution time when the number of SNPs varies in the dataset. The number of samples is 4,000 (2,000 cases and 2,000 controls) in all cases.

Test	Number of SNP	Execution Time (sec)
best test	50	0.82
	100	13.65
	200	207.58
	400	3320.27
α Test 2-SNP	5000	40.19
	10000	155.33
	20000	611.36
	40000	2423.67
α Test 3-SNP	250	8.04
	500	72.97
	1000	506.50
	2000	4047.00
α Test 4-SNP	50	0.82
	100	12.91
	200	207.16
	400	3327.03
β Test 2-SNP	5000	40.19
	10000	155.27
	20000	688.16
	40000	2711.73
β Test 3-SNP	250	7.94
	500	63.11
	1000	504.49
	2000	4034.00
β Test 4-SNP	50	0.75
	100	12.59
	200	202.91
	400	3281.52

Table 2: BitEpi execution time when the number of samples varies in the dataset.

Test	Number of SNP	Number of Sample	Execution Time (sec)
best test	200	2000	115.90
	200	4000	207.77
	200	8000	400.76
	200	16000	785.50
α Test 2-SNP	10000	2000	79.07
	10000	4000	155.62
	10000	8000	310.64
	10000	16000	618.94
α Test 3-SNP	500	2000	33.07
	500	4000	73.08
	500	8000	125.68
	500	16000	249.03
α Test 4-SNP	200	2000	111.88
	200	4000	207.26
	200	8000	408.13
	200	16000	785.06
β Test 2-SNP	10000	2000	100.42
	10000	4000	155.53
	10000	8000	310.31
	10000	16000	618.24
β Test 3-SNP	500	2000	32.83
	500	4000	63.09
	500	8000	124.77
	500	16000	247.52
β Test 4-SNP	200	2000	109.28
	200	4000	203.11
	200	8000	392.05
	200	16000	814.35

Table 3: BitEpi execution time when the number of threads varies. The number of samples is 4,000 (2,000 cases and 2,000 controls) in all cases.

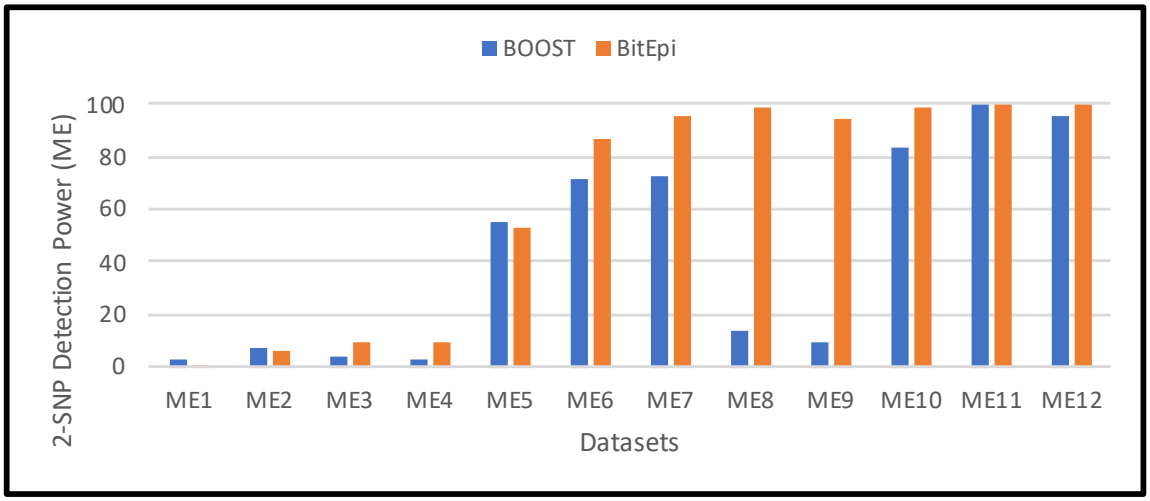
Test	Number of SNP	Number of Threads	Execution Time (sec)
best Test	400	1	3158.39
	400	2	1589.64
	400	4	811.48
	400	8	425.12
	400	16	236.35
α Test 2-SNP	40000	1	2370.38
	40000	2	1200.37
	40000	4	781.90
	40000	8	323.10
	40000	16	188.89
α Test 3-SNP	2000	1	3844.00
	2000	2	1927.50
	2000	4	973.27
	2000	8	503.19
	2000	16	255.58
α Test 4-SNP	400	1	3154.43
	400	2	1586.92
	400	4	806.27
	400	8	423.24
	400	16	244.00
β Test 2-SNP	40000	1	2653.23
	40000	2	1341.05
	40000	4	685.57
	40000	8	405.74
	40000	16	214.14
β Test 3-SNP	2000	1	3840.00
	2000	2	1917.02
	2000	4	970.26
	2000	8	504.73
	2000	16	255.69
β Test 4-SNP	400	1	3125.74
	400	2	1571.14
	400	4	801.53
	400	8	425.05
	400	16	219.61

Table 4: Description of epistasis model-simulated with GAMETES and 2-SNP detection power of BOOST and BitEpi for each model. For each model, 100 datasets are generated each with 100 SNPs and 2,000 samples (1,000 case and 1,000 controls). The minor allele frequency of SNPs in each dataset varies between 0.01 and 0.5. MAF1 and MAF2 are the minor allele frequency of the first and second interactive SNPs. Detection power is the number of datasets (out of 100) where the interactive pair is ranked first by the analysis metod.

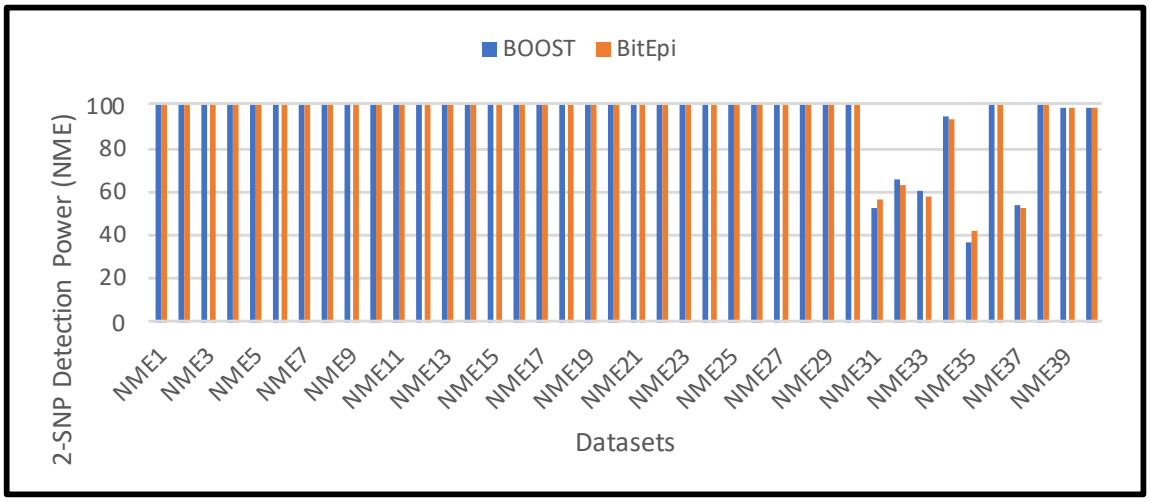
	Model Characteristics			Detection Power	
Model	Heritability	MAF1	MAF2	BOOST	BitEpi
PM1	0.005	0.050	0.050	10	6
PM2	0.005	0.050	0.250	66	81
PM3	0.005	0.050	0.500	45	55
PM4	0.005	0.250	0.250	68	88
PM5	0.005	0.250	0.500	55	79
PM6	0.005	0.500	0.500	64	82
PM7	0.050	0.050	0.050	70	100
PM8	0.050	0.050	0.250	75	100
PM9	0.050	0.250	0.250	71	100
PM10	0.200	0.500	0.500	75	100

Table 5: Description of epistasis model-simulated with GAMETES and 3-SNP detection power of MPI3SNP and BitEpi for each model. For each model, 100 datasets are generated each with 100 SNPs and 2,000 samples (1,000 cases and 1,000 controls). The minor allele frequency of SNPs in each dataset varies between 0.01 and 0.5. MAF1, MAF2, and MAF3 are the minor allele frequency of the first, second and third interactive SNPs. Detection power is the number of datasets (out of 100) where the interactive 3-SNP is ranked first by the analysis method.

	Model Characteristics				Detection Power	
Model	Heritability	MAF 1	MAF 2	MAF 3	MPI3SNP	BitEpi
TM1	0.005	0.050	0.050	0.050	0	0
TM2	0.005	0.050	0.250	0.500	16	25
TM3	0.005	0.050	0.500	0.500	9	16
TM4	0.005	0.250	0.250	0.250	13	36
TM5	0.005	0.250	0.250	0.500	15	36
TM6	0.005	0.500	0.500	0.500	27	52
TM7	0.050	0.250	0.250	0.250	100	100
TM8	0.050	0.250	0.250	0.500	100	100
TM9	0.050	0.500	0.500	0.500	100	100



(a) The effect of number of SNPs on BitEpi execution time.



(b) The effect of number of samples on BitEpi execution time.

Figure 2: The effect of number of SNPs, samples and threads on BitEpi execution time.

Table 6: Description of ME epistasis models simulated with GAMETES in [1] and 2-SNP detection power of BOOST and BitEpi for each model. For each model, 100 datasets are generated each with 100 SNPs and 1,600 samples (800 cases and 800 controls). Detection power is the number of datasets (out of 100) where the interactive pair is ranked first by the analysis method.

Model Identifier (Downloaded Data)	Model	Detection Power	
		BOOST	BitEpi
70	ME1	3	1
71	ME2	7	6
72	ME3	4	9
73	ME4	3	9
74	ME5	55	53
75	ME6	72	87
76	ME7	73	96
77	ME8	14	99
78	ME9	10	94
79	ME10	84	99
80	ME11	100	100
81	ME12	96	100

Table 7: Description of NME epistasis models simulated with GAMETES in and 2-SNP detection power of BOOST and BitEpi for each model. For each model, 100 datasets are generated each with 100 SNPs and 1,600 samples (800 cases and 800 controls). Detection power is the number of datasets (out of 100) where the interactive pair is ranked first by the analysis method.

Model Identifier (Downloaded Data)	Model	Detection Power	
		BOOST	BitEpi
0	NME1	100	100
1	NME2	100	100
2	NME3	100	100
3	NME4	100	100
4	NME5	100	100
5	NME6	100	100
6	NME7	100	100
7	NME8	100	100
8	NME9	100	100
9	NME10	100	100
15	NME11	100	100
16	NME12	100	100
17	NME13	100	100
18	NME14	100	100
19	NME15	100	100
25	NME16	100	100
26	NME17	100	100
27	NME18	100	100
28	NME19	100	100
29	NME20	100	100

Model Identifier (Downloaded Data)	Model	Detection Power	
		BOOST	BitEpi
30	NME21	100	100
31	NME22	100	100
32	NME23	100	100
33	NME24	100	100
34	NME25	100	100
40	NME26	100	100
41	NME27	100	100
42	NME28	100	100
43	NME29	100	100
44	NME30	100	100
55	NME31	52	57
56	NME32	66	63
57	NME33	60	58
58	NME34	95	93
59	NME35	37	42
65	NME36	100	100
66	NME37	54	53
67	NME38	100	100
68	NME39	99	99
69	NME40	99	99

Table 8: Overview of the tools used in this study

Tool	max. interactions
Boost	2
MPI3SNP	3
MDR	4
BitEpi	4

Proof of increasing β

Here we would like to prove that when adding a SNP to an interaction the β value always either increases or remains the same. For example, interaction ABC has an equal or higher β than interaction AB ($\beta_{ABC} \geq \beta_{AB}$) where A, B and C are three SNPs. As described in the manuscript, there are 3^m rows in the contingency table of an m-SNP interaction. Therefore in an $(m+1)$-SNP interaction there are $3^{(m+1)}$ rows (3×3^m rows). In other words, each row of the m-SNP interaction is divided into 3 rows in the $(m+1)$-SNP interaction. Table 9 clarifies this mapping, where $x = \sum_{i=1}^{3} x_i$ and $y = \sum_{i=1}^{3} y_i$ (i.e. the numbers of cases and controls with A=0/1 and B=1/1 do not change when adding C to the interaction).

Table 9: For $m = 2$: an m-SNP interaction on the left, an $(m+1)$-SNP interaction on the right, and the row mapping in the middle. The table shows that the "A=0/1, B=1/1" row is divided into 3 rows when adding C to the interaction. Note that the total number of cases and controls are the same.

m-SNP interaction					a m-SNP row $\longrightarrow$ 3 $(m+1)$-SNP row					$(m+1)$-SNP interaction				
A	B	Case	Control		AB	C	Cases	Controls		A	B	C	Cases	Controls
0/0	0/0	...	...		0/0 . 0/0	0/0	...	...		0/0	0/0	0/0	...	...
0/0	0/1	...	...		...	...	...	...		...	...	...	...	...
...	...	...	...		**0/1 . 1/1**	**0/0**	x_1	y_1		**0/1**	**1/1**	**0/0**	x_1	y_1
0/1	**1/1**	x	y			**0/1**	x_2	y_2		**0/1**	**1/1**	**0/1**	x_2	y_2
...	...	...	...			**1/1**	x_3	y_3		**0/1**	**1/1**	**1/1**	x_3	y_3
1/1	0/1	...	...		...	...	...	...		...	...	...	...	...
1/1	1/1	...	v		1/1 . 1/1	1/1	...	...		1/1	1/1	1/1	...	...

β is the weighted average of the purity of all rows. Let K_r be the r^{th} row of the m-SNP interaction with x cases and y controls. Let $K3_r$ be the corresponding 3 rows in the $(m+1)$-SNP interaction, where x_i and y_i represent the number of cases and controls in the i^{th} row (i.e. $x_1, x_2, x_3, y_1, y_2, y_3$). To show $\beta_{ABC} \geq \beta_{AB}$ it is enough to show that for each row in an m-SNP interaction (r) the contribution of $K3_r$ to $(m+1)$-SNP β (i.e. β_{ABC} in Table 9) is higher than the contribution of K_r to m-SNP β (i.e. β_{AB} in Table 9). We represent the former contribution with P_{m+1} (Equation 4) and the latter contribution with P_m (Equation 3). S is the total number of samples. Therfore we should prove Inequality 5. We expand and simplify this inequality in several steps (shown below) to form Inequality 13. It can be seen that Inequality 13 holds true as $x_i \geq 0$ and $y_i \geq 0$ and the possible negative values are squared.

$$x = \sum_{i=1}^{3} x_i \tag{1}$$

$$y = \sum_{i=1}^{3} y_i \tag{2}$$

$$\begin{aligned} P_m &= \frac{x+y}{S} \times \frac{x^2+y^2}{(x+y)^2} \\ &= \frac{1}{S} \times \frac{x^2+y^2}{(x+y)} \end{aligned} \tag{3}$$

$$\begin{aligned} P_{m+1} &= \sum_{i=1}^{3} (\frac{x_i+y_i}{S}) \times (\frac{{x_i}^2+{y_i}^2}{(x_i+y_i)^2}) \\ &= \frac{1}{S} \times \sum_{i=1}^{3} \frac{{x_i}^2+{y_i}^2}{(x_i+y_i)} \end{aligned} \tag{4}$$

$$P_{m+1} \geq P_m \tag{5}$$

$$\frac{1}{S} \times \sum_{i=1}^{3} \frac{{x_i}^2+{y_i}^2}{(x_i+y_i)} \geq \frac{1}{S} \times \frac{x^2+y^2}{(x+y)} \tag{6}$$

$$\sum_{i=1}^{3} \frac{{x_i}^2+{y_i}^2}{(x_i+y_i)} \geq \frac{x^2+y^2}{x+y} \tag{7}$$

$$\sum_{i=1}^{3} \frac{{x_i}^2+{y_i}^2}{(x_i+y_i)} \geq \frac{(\sum_{i=1}^{3} x_i)^2 + (\sum_{i=1}^{3} y_i)^2}{\sum_{i=1}^{3} x_i + \sum_{i=1}^{3} y_i} \tag{8}$$

$$\frac{{x_1}^2+{y_1}^2}{(x_1+y_1)} + \frac{{x_2}^2+{y_2}^2}{(x_2+y_2)} + \frac{{x_3}^2+{y_3}^2}{(x_3+y_3)} \geq \frac{(x_1+x_2+x_3)^2 + (y_1+y_2+y_3)^2}{x_1+x_2+x_3+y_1+y_2+y_3} \tag{9}$$

$$\begin{aligned} x_1x_2^2y_3^2 + x_1y_2^2x_3^2 + y_1x_2^2y_3^2 + y_1y_2^2x_3^2 + x_1^2x_2y_3^2 + y_1^2x_2x_3^2 + \\ x_1^2y_2y_3^2 + y_1^2y_2x_3^2 + x_1^2y_2^2x_3 + y_1^2x_2^2x_3 + x_1^2y_2^2y_3 + y_1^2x_2^2y_3 \geq \\ 2x_1x_2x_3y_1y_2 + 2x_1x_2x_3y_1y_3 + 2x_1x_2x_3y_2y_3 + \\ 2x_1x_2y_1y_2y_3 + 2x_1x_3y_1y_2y_3 + 2x_2x_3y_1y_2y_3 \end{aligned} \tag{10}$$

$$\begin{aligned} x_1x_2^2y_3^2 + x_1y_2^2x_3^2 + y_1x_2^2y_3^2 + y_1y_2^2x_3^2 + \\ x_1^2x_2y_3^2 + y_1^2x_2x_3^2 + x_1^2y_2y_3^2 + y_1^2y_2x_3^2 + \\ x_1^2y_2^2x_3 + y_1^2x_2^2x_3 + x_1^2y_2^2y_3 + y_1^2x_2^2y_3 - \\ 2x_1x_2x_3y_1y_2 - 2x_1x_2x_3y_1y_3 - 2x_1x_2x_3y_2y_3 - \\ 2x_1x_2y_1y_2y_3 - 2x_1x_3y_1y_2y_3 - 2x_2x_3y_1y_2y_3 \geq 0 \end{aligned} \tag{11}$$

$$
\begin{aligned}
&(x_1x_2^2y_3^2 - 2x_1x_2x_3y_2y_3 + x_1y_2^2x_3^2)+\\
&(y_1x_2^2y_3^2 - 2x_2x_3y_1y_2y_3 + y_1y_2^2x_3^2)+\\
&(x_1^2x_2y_3^2 - 2x_1x_2x_3y_1y_3 + y_1^2x_2x_3^2)+\\
&(x_1^2y_2y_3^2 - 2x_1x_3y_1y_2y_3 + y_1^2y_2x_3^2)+\\
&(x_1^2y_2^2x_3 - 2x_1x_2x_3y_1y_2 + y_1^2x_2^2x_3)+\\
&(x_1^2y_2^2y_3 - 2x_1x_2y_1y_2y_3 + y_1^2x_2^2y_3) \geq 0
\end{aligned}
\tag{12}
$$

$$
\begin{aligned}
&x_1(x_2y_3 - y_2x_3)^2+\\
&y_1(x_2y_3 - y_2x_3)^2+\\
&x_2(x_1y_3 - y_1x_3)^2+\\
&y_2(x_1y_3 - y_1x_3)^2+\\
&x_3(x_1y_2 - y_1x_2)^2+\\
&y_3(x_1y_2 - y_1x_2)^2 \geq 0
\end{aligned}
\tag{13}
$$

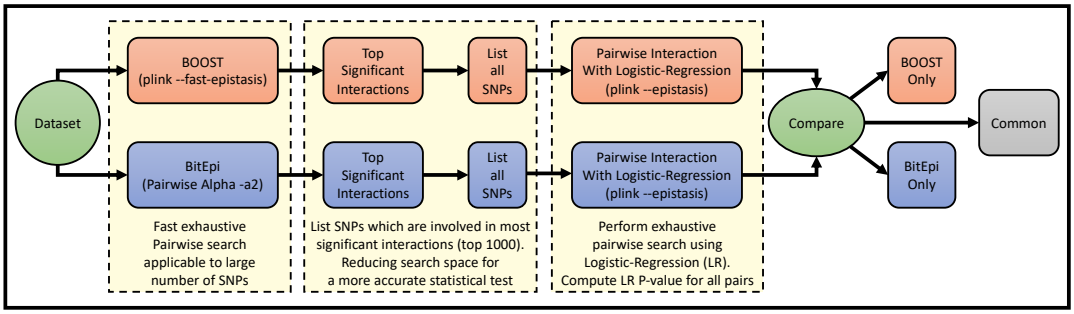


Figure 3: Recommended plink epistasis pipeline.

References

[1] Peng-Jie Jing and Hong-Bin Shen. Macoed: a multi-objective ant colony optimization algorithm for snp epistasis detection in genome-wide association studies. *Bioinformatics*, 31(5):634–641, 2014.