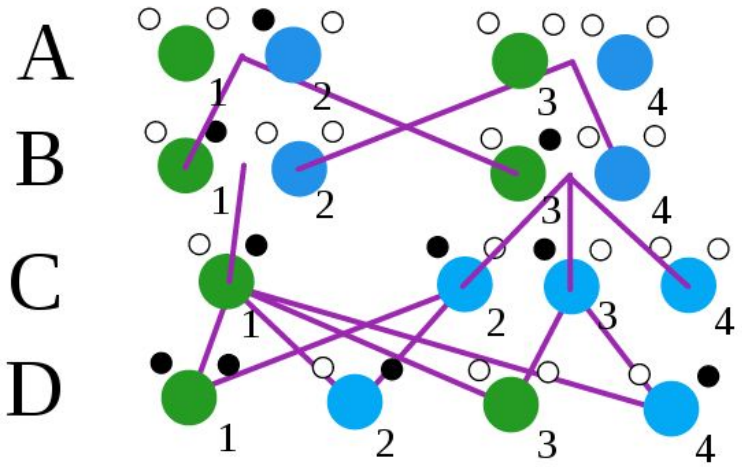
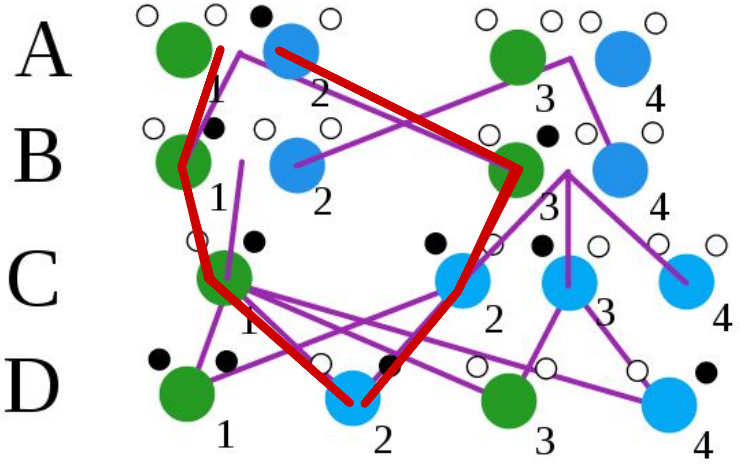
The effect of natural selection on relatedness in randomly mating populations.



Adam Kurkiewicz

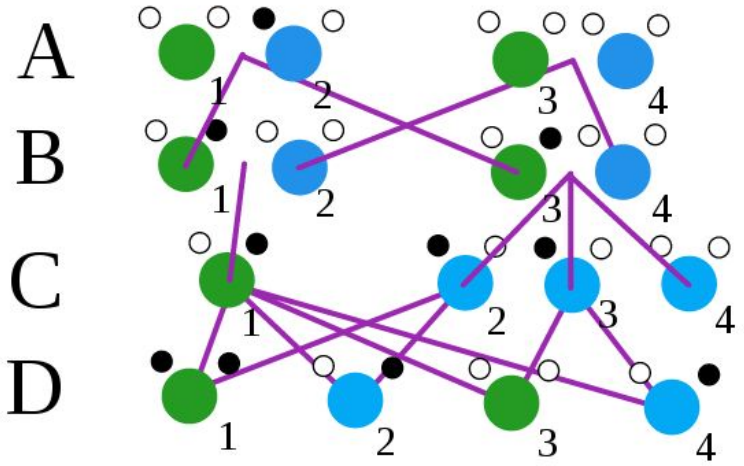
Family tree not a tree...



It's a DAG!

Measuring Relatedness

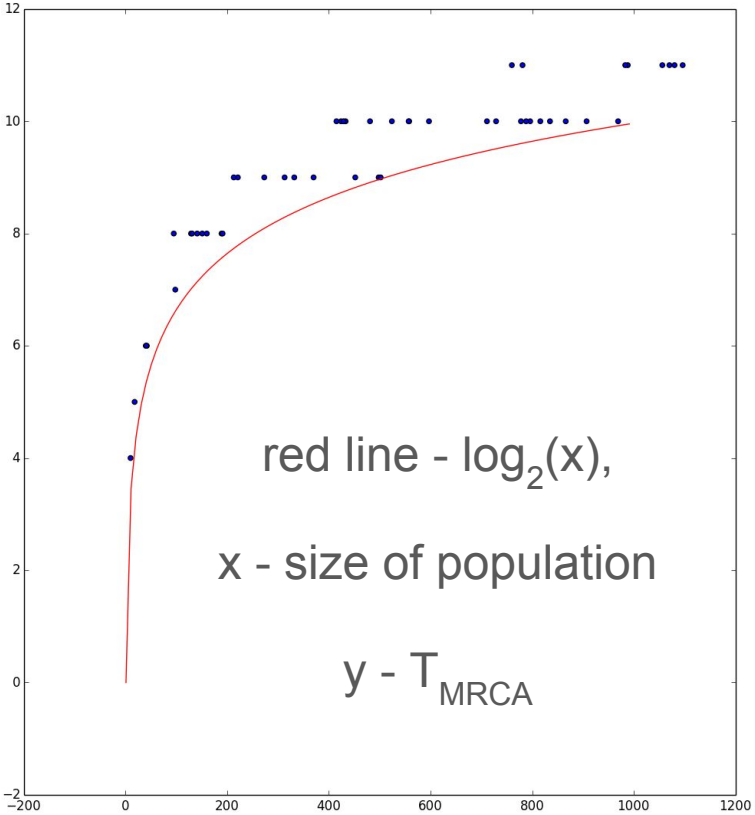
- based on population graph:
  - kth-generation pedigree collapse
  - T_{MRCA}
- based on individual's biology:
  - trait-based
  - Simple Tandem Repeats (STR)
  - Single Nucleotide Polymorphism (SNP)



What we know about T_{MRCA}

Rohde, Olsen and Chang* estimate T_{MRCA} for entire humanity to be ~ 100 generations.

In my simulations T_MRCA is no greater than ~ 10 (due to population size)



$T_{MRCA} \sim \log_2(n)^*$,
n is the size of population,
valid for randomly mating populations

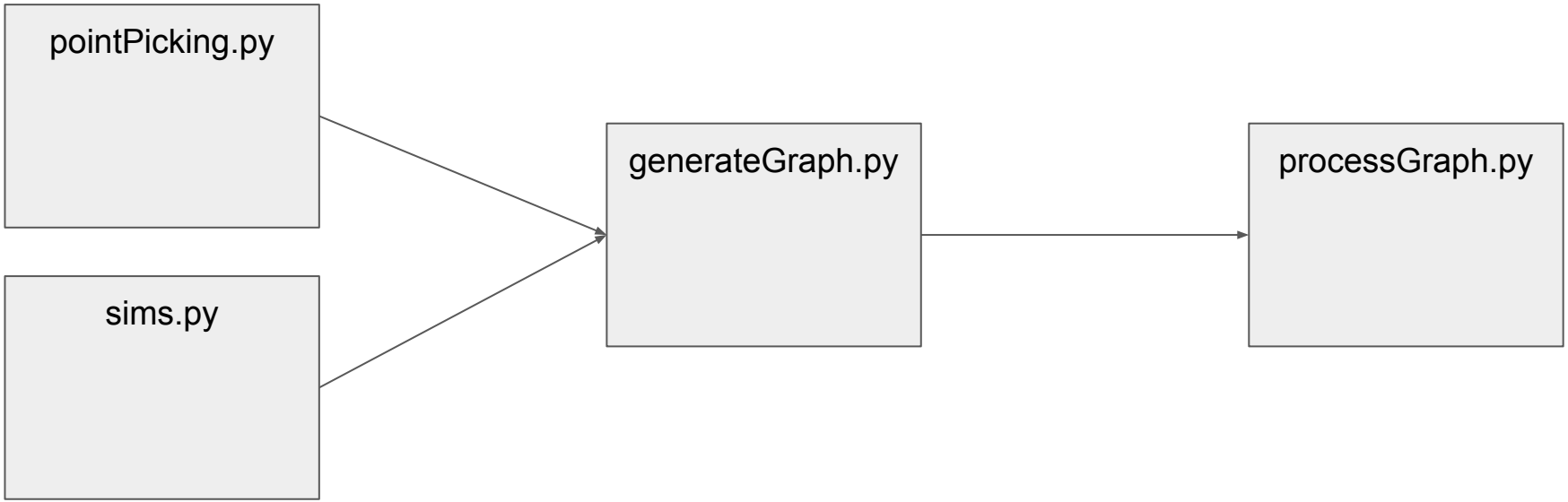
Formula becomes more complicated if the population is not randomly mating*

* Rohde, Douglas L. T., Steve Olson, and Joseph T. Chang (Sept. 2004). “Modelling the recent common ancestry of all living humans”. In: Nature 431.7008, pp. 562–566. ISSN : 0028-0836. DOI : 10 . 1038 /nature02842

The effects of natural selection were not researched before

But it seemed that they should have big effect. Somebody with a really useful trait should achieve reproductive success and go on to become a MRCA.

The framework

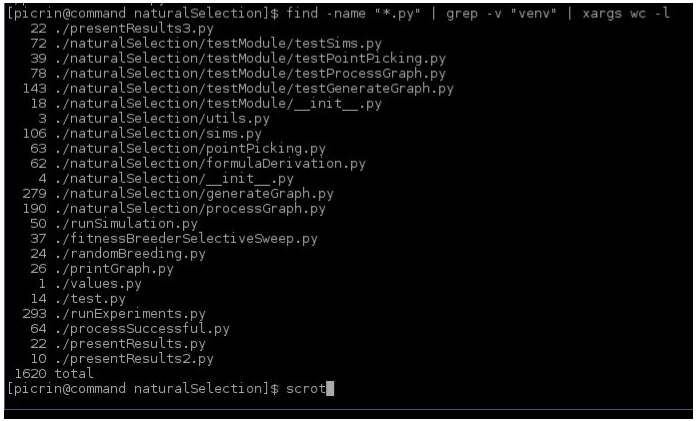


location
genotype
parent-child relation

mating
breeding
inheritance
mutation

T_{MRCA}
feature ratio
statistical analysis

- moderately complex codebase ~ 1600 lines of code



- most complex part is the MRCA algorithm (also most extensively tested)
- 25 test cases, ~75% test coverage.

5 sigma testing

```
def testFitnessBreeder(self):
    """
    Tests that the results of fitness breeder are within 5 sigma around mean.
    The feature boosts absolute fitness by the factor of 2.0
    The distribution is assumed to be binomial with the following probabilities:
    A = p(both parents have feature) = 2/3 * 1/2 = 1/3
    B = p(both parents have no feature) =  1/3 * 1/2  = 1/6
    C = p(exactly one parent has the feauture) = 2/3 * 1/2 + 1/3 * 1/2 = 1/2

    A + B + C = 1, as expected.

    D = p(at least one parent has no feature) =  C + B = 2/3
    E = p(at least one parent has a feature) = C + A = 5/6

    we then use standard deviation result for binomial distribution, say, repeated 100 times.
    The formula is sqrt(n(1-p)p).
    """
    totalSize = 100
    size = int(totalSize/2)

    D = 2.0/3
    E = 5.0/6
    DSsigma = sigmaBinomial(100, D, 5)
    ESsigma = sigmaBinomial(100, E, 5)
    self.assertAlmostEquals(DSsigma, 23.57, delta=0.1)
    self.assertAlmostEquals(ESsigma, 18.6, delta=0.1)
    unsuccessfulSims = [createRandomlyPositionedSim() for i in range(size)]
    successfulSims = [createRandomlyPositionedSim() for i in range(size)]
    successfulSimsIDs = [sim["uid"] for sim in successfulSims]
    unsuccessfulSimsIDs = [sim["uid"] for sim in unsuccessfulSims]
    for sim in successfulSims:
        makeHomozygous(sim)
    for sim in unsuccessfulSims:
        cancelFeature(sim)
    sims = successfulSims + unsuccessfulSims
    for sim in sims:
        makeDominant(sim)
    nextGeneration = fitnessBreeder(sims, 2.0, len(sims))
    successfulParents = 0
    unsuccessfulParents = 0
    self.assertTrue(len(nextGeneration) == totalSize)
    for sim in nextGeneration:
        if sim["parentA"]["uid"] in successfulSimsIDs or sim["parentB"]["uid"] in successfulSimsIDs:
            successfulParents += 1
        if sim["parentA"]["uid"] in unsuccessfulSimsIDs or sim["parentB"]["uid"] in unsuccessfulSimsIDs:
            unsuccessfulParents += 1
    self.assertTrue(-ESsigma <= successfulParents - E*totalSize <= ESsigma)
    self.assertTrue(-DSsigma <= unsuccessfulParents - D*totalSize <= DSsigma)
```

```
testing with python2
random state dumped to .randomstate
testAdjustFitness (naturalSelection.testModule.testSims.TestSims) ... ok
testHasFeature (naturalSelection.testModule.testSims.TestSims) ... ok
testIterativeHomebody (naturalSelection.testModule.testSims.TestSims)
Impressive, I can get 10^-14 accuracy of the point staying ... ok
testRandomGeneCopy (naturalSelection.testModule.testSims.TestSims) ... ok
testSimsBreed (naturalSelection.testModule.testSims.TestSims) ... ok
testBuckets (naturalSelection.testModule.testPointPicking.TestPointPicking) ... ok
testDistance (naturalSelection.testModule.testPointPicking.TestPointPicking) ... ok
testMove (naturalSelection.testModule.testPointPicking.TestPointPicking) ... ok
testBreeder (naturalSelection.testModule.testGenerateGraph.TestGenerateGraph) ... ok
testCondWriter (naturalSelection.testModule.testGenerateGraph.TestGenerateGraph) ... ok
testFitnessBreeder (naturalSelection.testModule.testGenerateGraph.TestGenerateGraph) ... ok
testFitnessCDF (naturalSelection.testModule.testGenerateGraph.TestGenerateGraph) ... ok
testMater (naturalSelection.testModule.testGenerateGraph.TestGenerateGraph) ... ok
testMater2 (naturalSelection.testModule.testGenerateGraph.TestGenerateGraph) ... ok
testParentChildFirstPart (naturalSelection.testModule.testGenerateGraph.TestGenerateGraph) ... ok
testAlleleProportion (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testFeatureProportion (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testMRCA (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testRandomMRCA (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testRepeatedMRCA (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testSatQuickMRCA (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testTracers (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testUnsatQuickMRCA (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testValidGenerationNumbers (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testValidJson (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok

----------------------------------------------------------------------
Ran 25 tests in 0.202s

OK
testing with python3
random state dumped to .randomstate
testAdjustFitness (naturalSelection.testModule.testSims.TestSims) ... ok
testHasFeature (naturalSelection.testModule.testSims.TestSims) ... ok
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testValidGenerationNumbers (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok
testValidJson (naturalSelection.testModule.testProcessGraph.TestProcessGraph) ... ok

----------------------------------------------------------------------
Ran 25 tests in 0.294s

OK
[picrin@command naturalSelection]$ scrot -d 2
```

Parameter choice

- population kept constant throughout the simulation (e.g. n = 100)
- discrete generations
- probability of becoming the first parent proportional to relative advantage, computed from absolute advantage (e.g. 1.05):

$$p(s, S) = \frac{f(s)}{\sum_{s' \in S} f(s')}$$

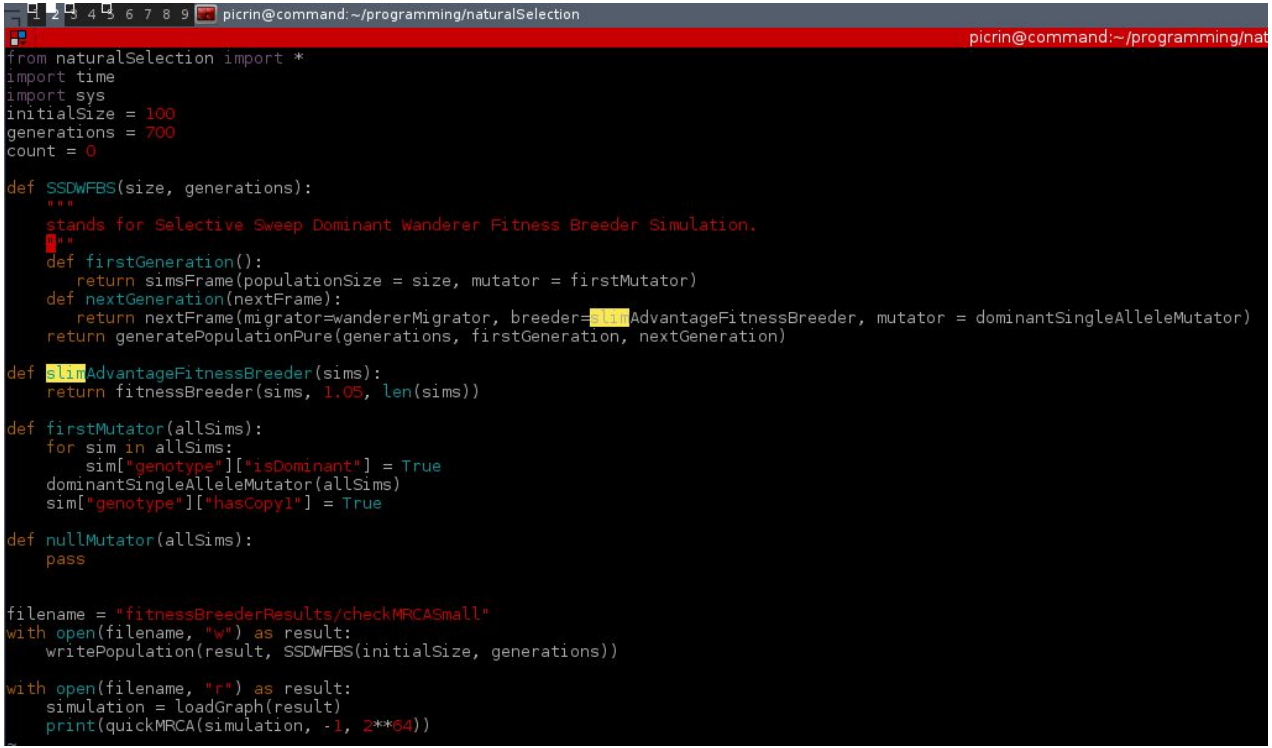
where S is the set of all sims in the previous generation (including s), and $f(s)$, the sim's absolute fitness, is defined by

$$f(s) = \begin{cases} 1.05, \text{ if sim } s \text{ has the trait} \\ 1, \text{ if sim } s \text{ does not have the trait} \end{cases}$$

- case - control study
- closely follows the approach of Peng and Amos *

* Peng, Bo and Christopher I. Amos (2010). "Forward-time simulation of realistic samples for genome-wide association studies". In: BMC Bioinformatics 11, p. 442. ISSN : 1471-2105

Simulating a concrete population easy



Unfortunately the results are inconclusive

T_{MRCA}

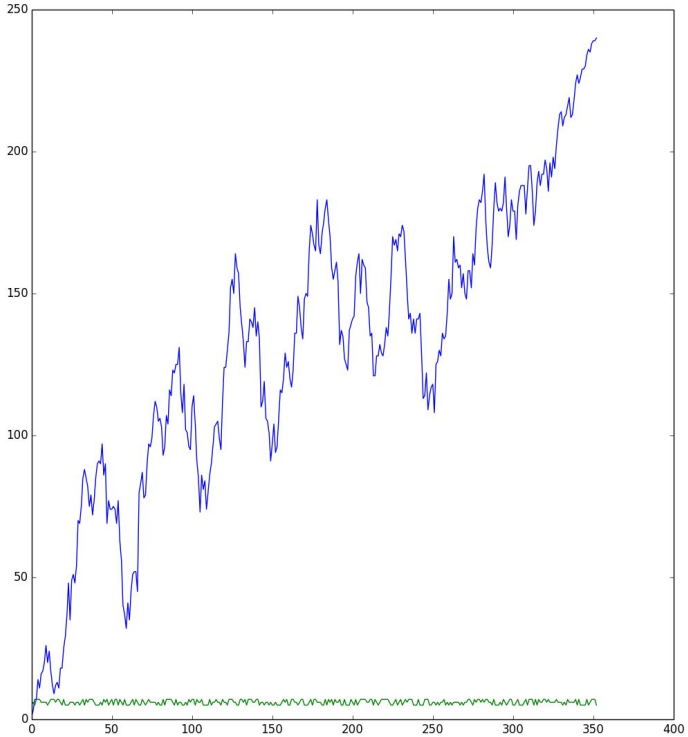
	sample	control
average	6.415	6.37
median	6	6
mode	7	7
min	5	5
max	7	7

Table 3.1: statistics for Selective Sweep in Randomly Mating Population experiment

	Mann-Whitney	Kolomogorov-Smirnov
p-values	0.258987	0.999987

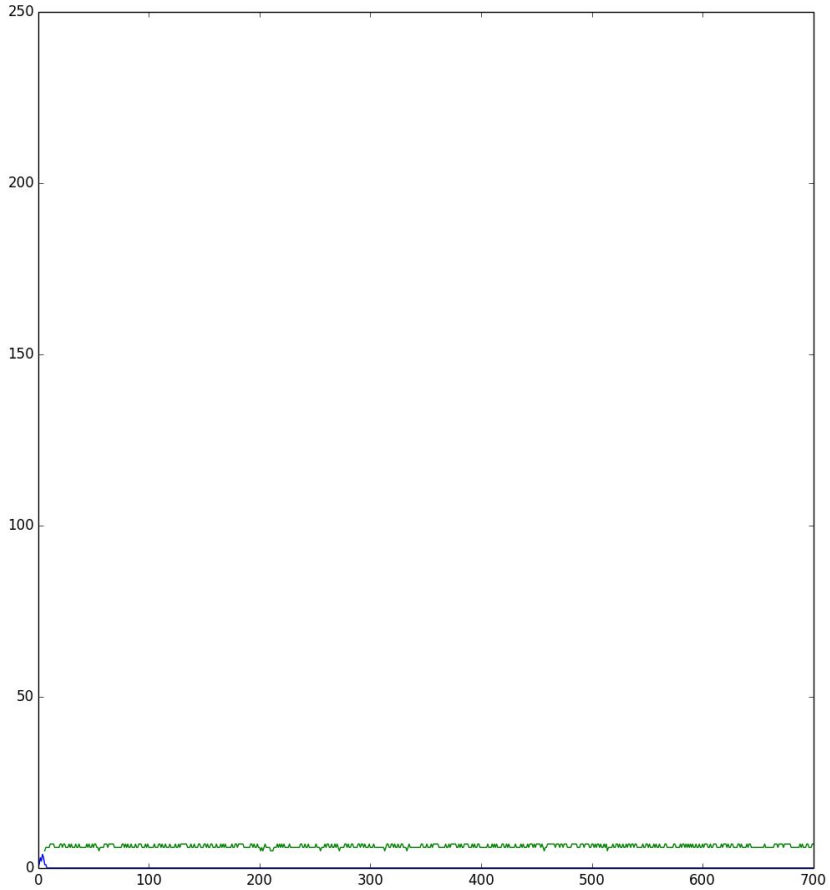
Table 3.2: p-values of null-hypothesis for Selective Sweep in Randomly Mating Population experiment

Why?



Natural selection is sloooow.

x-axis: generation
green - T_{MRCA}
blue - allele proportion.



And it rarely works. Only about 4% of simulations end in advantageous feature spreading to the entire population.

x-axis: generation
green - T_{MRCA}
blue - allele proportion.

Future work

- Run the experiments for populations with more structure -> bigger T_{MRCA}
- Is natural selection enough? Consider sexual selection.