Introduction to Wright-Fisher Simulations

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Goals

- Simulate the standard neutral model, demographic effects, and natural selection

Hardy-Weinberg Principle

Godfrey H. Hardy: 1877-1947

Wilhelm Weinberg: 1862-1937

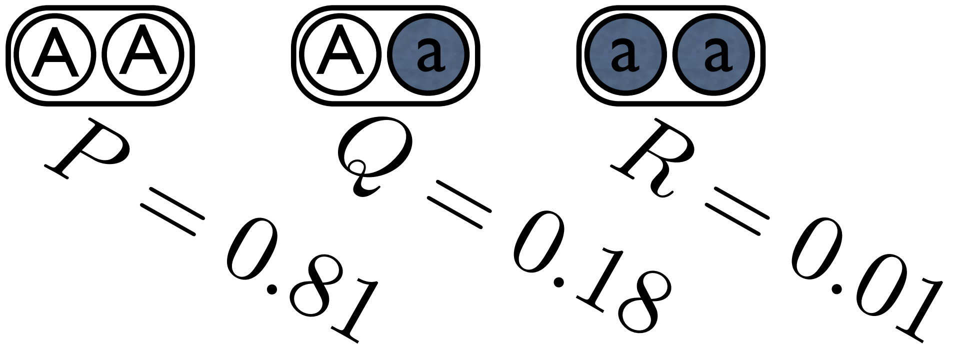
- **Assumptions:**
  - Diploid organism
  - Sexual reproduction
  - Non-overlapping generations
  - Only two alleles
  - Random mating
  - Identical frequencies in males/females
  - Infinite population size
  - No migration
  - No mutation
  - No natural selection
- **Conclusion 1:**

Both allele AND genotype frequencies will remain constant at **HWE** generation after generation... forever!

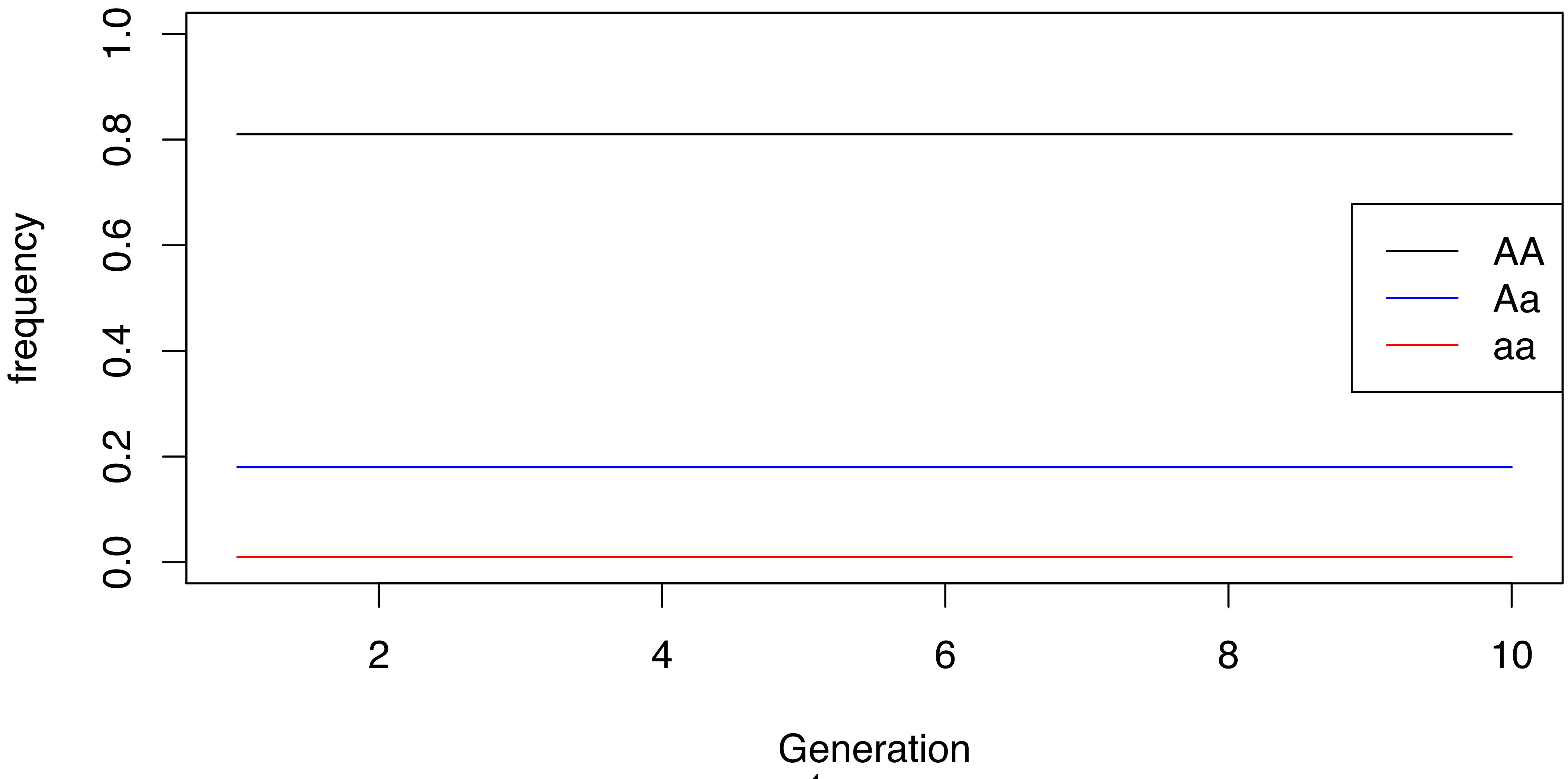
$$P=p^2$$
$$Q=2p(1-p)$$
$$R=(1-p)^2$$

Hardy-Weinberg Principle

- Imagine a population of diploid individuals

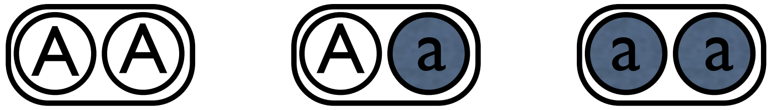


$P = 0.81$ $Q = 0.18$ $R = 0.01$



Hardy-Weinberg Principle

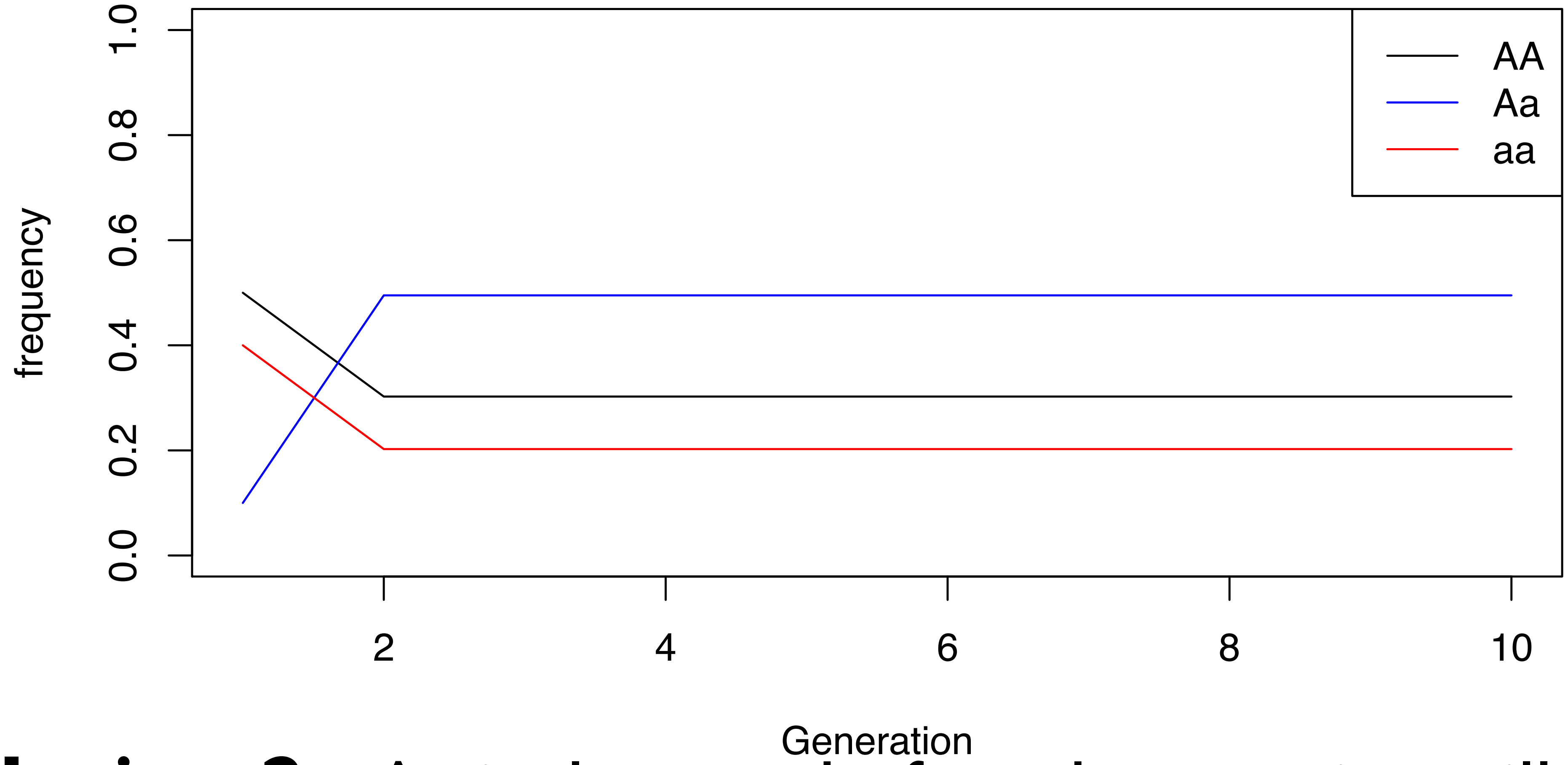
- Imagine a population of diploid individuals



$P = 0.5$ $Q = 0.1$ $R = 0.4$

$$p = P + Q/2 = 0.55$$

$$p^2 = 0.3025$$
$$2p(1-p) = 0.495$$
$$(1-p)^2 = 0.2025$$



- **Conclusion 2:** A single round of random mating will return the population to HWE frequencies!

Hardy-Weinberg Principle

Godfrey H. Hardy: 1877-1947

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Genetic Drift

- In finite populations, allele frequencies can and do change over time.
- In fact, EVERY genetic variant will either be lost from the population (p=0) or fixed in the population (p=1) some time in the future.
- The most common model for finite populations is the **Wright-Fisher model.**
- This model makes explicit use of the *binomial distribution*.

Wright-Fisher Model

Sewall Wright: 1889-1988

Sir Ronald Fisher 1890-1962

- Suppose a population of N individuals.
- Let X(t) be the #chromosomes carrying an allele A in generation t:

$$P(X(t+1)=j|X(t)=i) \quad = \mathrm{Bin}(j|N,i/N)$$

$$= \binom{N}{j} p^j (1-p)^{N-j} \quad = \binom{N}{j} \left(\frac{i}{N}\right)^j \left(\frac{N-i}{N}\right)^{N-j}$$

Wright-Fisher Model

- A simple R function to simulation genetic drift:

Initial pop size

Starting frequency

number of simulated generations

```
WF=function(N, p, G){
  t=array(NA,dim=G);
  t[1] = p;
  for(i in 2:G){
    t[i] = rbinom(1,N,t[i-1])/N;
  }
  return(t);
}
```

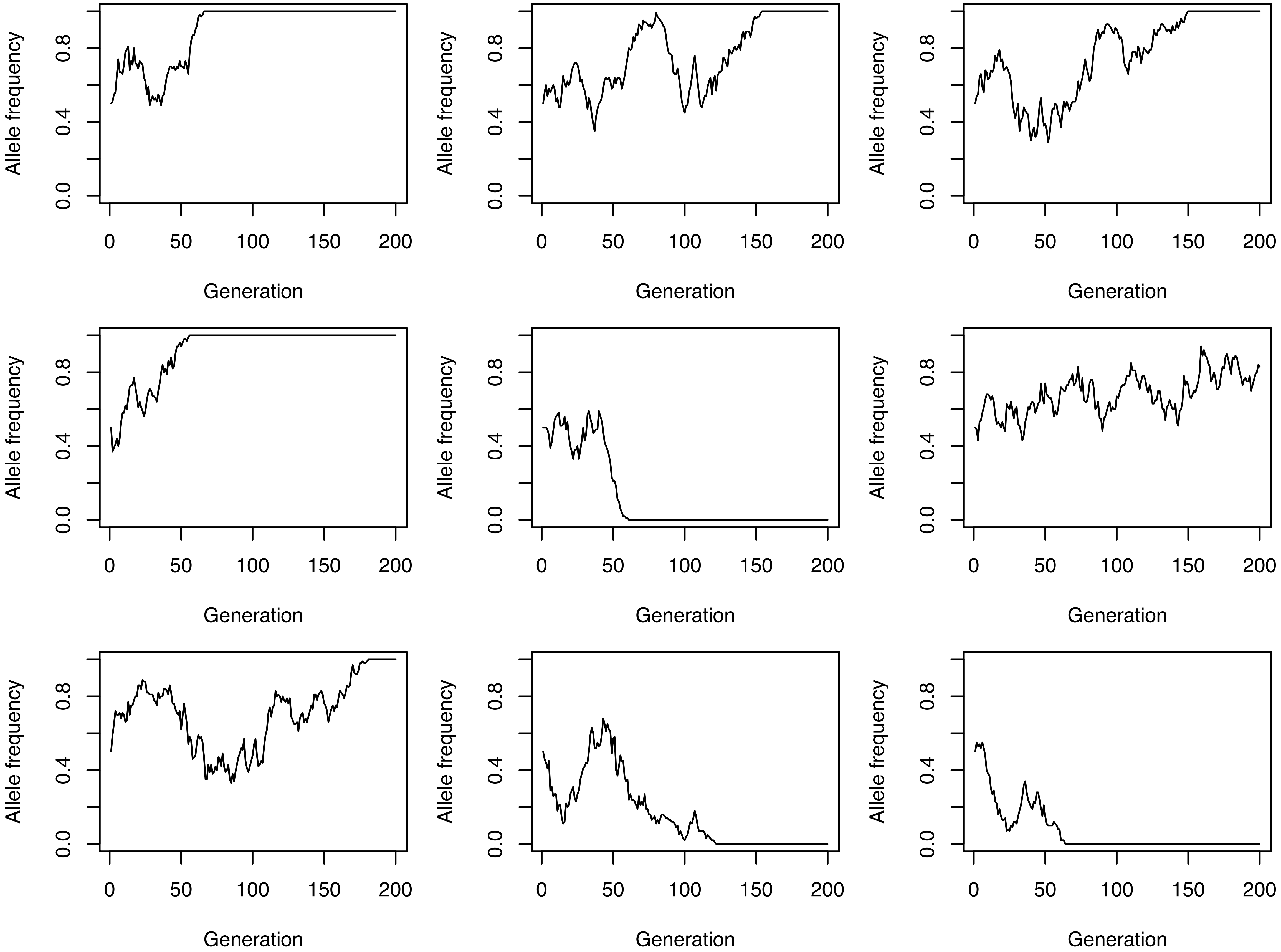
- Run it in R using:

```
f=WF(100, 0.5, 200)
plot(f)
```

Breakout Groups

- Please work together to code this up and generate the plot.
- Let us know if you have questions, or call for help! (“Ask for help” feature in Zoom)
- What happens in your plot?
- Were you able to get any fixations or losses?

Wright-Fisher Model



Demographic Effects

- Population changes size at a given generation

Wright-Fisher Model

Sewall Wright:
1889-1988

Sir Ronald Fisher
1890-1962

- Suppose a population of N individuals.
- Let X(t) be the #chromosomes carrying an allele A in generation t:

$$
\begin{aligned}
P(X(t+1)=j|X(t)=i) \quad &= \binom{N}{j} p^j (1-p)^{N-j} \\
= \mathrm{Bin}(j|N, i/N) \quad &= \binom{N}{j} \left(\frac{i}{N}\right)^j \left(\frac{N-i}{N}\right)^{N-j}
\end{aligned}
$$

Wright-Fisher Model

- A simple R function to simulation demographic effects:

Initial pop size
Starting frequency
Generations to simulate
Gen demographic event happens
Magnitude of size change

```
WFdemog = function(N, p, G, Gd, v){
     t=array(,dim=G);
     t[1] = p;
     for(i in 2:G){
          if(i == Gd){
               N = N*v;
          }
          t[i] = rbinom(1,N,t[i-1])/N;
     }
     return(t);
}
```

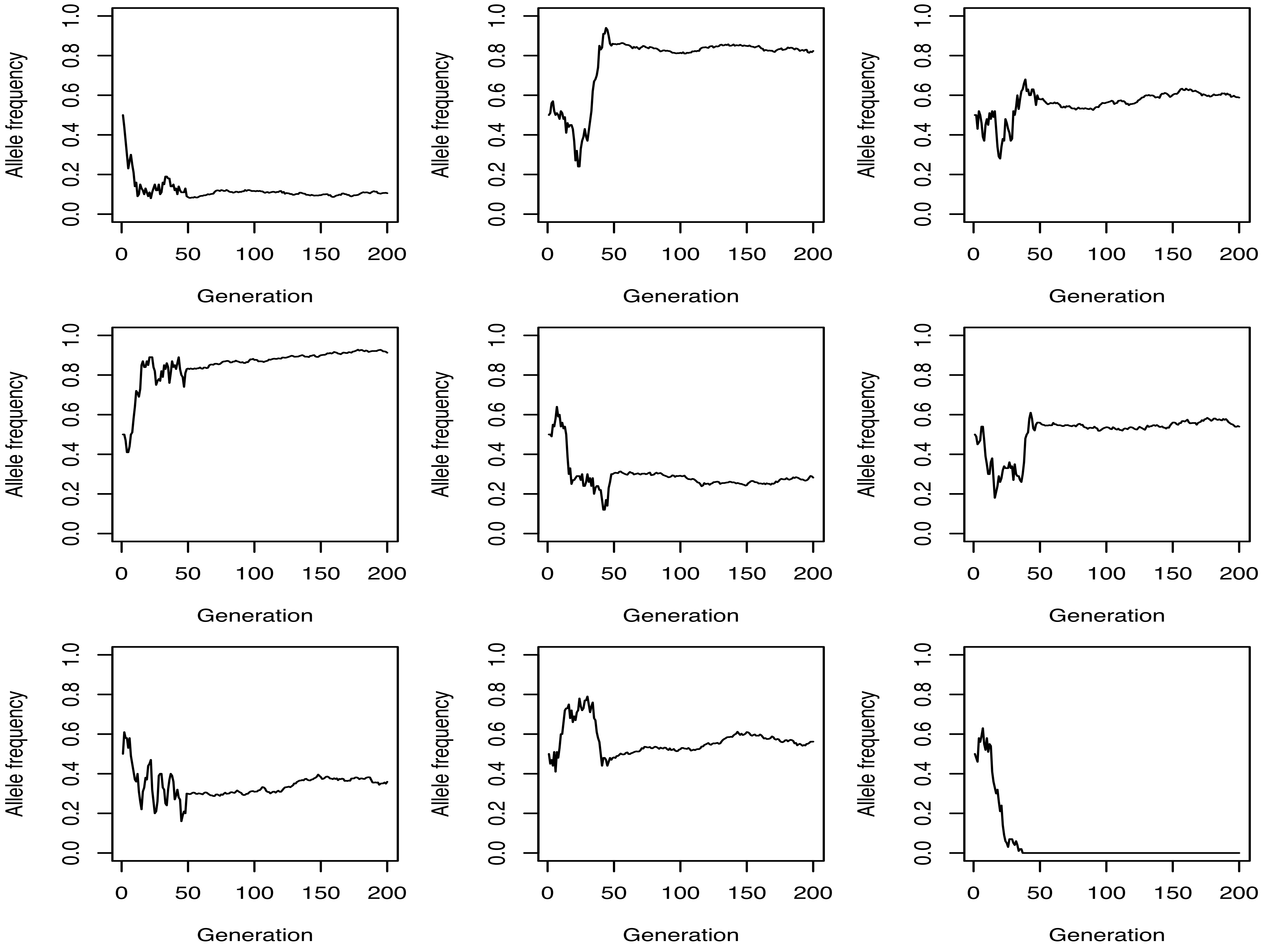
- Run it using:

```
f=WFdemog(100, 0.5, 200, 50, 100)
plot(f)
```

Breakout Groups

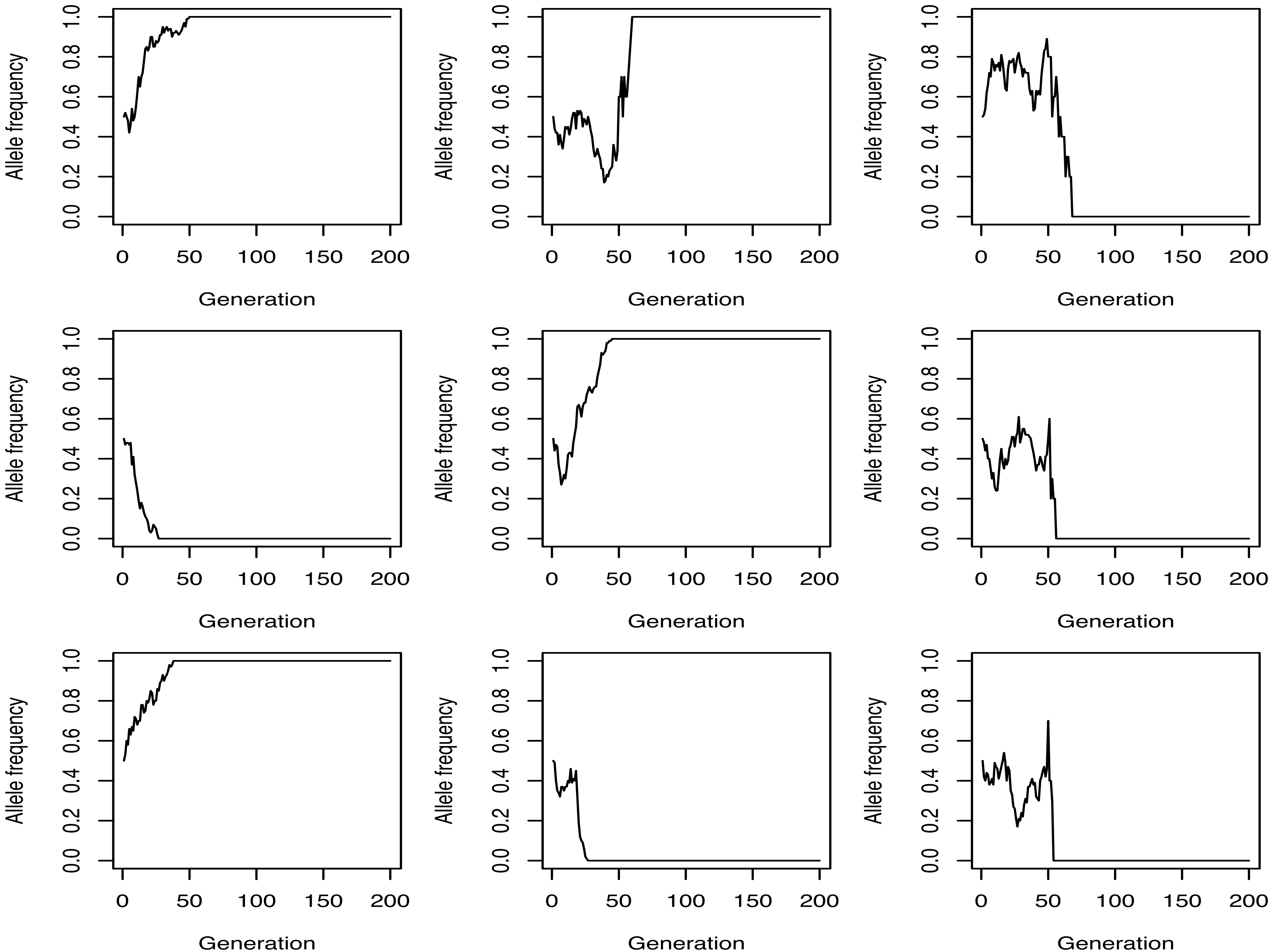
- Please work together to code this up and generate the plot.
- Let us know if you have questions, or call for help!
- What happens in your plot?
  - Were you able to get any fixations or losses?
- Can you simulate a 10-fold contraction?
  - How does it change the trajectory?

Wright-Fisher Model with Expansion



Wright-Fisher Model with Contraction

- Run it using: `WFdemog(100, 0.5, 200, 50, 0.1)`



Hardy-Weinberg Principle

- **Assumptions:**
  - Diploid organism
  - Sexual reproduction
  - Non-overlapping generations
  - Only two alleles
  - Random mating
  - Identical frequencies in males/females
  - Infinite population size
  - No migration
  - No mutation
  - No natural selection
- What happens when we allow natural selection to occur?
- Alleles change frequency!

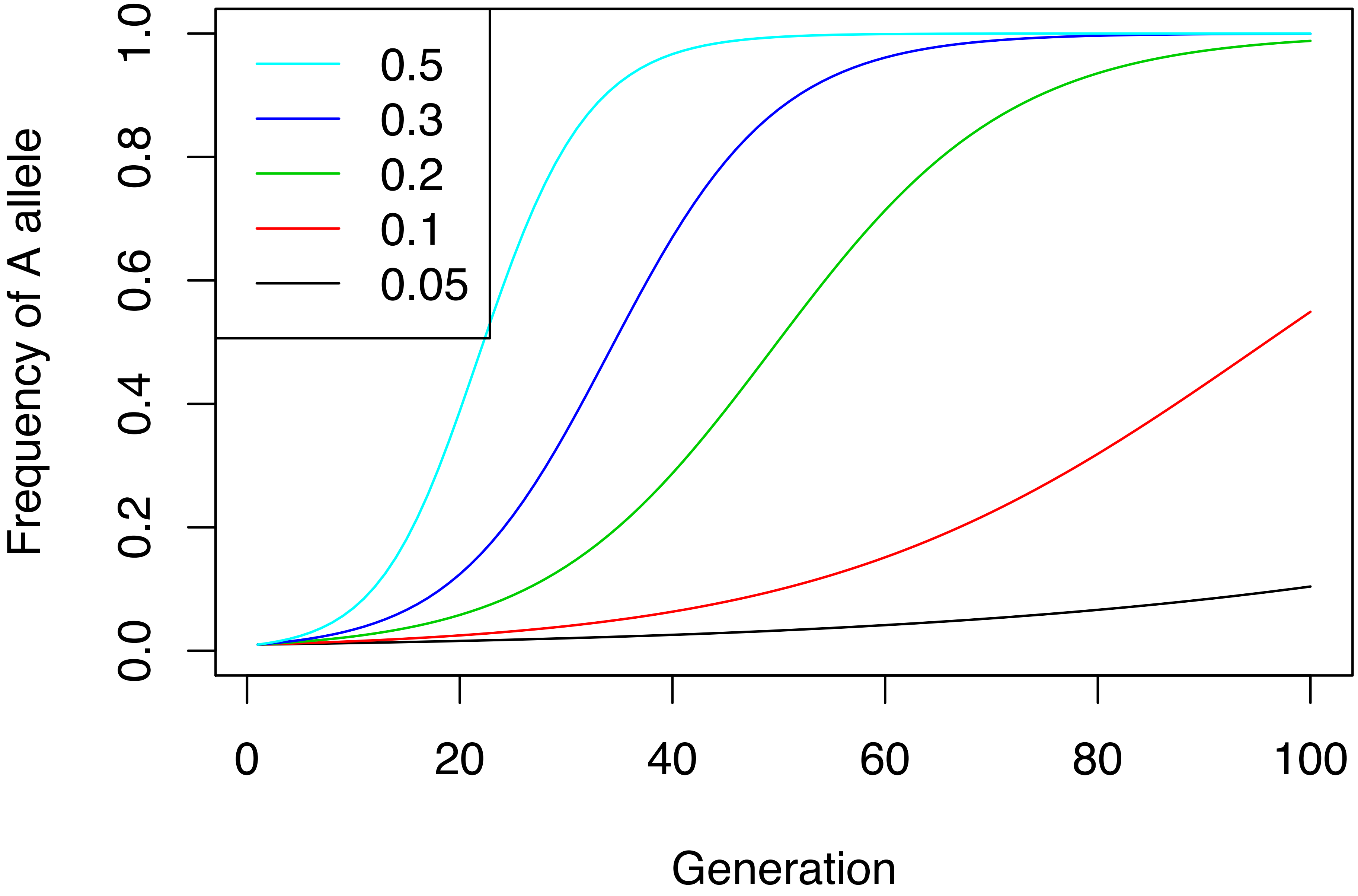
Natural Selection

Genotype	AA	Aa	aa
Frequency	p^2	2pq	q^2
Fitness	1	1+hs	1+s

- The *expected frequency* in the next generation (q') is then the density of offspring produced by carriers of the derived allele divided by the population fitness:
  - $$q' = \frac{q^2(1+s) + pq(1+hs)}{1 + sq(2hp + q)}$$

Natural Selection

- Trajectory of selected allele with various selection coefficients under genic selection (h=0.5) in an “infinite” population



Hardy-Weinberg Principle

- **Assumptions:**
  - Diploid organism
  - Sexual reproduction
  - Non-overlapping generations
  - Only two alleles
  - Random mating
  - Identical frequencies in males/females
  - Infinite population size
  - No migration
  - No mutation
  - No natural selection

- What happens with natural selection in a finite population?
  - Directional selection AND drift!

Simulating Natural Selection

- First write an R function for the change in allele frequencies:

initial freq
dominance
fitness

```
fitfreq = function(q, h, s){
  p=1-q;
  return((q^2*(1+s) + p*q*(1+h*s))/( 1 + s*q*(2*h*p+q)));
}
```

- Now use this in an updated WF simulator:

pop size
initial freq
dominance
fitness
gens to simulate

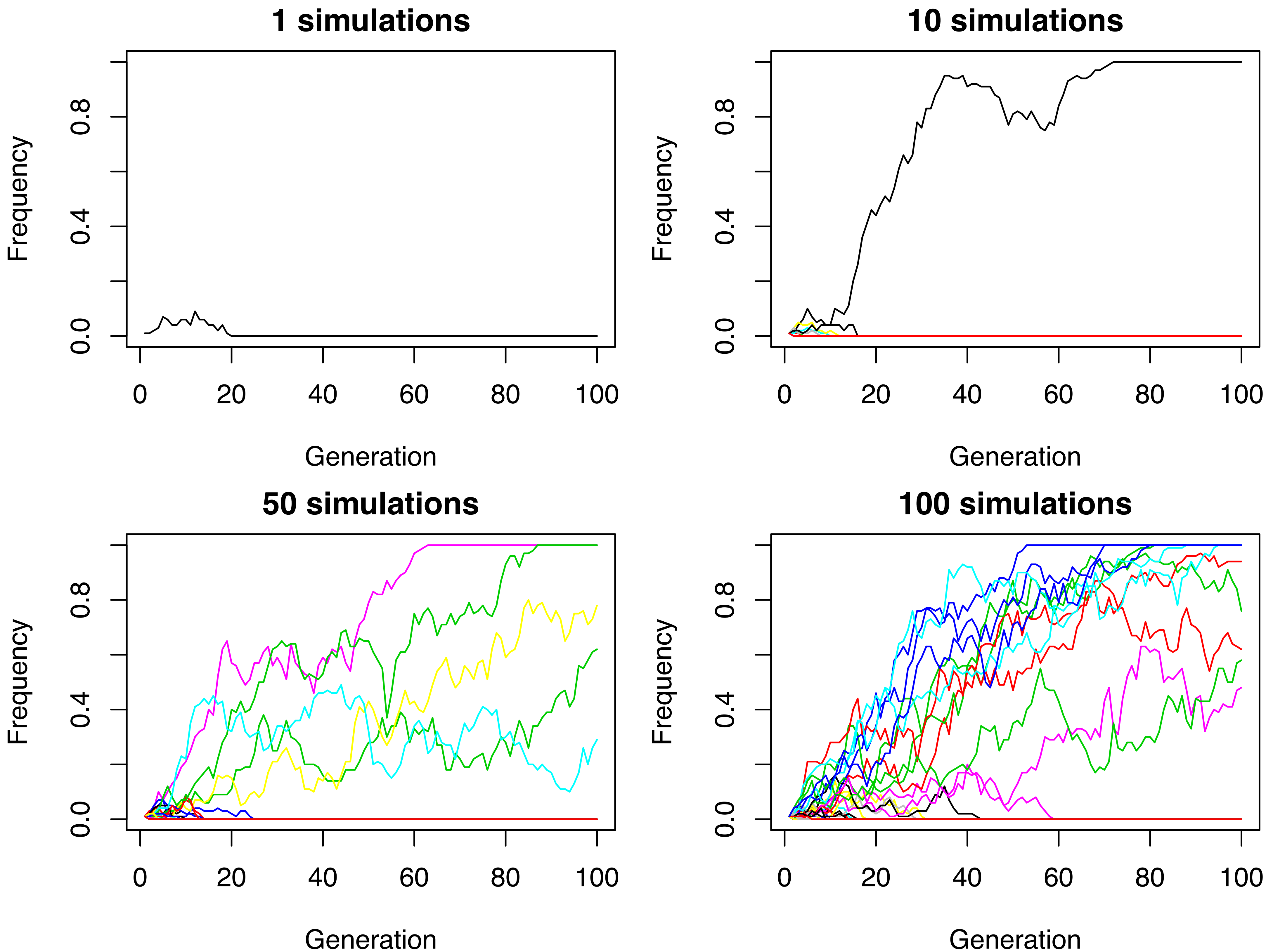
```
WF.sel=function(N, q, h, s, G){
  t=array(NA, dim=G);
  t[1] = q;
  for(i in 2:G){
    t[i] = rbinom(1, N, fitfreq(t[i-1], h, s))/N;
  }
  return(t);
}
```

Breakout Groups

- Please work together to code this up.
- Can you simulate a trajectory for 100 generations with these characteristics:
  - Population size = 100
  - Initial frequency is 1%
  - Allele has a 50% fitness advantage
- What happens in your plot?
  - Were you able to get any fixations or losses?

Natural Selection

```
WF.sel(100, 0.01, 0.5, 0.1, 100)
```



Simulating Natural Selection

- How would you simulate both selection AND demographic effects?
- Now use this in an updated WF simulator:

pop size

initial freq

dominance

fitness

gens to simulate

Gen demographic event happens

Magnitude of size change

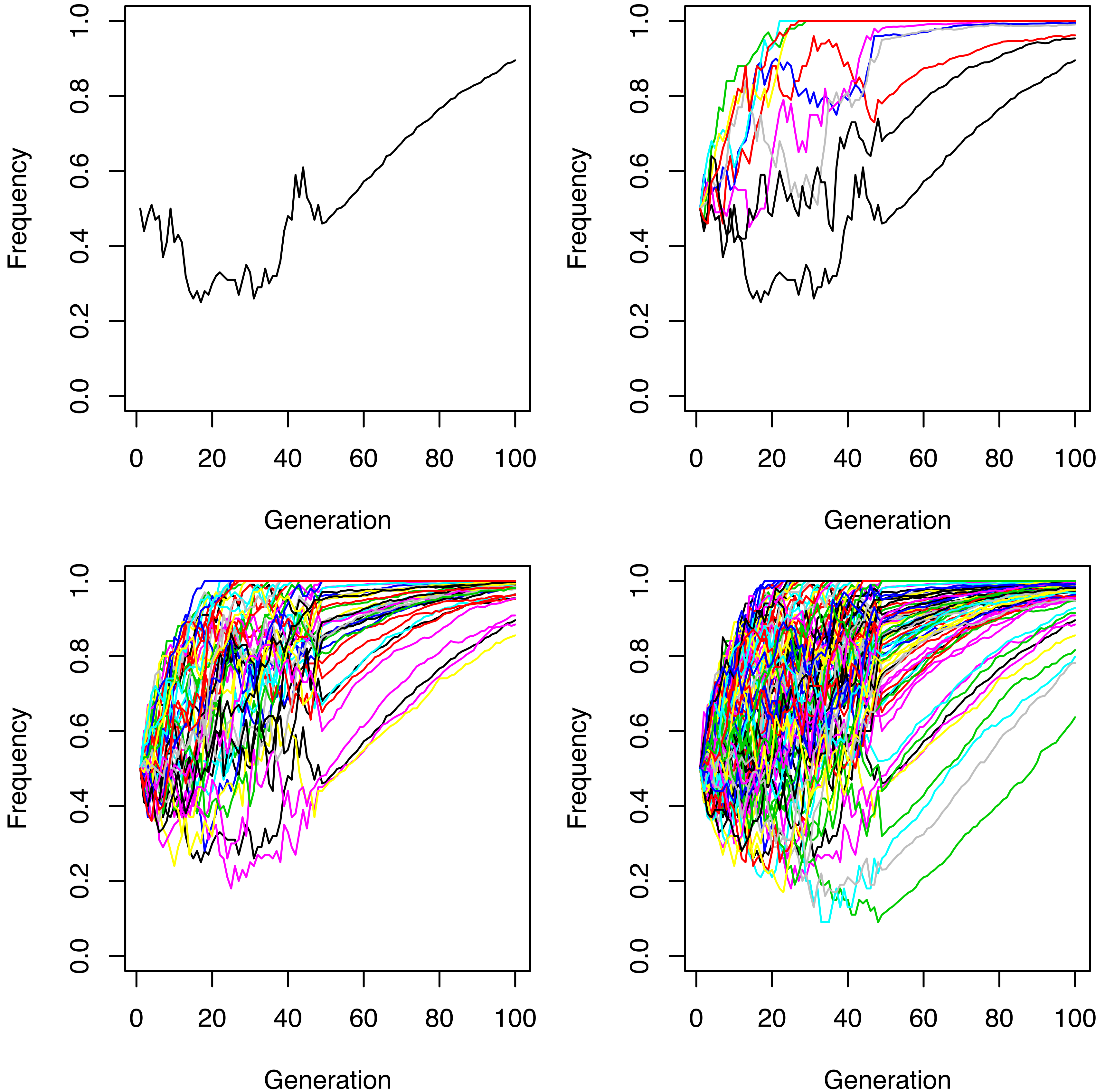
```
WF.demsel=function(N, q, h, s, G, Gd, v){
  t=array(NA,dim=G);
  t[1] = q;
  for(i in 2:G){
    if(i == Gd){
      N = N*v;
    }
    t[i] = rbinom(1, N, fitfreq(t[i-1], h, s))/N;
  }
  return(t);
}
```

Breakout Groups

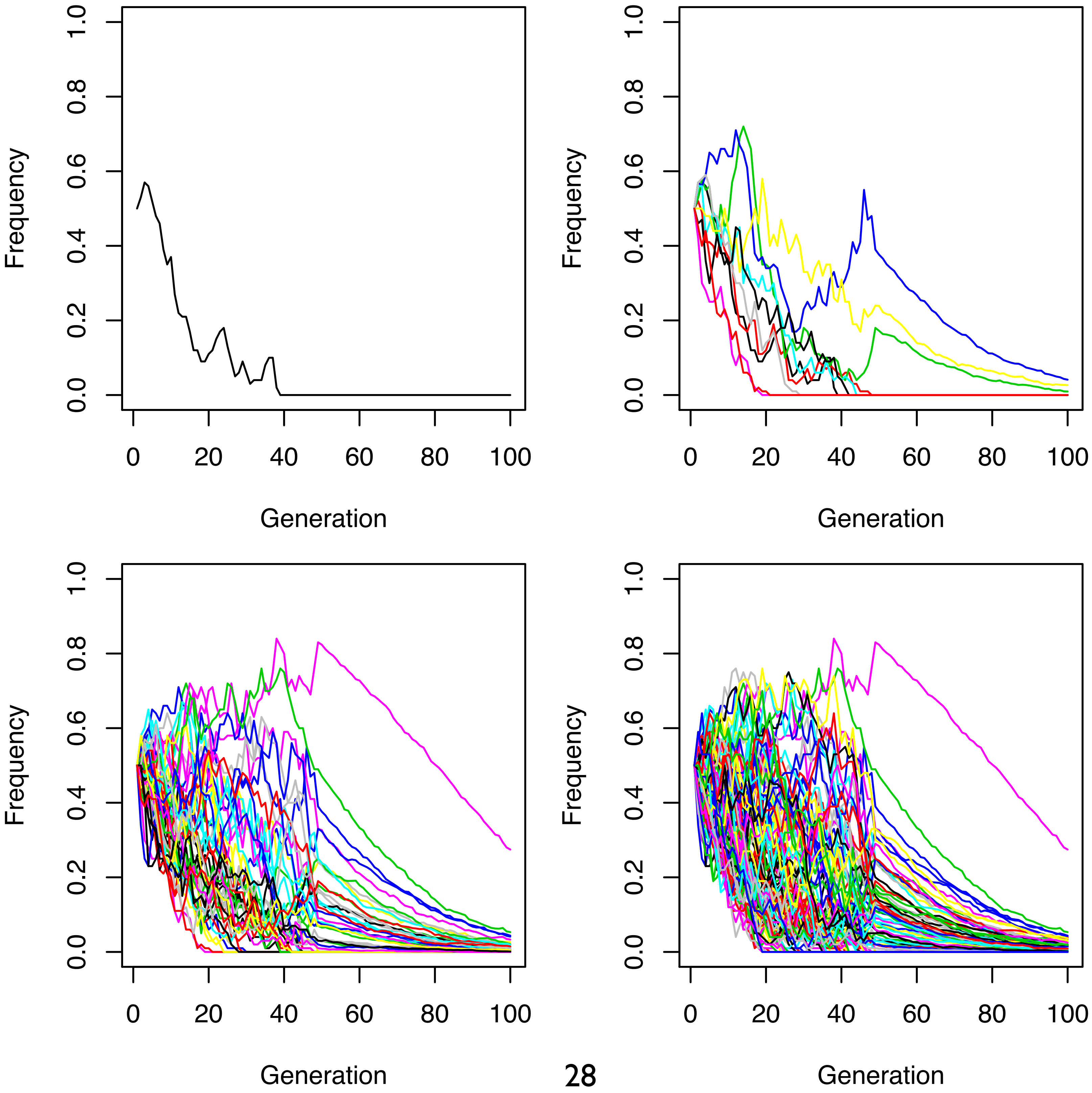
- Please work together to code this up.
- Can you add 100-fold population growth at generation 50 to your previous simulation?
- What happens in your plot?
- What if the initial frequency is 50%?

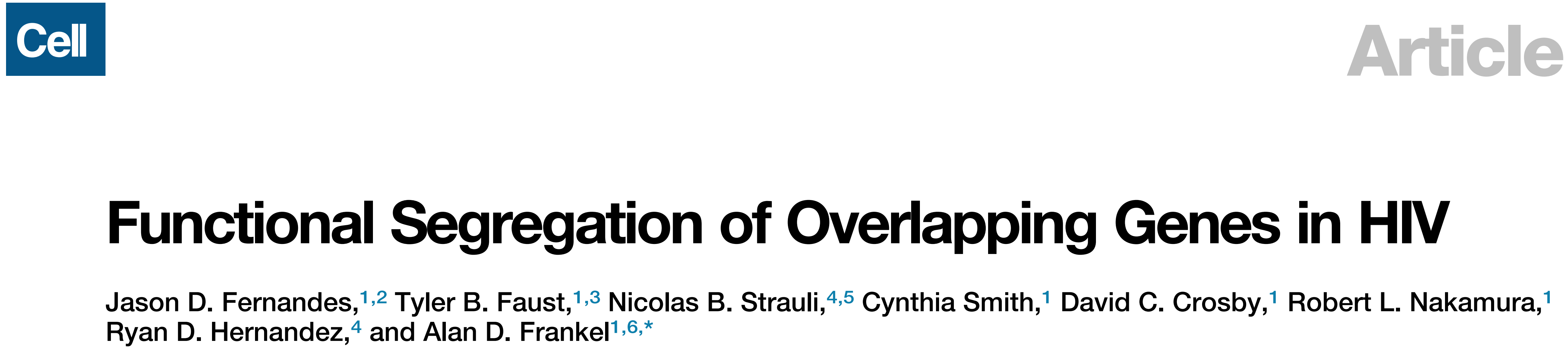
Wright-Fisher Model with Contraction

- Run it using: `WF.demsel(100,0.5,0.5,0.1,100,50,100)`



What parameters generated these?



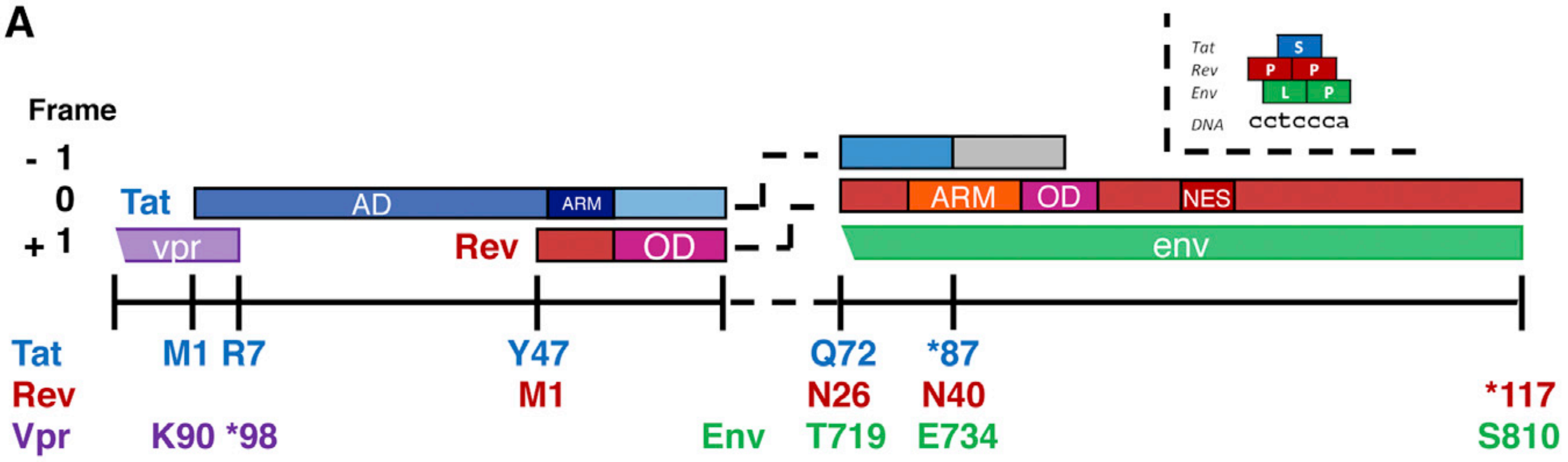


Cell

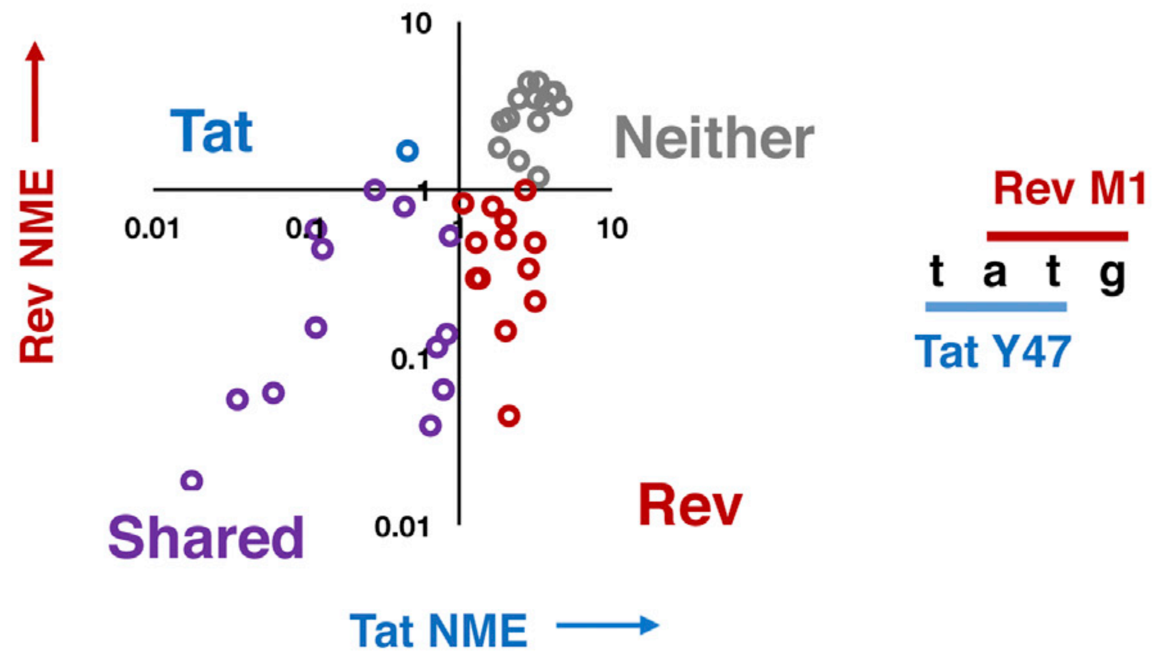
Article

Functional Segregation of Overlapping Genes in HIV

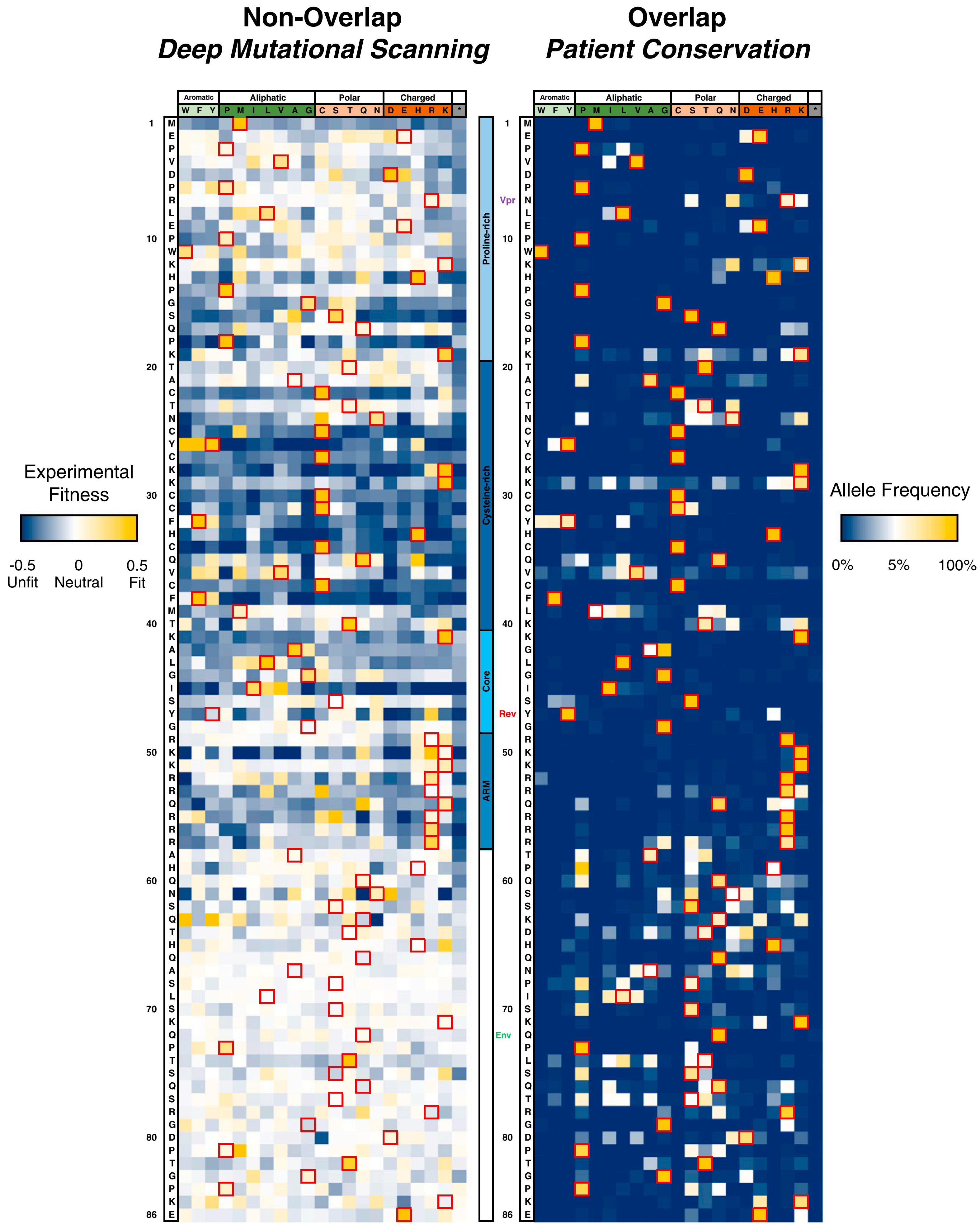
Jason D. Fernandes,[1,2] Tyler B. Faust,[1,3] Nicolas B. Strauli,[4,5] Cynthia Smith,[1] David C. Crosby,[1] Robert L. Nakamura,[1] Ryan D. Hernandez,[4] and Alan D. Frankel[1,6,*]



- HIV genes Tat and Rev overlap.
- At protein level, many overlapping sites are conserved in both, but some sites only conserved in Rev.
- Is joint conservation due to dual function or genetic code?



Fernandez, et al., Cell (2016)



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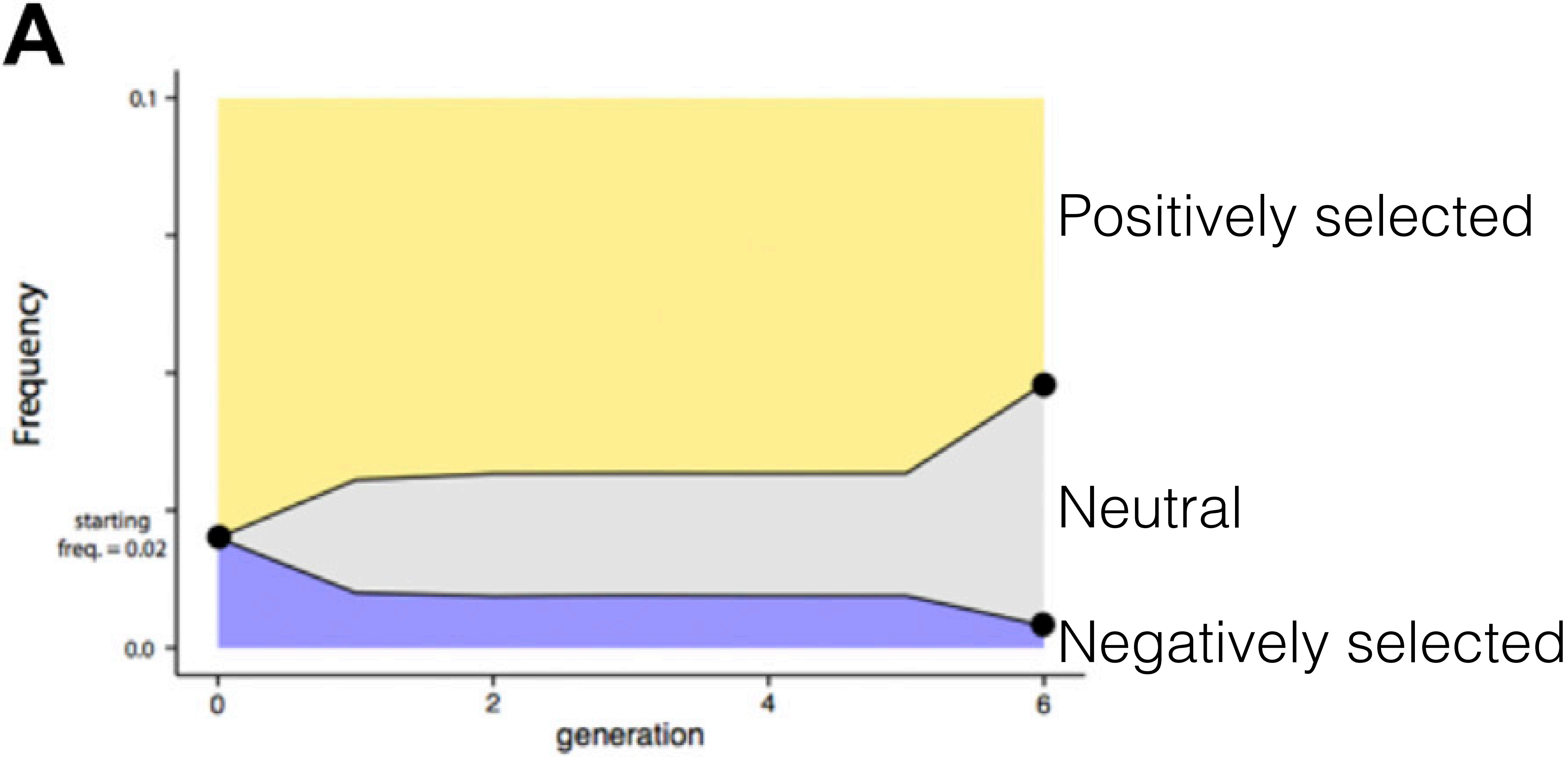
- In patient data, Tat sites that overlap with Rev are highly conserved.
- HIV can be engineered so that Tat and Rev do not overlap
- Deep mutational scanning in non-overlap context (all possible codons at each position) shows that many sites lack conservation in cell lines.
- Is this due to drift (neutral) or selection?

Fernandez, et al., Cell (2016)

Functional Segregation of Overlapping Genes in HIV

- **Deep mutational scanning:**
  - Create exhaustive libraries with all possible codons at all overlapping positions
  - Allow population mixture to evolve for ***G*** generations, then sequence to measure final frequencies of all amino acids
  - Simulate to evaluate significance of allele frequency change
- **Factors you might want to include in your simulation:**
  - the overall population growth function
  - the number of generations
  - the starting allele frequency
  - the read depth for the experiment

Fernandez, et al., Cell (2016)



Positively selected

Neutral

Negatively selected

Fernandez, et al., Cell (2016)

Natural Selection

Time-course data from artificial selection/ancient DNA

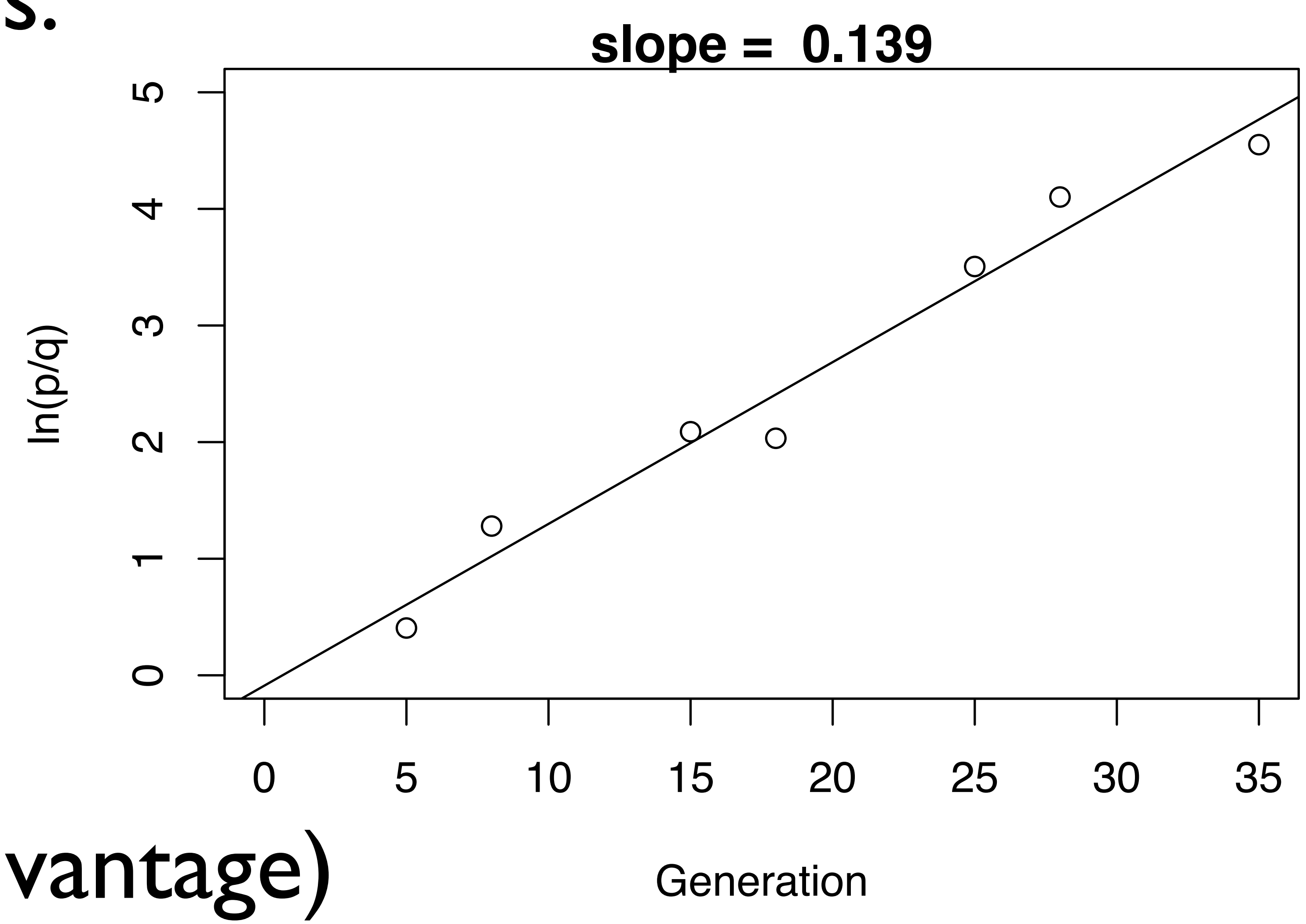
- Let's estimate some selection coefficients!
- Given 2 alleles at a locus with frequencies p_0 and q_0, and fitnesses w_1 and w_2 (with w the population-wide fitness).
- Expected freq. in next generation is: $p_1 = p' = p_0 w_1 / w$.
- We can then write:
  - $\dfrac{p_1}{q_1} = \dfrac{p_0 w_1 / w}{q_0 w_2 / w} = \left(\dfrac{p_0}{q_0}\right)\left(\dfrac{w_1}{w_2}\right)$
- Using induction, you could prove for any generation t:
  - $\dfrac{p_t}{q_t} = \left(\dfrac{p_0}{q_0}\right)\left(\dfrac{w_1}{w_2}\right)^t$

Natural Selection

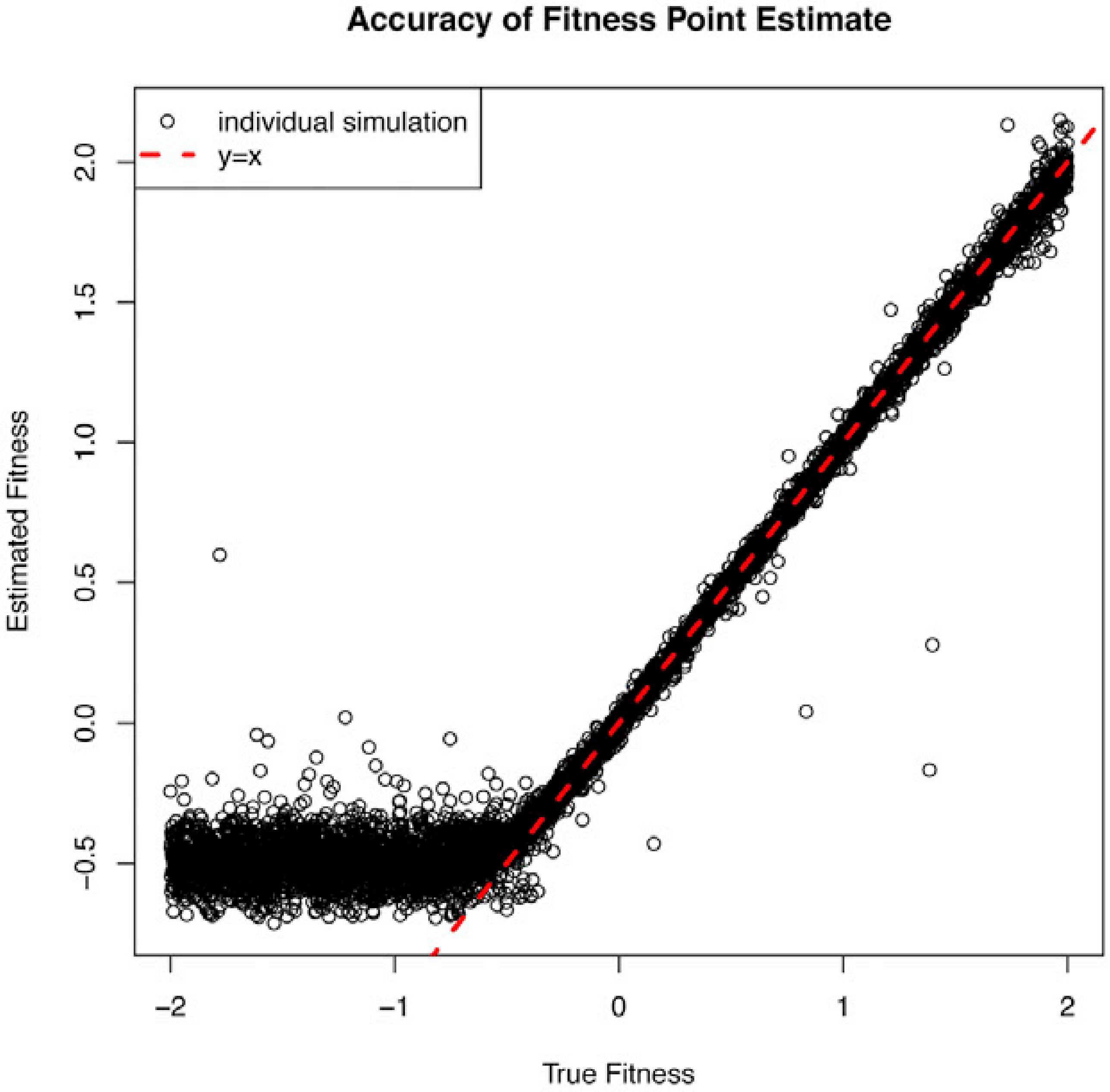
- Taking the natural log of this equation:
  - $$\log\left(\frac{p_t}{q_t}\right) = \log\left(\frac{w_1}{w_2}\right) t + \log\left(\frac{p_0}{q_0}\right)$$
- Which is now a **linear function** of *t*, the number of generations.
- We can now estimate the ratio of fitnesses by regression!

Natural Selection

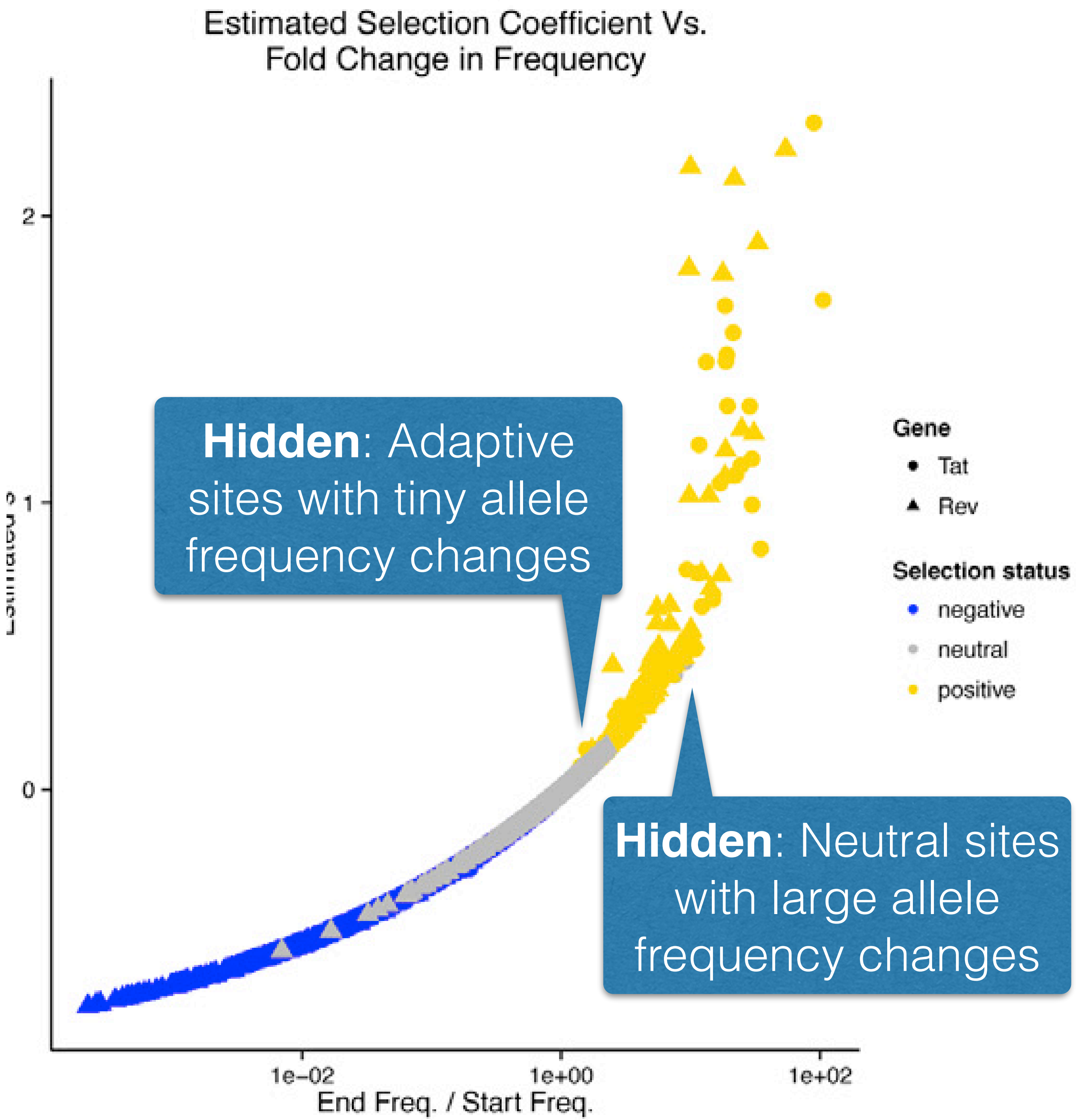
- Experiment: Set up a population of bacteria in a chemostat, and let them reproduce.
- Sample roughly every 5 generations.
- A slope of 0.139 implies: $w_1/w_2 = e^{0.139} = 1.15$
- Assume w_2=1.
- Thus, allele p has a 15% fitness advantage over allele q!
- (simulated with 20% advantage)



Accuracy of Fitness Point Estimate



Estimated Selection Coefficient Vs.
Fold Change in Frequency



Hidden: Adaptive sites with tiny allele frequency changes

Hidden: Neutral sites with large allele frequency changes

Fernandez, et al., Cell (2016)

Existing forward simulators

- **SFS_CODE: Hernandez (2008)**
  - Command-line flexibility… shameless plug!
- **FWDPP: Thornton (2014)**
  - C++ library of routines intended to facilitate the development of forward-time simulations under arbitrary mutation and fitness models
- **SLiM 3: Haller & Messer (2019)**
  - Command-line, GUI, and R-like scripting environment that provides control over most aspects of the simulated evolutionary scenarios