

INPower Package

April 24, 2017

Introduction

An R package to estimate the number of susceptibility loci and the distribution of their effect sizes for a trait on the basis of discoveries from existing genome-wide association studies (GWASs).

```
> library(INPower)
```

Height example

Get the path to the data which contains a known set of susceptibility SNPs for height.

```
> datafile <- system.file("sampleData", "data.rda", package="INPower")
```

Load and print the data frame.

```
> load(datafile)
```

```
> data
```

| | SNP | MAF | Beta | Power |
|----|------------|------|-------------|------------|
| 1 | rs314277 | 0.13 | 0.03538462 | 0.01005508 |
| 2 | rs4713858 | 0.14 | -0.03900000 | 0.02774654 |
| 3 | rs12198986 | 0.50 | 0.03300000 | 0.12273508 |
| 4 | rs1492820 | 0.48 | -0.03353846 | 0.13659137 |
| 5 | rs10946808 | 0.28 | -0.04830769 | 0.57978559 |
| 6 | rs2274432 | 0.37 | 0.04500000 | 0.58359100 |
| 7 | rs678962 | 0.22 | 0.05400000 | 0.65003547 |
| 8 | rs8007661 | 0.30 | -0.05015385 | 0.70992649 |
| 9 | rs12735613 | 0.24 | -0.05500000 | 0.75566530 |
| 10 | rs724016 | 0.48 | 0.04723077 | 0.76483843 |
| 11 | rs1812175 | 0.14 | -0.06900000 | 0.79323028 |
| 12 | rs4800148 | 0.21 | -0.05900000 | 0.80022419 |
| 13 | rs4896582 | 0.27 | -0.05615385 | 0.86294616 |
| 14 | rs11205277 | 0.44 | 0.05400000 | 0.94813202 |
| 15 | rs4549631 | 0.50 | 0.05500000 | 0.96621958 |
| 16 | rs7153027 | 0.48 | -0.05700000 | 0.98270897 |
| 17 | rs3760318 | 0.37 | -0.06000000 | 0.98802127 |
| 18 | rs2844479 | 0.33 | -0.06300000 | 0.99289585 |

```

19 rs6060369 0.36 0.06307692 0.99593942
20 rs3791675 0.23 0.07500000 0.99879522
21 rs6830062 0.11 -0.10500000 0.99969644
22 rs2282978 0.31 0.07150000 0.99976245
23 rs2814993 0.15 0.09500000 0.99991429
24 rs1042725 0.50 0.06792308 0.99991841
25 rs798544 0.28 -0.07700000 0.99996252
26 rs8756 0.48 -0.07200000 0.99999452
27 rs6060373 0.38 -0.07500000 0.99999710
28 rs3748069 0.26 -0.08300000 0.99999711
29 rs6440003 0.44 0.09500000 1.00000000
30 rs6763931 0.45 0.13500000 1.00000000

```

For each known susceptibility SNP, we will need the MAF, effect size and power of detection.

```

> MAFs <- data[, "MAF"]
> betas <- data[, "Beta"]
> pow <- data[, "Power"]

```

Suppose that a one-stage design with a genome-wide significant level of $1e-7$ is considered for a future study. It is known that the heritability of height is 0.8. It is of interest to predict the expected number of discoveries with sample sizes from 25,000 to 125,000 with an increment of 25,000. In addition, for the given sample sizes, it is also of interest to find power to detect at least k loci, with k ranging from 25 to 125 with an increment of 25.

```

> INPower(MAFs, betas, pow, span=0.5, binary.outcome=FALSE,
+         sample.size=seq(25000,125000,by=25000),
+         signif.lvl=10^(-7), tgv=0.8, k=seq(25,125,by=25))

```

```

[1] FALSE
$esdist.summary
$esdist.summary$t.n.loci
[1] 200.8

```

```

$esdist.summary$gve
[1] "16.39% of the total genetic variance"

```

```

$esdist.summary$es.dist
      MAFs      betas      pow effect.size est.num.loci
1  0.13 0.03538462 0.01005508 0.0002832185      54.0
2  0.14 -0.03900000 0.02774654 0.0003662568      47.3
3  0.50 0.03300000 0.12273508 0.0005445000      33.4
4  0.48 -0.03353846 0.13659137 0.0005615143      32.2
5  0.28 -0.04830769 0.57978559 0.0009409209       3.1
6  0.37 0.04500000 0.58359100 0.0009440550       3.0
7  0.22 0.05400000 0.65003547 0.0010007712       2.3
8  0.30 -0.05015385 0.70992649 0.0010564715       1.7
9  0.24 -0.05500000 0.75566530 0.0011035200       1.4
10 0.48 0.04723077 0.76483843 0.0011135882       1.4

```

| | | | | | |
|----|------|-------------|------------|--------------|-----|
| 11 | 0.14 | -0.06900000 | 0.79323028 | 0.0011464488 | 1.3 |
| 12 | 0.21 | -0.05900000 | 0.80022419 | 0.0011549958 | 1.3 |
| 13 | 0.27 | -0.05615385 | 0.86294616 | 0.0012430129 | 1.2 |
| 14 | 0.44 | 0.05400000 | 0.94813202 | 0.0014370048 | 1.1 |
| 15 | 0.50 | 0.05500000 | 0.96621958 | 0.0015125000 | 1.1 |
| 16 | 0.48 | -0.05700000 | 0.98270897 | 0.0016219008 | 1.0 |
| 17 | 0.37 | -0.06000000 | 0.98802127 | 0.0016783200 | 1.0 |
| 18 | 0.33 | -0.06300000 | 0.99289585 | 0.0017550918 | 1.0 |
| 19 | 0.36 | 0.06307692 | 0.99593942 | 0.0018333841 | 1.0 |
| 20 | 0.23 | 0.07500000 | 0.99879522 | 0.0019923750 | 1.0 |
| 21 | 0.11 | -0.10500000 | 0.99969644 | 0.0021586950 | 1.0 |
| 22 | 0.31 | 0.07150000 | 0.99976245 | 0.0021870205 | 1.0 |
| 23 | 0.15 | 0.09500000 | 0.99991429 | 0.0023013750 | 1.0 |
| 24 | 0.50 | 0.06792308 | 0.99991841 | 0.0023067722 | 1.0 |
| 25 | 0.28 | -0.07700000 | 0.99996252 | 0.0023905728 | 1.0 |
| 26 | 0.48 | -0.07200000 | 0.99999452 | 0.0025878528 | 1.0 |
| 27 | 0.38 | -0.07500000 | 0.99999710 | 0.0026505000 | 1.0 |
| 28 | 0.26 | -0.08300000 | 0.99999711 | 0.0026508872 | 1.0 |
| 29 | 0.44 | 0.09500000 | 1.00000000 | 0.0044475200 | 1.0 |
| 30 | 0.45 | 0.13500000 | 1.00000000 | 0.0090213750 | 1.0 |

```
$future.study.summary
$future.study.summary$e.discov
  sample.size e.discov
1      25000      27.3
2      50000      74.4
3      75000     125.6
4     100000     161.5
5     125000     182.8
```

```
$future.study.summary$e.gve
  sample.size e.gve
1      25000 6.58% of the total genetic variance
2      50000 10.28% of the total genetic variance
3      75000 13.17% of the total genetic variance
4     100000 14.85% of the total genetic variance
5     125000 15.71% of the total genetic variance
```

```
$future.study.summary$prob.k
      k Pr(X>=k).n=25000      k Pr(X>=k).n=50000      k Pr(X>=k).n=75000      k
1    24                0.90 25                1.00 25                1.00 25
2    25                0.82 50                1.00 50                1.00 50
3    25                0.82 68                0.91 75                1.00 75
4    26                0.72 70                0.83 100               1.00 100
5    27                0.59 72                0.71 119               0.90 125
6    28                0.46 74                0.57 121               0.82 155
7    28                0.46 75                0.49 123               0.71 158
8    29                0.34 75                0.49 125               0.57 159
9    30                0.23 76                0.42 125               0.57 161
```

| | | | | | | | |
|----|-----|------|-----|------|-----|------|-----|
| 10 | 32 | 0.09 | 78 | 0.28 | 126 | 0.50 | 162 |
| 11 | 50 | 0.00 | 79 | 0.22 | 127 | 0.43 | 163 |
| 12 | 75 | 0.00 | 82 | 0.09 | 129 | 0.30 | 165 |
| 13 | 100 | 0.00 | 100 | 0.00 | 131 | 0.19 | 166 |
| 14 | 125 | 0.00 | 125 | 0.00 | 133 | 0.11 | 168 |

| | Pr(X>=k) .n=1e+05 | k | Pr(X>=k) .n=125000 |
|----|-------------------|-----|--------------------|
| 1 | 1.00 | 25 | 1.00 |
| 2 | 1.00 | 50 | 1.00 |
| 3 | 1.00 | 75 | 1.00 |
| 4 | 1.00 | 100 | 1.00 |
| 5 | 1.00 | 125 | 1.00 |
| 6 | 0.92 | 178 | 0.90 |
| 7 | 0.78 | 180 | 0.79 |
| 8 | 0.72 | 181 | 0.72 |
| 9 | 0.58 | 182 | 0.63 |
| 10 | 0.50 | 183 | 0.53 |
| 11 | 0.42 | 184 | 0.43 |
| 12 | 0.27 | 185 | 0.34 |
| 13 | 0.21 | 187 | 0.18 |
| 14 | 0.11 | 188 | 0.12 |

The function call below shows the same results as the above, but without the `tg` (total genetic variance) argument. As a result, the genetic variance explained is expressed as a percentage of the total variance of the outcome, not of the total genetic variance.

```
> INPower(MAFs, betas, pow, span=0.5, binary.outcome=FALSE,
+         sample.size=seq(25000,125000,by=25000),
+         signif.lvl=10^(-7), k=seq(25,125,by=25))
```

```
[1] FALSE
```

```
$esdist.summary
```

```
$esdist.summary$t.n.loci
```

```
[1] 200.8
```

```
$esdist.summary$gve
```

```
[1] "13.11% of the total variance of the outcome"
```

```
$esdist.summary$es.dist
```

| | MAFs | betas | pow | effect.size | est.num.loci |
|----|------|-------------|------------|--------------|--------------|
| 1 | 0.13 | 0.03538462 | 0.01005508 | 0.0002832185 | 54.0 |
| 2 | 0.14 | -0.03900000 | 0.02774654 | 0.0003662568 | 47.3 |
| 3 | 0.50 | 0.03300000 | 0.12273508 | 0.0005445000 | 33.4 |
| 4 | 0.48 | -0.03353846 | 0.13659137 | 0.0005615143 | 32.2 |
| 5 | 0.28 | -0.04830769 | 0.57978559 | 0.0009409209 | 3.1 |
| 6 | 0.37 | 0.04500000 | 0.58359100 | 0.0009440550 | 3.0 |
| 7 | 0.22 | 0.05400000 | 0.65003547 | 0.0010007712 | 2.3 |
| 8 | 0.30 | -0.05015385 | 0.70992649 | 0.0010564715 | 1.7 |
| 9 | 0.24 | -0.05500000 | 0.75566530 | 0.0011035200 | 1.4 |
| 10 | 0.48 | 0.04723077 | 0.76483843 | 0.0011135882 | 1.4 |
| 11 | 0.14 | -0.06900000 | 0.79323028 | 0.0011464488 | 1.3 |

| | | | | | |
|----|------|-------------|------------|--------------|-----|
| 12 | 0.21 | -0.05900000 | 0.80022419 | 0.0011549958 | 1.3 |
| 13 | 0.27 | -0.05615385 | 0.86294616 | 0.0012430129 | 1.2 |
| 14 | 0.44 | 0.05400000 | 0.94813202 | 0.0014370048 | 1.1 |
| 15 | 0.50 | 0.05500000 | 0.96621958 | 0.0015125000 | 1.1 |
| 16 | 0.48 | -0.05700000 | 0.98270897 | 0.0016219008 | 1.0 |
| 17 | 0.37 | -0.06000000 | 0.98802127 | 0.0016783200 | 1.0 |
| 18 | 0.33 | -0.06300000 | 0.99289585 | 0.0017550918 | 1.0 |
| 19 | 0.36 | 0.06307692 | 0.99593942 | 0.0018333841 | 1.0 |
| 20 | 0.23 | 0.07500000 | 0.99879522 | 0.0019923750 | 1.0 |
| 21 | 0.11 | -0.10500000 | 0.99969644 | 0.0021586950 | 1.0 |
| 22 | 0.31 | 0.07150000 | 0.99976245 | 0.0021870205 | 1.0 |
| 23 | 0.15 | 0.09500000 | 0.99991429 | 0.0023013750 | 1.0 |
| 24 | 0.50 | 0.06792308 | 0.99991841 | 0.0023067722 | 1.0 |
| 25 | 0.28 | -0.07700000 | 0.99996252 | 0.0023905728 | 1.0 |
| 26 | 0.48 | -0.07200000 | 0.99999452 | 0.0025878528 | 1.0 |
| 27 | 0.38 | -0.07500000 | 0.99999710 | 0.0026505000 | 1.0 |
| 28 | 0.26 | -0.08300000 | 0.99999711 | 0.0026508872 | 1.0 |
| 29 | 0.44 | 0.09500000 | 1.00000000 | 0.0044475200 | 1.0 |
| 30 | 0.45 | 0.13500000 | 1.00000000 | 0.0090213750 | 1.0 |

```
$future.study.summary
$future.study.summary$e.discov
```

| | sample.size | e.discov |
|---|-------------|----------|
| 1 | 25000 | 27.3 |
| 2 | 50000 | 74.4 |
| 3 | 75000 | 125.6 |
| 4 | 100000 | 161.5 |
| 5 | 125000 | 182.8 |

```
$future.study.summary$e.gve
```

| | sample.size | e.gve |
|---|-------------|---|
| 1 | 25000 | 5.26% of the total variance of the outcome |
| 2 | 50000 | 8.23% of the total variance of the outcome |
| 3 | 75000 | 10.54% of the total variance of the outcome |
| 4 | 100000 | 11.88% of the total variance of the outcome |
| 5 | 125000 | 12.57% of the total variance of the outcome |

```
$future.study.summary$prob.k
```

| | k | Pr(X>=k).n=25000 | k | Pr(X>=k).n=50000 | k | Pr(X>=k).n=75000 | k |
|----|----|------------------|----|------------------|-----|------------------|-----|
| 1 | 24 | 0.90 | 25 | 1.00 | 25 | 1.00 | 25 |
| 2 | 25 | 0.82 | 50 | 1.00 | 50 | 1.00 | 50 |
| 3 | 25 | 0.82 | 68 | 0.91 | 75 | 1.00 | 75 |
| 4 | 26 | 0.72 | 70 | 0.83 | 100 | 1.00 | 100 |
| 5 | 27 | 0.59 | 72 | 0.71 | 119 | 0.90 | 125 |
| 6 | 28 | 0.46 | 74 | 0.57 | 121 | 0.82 | 155 |
| 7 | 28 | 0.46 | 75 | 0.49 | 123 | 0.71 | 158 |
| 8 | 29 | 0.34 | 75 | 0.49 | 125 | 0.57 | 159 |
| 9 | 30 | 0.23 | 76 | 0.42 | 125 | 0.57 | 161 |
| 10 | 32 | 0.09 | 78 | 0.28 | 126 | 0.50 | 162 |

| | | | | | | | |
|----|-----|------|-----|------|-----|------|-----|
| 11 | 50 | 0.00 | 79 | 0.22 | 127 | 0.43 | 163 |
| 12 | 75 | 0.00 | 82 | 0.09 | 129 | 0.30 | 165 |
| 13 | 100 | 0.00 | 100 | 0.00 | 131 | 0.19 | 166 |
| 14 | 125 | 0.00 | 125 | 0.00 | 133 | 0.11 | 168 |

| | Pr(X>=k) .n=1e+05 | k | Pr(X>=k) .n=125000 |
|----|-------------------|-----|--------------------|
| 1 | 1.00 | 25 | 1.00 |
| 2 | 1.00 | 50 | 1.00 |
| 3 | 1.00 | 75 | 1.00 |
| 4 | 1.00 | 100 | 1.00 |
| 5 | 1.00 | 125 | 1.00 |
| 6 | 0.92 | 178 | 0.90 |
| 7 | 0.78 | 180 | 0.79 |
| 8 | 0.72 | 181 | 0.72 |
| 9 | 0.58 | 182 | 0.63 |
| 10 | 0.50 | 183 | 0.53 |
| 11 | 0.42 | 184 | 0.43 |
| 12 | 0.27 | 185 | 0.34 |
| 13 | 0.21 | 187 | 0.18 |
| 14 | 0.11 | 188 | 0.12 |

Now a two-stage study is considered with all the other conditions remaining the same (including the estimate of total heritability). In addition, the selection criterion for SNPs taken toward the second stage is $5e-5$ and 30 assigned to the first stage (and hence 70)

```
> INPower(MAFs, betas, pow, span=0.5, binary.outcome=FALSE,
+         sample.size=seq(25000,125000,by=25000),
+         signif.lvl=10^(-7), multi.stage.option=list(al=5*10^(-5), pi=0.3),
+         tgv=0.8 , k=seq(25,125,by=25))
```

```
$esdist.summary
$esdist.summary$t.n.loci
[1] 200.8
```

```
$esdist.summary$gve
[1] "16.39% of the total genetic variance"
```

```
$esdist.summary$es.dist
```

| | MAFs | betas | pow | effect.size | est.num.loci |
|----|------|-------------|------------|--------------|--------------|
| 1 | 0.13 | 0.03538462 | 0.01005508 | 0.0002832185 | 54.0 |
| 2 | 0.14 | -0.03900000 | 0.02774654 | 0.0003662568 | 47.3 |
| 3 | 0.50 | 0.03300000 | 0.12273508 | 0.0005445000 | 33.4 |
| 4 | 0.48 | -0.03353846 | 0.13659137 | 0.0005615143 | 32.2 |
| 5 | 0.28 | -0.04830769 | 0.57978559 | 0.0009409209 | 3.1 |
| 6 | 0.37 | 0.04500000 | 0.58359100 | 0.0009440550 | 3.0 |
| 7 | 0.22 | 0.05400000 | 0.65003547 | 0.0010007712 | 2.3 |
| 8 | 0.30 | -0.05015385 | 0.70992649 | 0.0010564715 | 1.7 |
| 9 | 0.24 | -0.05500000 | 0.75566530 | 0.0011035200 | 1.4 |
| 10 | 0.48 | 0.04723077 | 0.76483843 | 0.0011135882 | 1.4 |
| 11 | 0.14 | -0.06900000 | 0.79323028 | 0.0011464488 | 1.3 |
| 12 | 0.21 | -0.05900000 | 0.80022419 | 0.0011549958 | 1.3 |

| | | | | | |
|----|------|-------------|------------|--------------|-----|
| 13 | 0.27 | -0.05615385 | 0.86294616 | 0.0012430129 | 1.2 |
| 14 | 0.44 | 0.05400000 | 0.94813202 | 0.0014370048 | 1.1 |
| 15 | 0.50 | 0.05500000 | 0.96621958 | 0.0015125000 | 1.1 |
| 16 | 0.48 | -0.05700000 | 0.98270897 | 0.0016219008 | 1.0 |
| 17 | 0.37 | -0.06000000 | 0.98802127 | 0.0016783200 | 1.0 |
| 18 | 0.33 | -0.06300000 | 0.99289585 | 0.0017550918 | 1.0 |
| 19 | 0.36 | 0.06307692 | 0.99593942 | 0.0018333841 | 1.0 |
| 20 | 0.23 | 0.07500000 | 0.99879522 | 0.0019923750 | 1.0 |
| 21 | 0.11 | -0.10500000 | 0.99969644 | 0.0021586950 | 1.0 |
| 22 | 0.31 | 0.07150000 | 0.99976245 | 0.0021870205 | 1.0 |
| 23 | 0.15 | 0.09500000 | 0.99991429 | 0.0023013750 | 1.0 |
| 24 | 0.50 | 0.06792308 | 0.99991841 | 0.0023067722 | 1.0 |
| 25 | 0.28 | -0.07700000 | 0.99996252 | 0.0023905728 | 1.0 |
| 26 | 0.48 | -0.07200000 | 0.99999452 | 0.0025878528 | 1.0 |
| 27 | 0.38 | -0.07500000 | 0.99999710 | 0.0026505000 | 1.0 |
| 28 | 0.26 | -0.08300000 | 0.99999711 | 0.0026508872 | 1.0 |
| 29 | 0.44 | 0.09500000 | 1.00000000 | 0.0044475200 | 1.0 |
| 30 | 0.45 | 0.13500000 | 1.00000000 | 0.0090213750 | 1.0 |

```
$future.study.summary
$future.study.summary$e.discov
```

| | sample.size | e.discov |
|---|-------------|----------|
| 1 | 25000 | 10.8 |
| 2 | 50000 | 31.5 |
| 3 | 75000 | 56.0 |
| 4 | 100000 | 82.1 |
| 5 | 125000 | 106.7 |

```
$future.study.summary$e.gve
```

| | sample.size | e.gve |
|---|-------------|--------------------------------------|
| 1 | 25000 | 3.75% of the total genetic variance |
| 2 | 50000 | 6.81% of the total genetic variance |
| 3 | 75000 | 8.89% of the total genetic variance |
| 4 | 100000 | 10.61% of the total genetic variance |
| 5 | 125000 | 12.04% of the total genetic variance |

```
$future.study.summary$prob.k
```

| | k | Pr(X>=k).n=25000 | k | Pr(X>=k).n=50000 | k | Pr(X>=k).n=75000 | k |
|----|----|------------------|----|------------------|----|------------------|----|
| 1 | 8 | 0.93 | 25 | 0.98 | 25 | 1.00 | 25 |
| 2 | 9 | 0.84 | 27 | 0.92 | 50 | 0.91 | 50 |
| 3 | 10 | 0.70 | 29 | 0.79 | 50 | 0.91 | 75 |
| 4 | 11 | 0.53 | 30 | 0.70 | 52 | 0.82 | 75 |
| 5 | 11 | 0.53 | 31 | 0.60 | 54 | 0.69 | 78 |
| 6 | 12 | 0.36 | 32 | 0.49 | 55 | 0.62 | 80 |
| 7 | 12 | 0.36 | 33 | 0.38 | 56 | 0.54 | 81 |
| 8 | 13 | 0.22 | 34 | 0.29 | 58 | 0.38 | 83 |
| 9 | 14 | 0.12 | 35 | 0.20 | 59 | 0.30 | 84 |
| 10 | 25 | 0.00 | 37 | 0.09 | 61 | 0.18 | 86 |
| 11 | 50 | 0.00 | 50 | 0.00 | 63 | 0.10 | 87 |

| | | | | | | | |
|----|-----|------|-----|------|-----|------|-----|
| 12 | 75 | 0.00 | 75 | 0.00 | 75 | 0.00 | 90 |
| 13 | 100 | 0.00 | 100 | 0.00 | 100 | 0.00 | 100 |
| 14 | 125 | 0.00 | 125 | 0.00 | 125 | 0.00 | 125 |

| | Pr(X>=k) .n=1e+05 | k | Pr(X>=k) .n=125000 |
|----|-------------------|-----|--------------------|
| 1 | 1.00 | 25 | 1.00 |
| 2 | 1.00 | 50 | 1.00 |
| 3 | 0.91 | 75 | 1.00 |
| 4 | 0.91 | 100 | 0.89 |
| 5 | 0.79 | 100 | 0.89 |
| 6 | 0.67 | 102 | 0.81 |
| 7 | 0.60 | 104 | 0.70 |
| 8 | 0.47 | 106 | 0.58 |
| 9 | 0.40 | 107 | 0.51 |
| 10 | 0.27 | 109 | 0.38 |
| 11 | 0.22 | 110 | 0.32 |
| 12 | 0.10 | 112 | 0.21 |
| 13 | 0.00 | 115 | 0.10 |
| 14 | 0.00 | 125 | 0.00 |

Session Information

```
> sessionInfo()
```

```
R version 3.4.0 (2017-04-21)
```

```
Platform: x86_64-apple-darwin15.6.0 (64-bit)
```

```
Running under: OS X El Capitan 10.11.6
```

```
Matrix products: default
```

```
BLAS: /Library/Frameworks/R.framework/Versions/3.4/Resources/lib/libRblas.0.dylib
```

```
LAPACK: /Library/Frameworks/R.framework/Versions/3.4/Resources/lib/libRlapack.dylib
```

```
locale:
```

```
[1] C/en_US.UTF-8/en_US.UTF-8/C/en_US.UTF-8/en_US.UTF-8
```

```
attached base packages:
```

```
[1] stats      graphics  grDevices  utils      datasets  methods    base
```

```
other attached packages:
```

```
[1] INPower_1.12.0 mvtnorm_1.0-6
```

```
loaded via a namespace (and not attached):
```

```
[1] compiler_3.4.0 tools_3.4.0
```