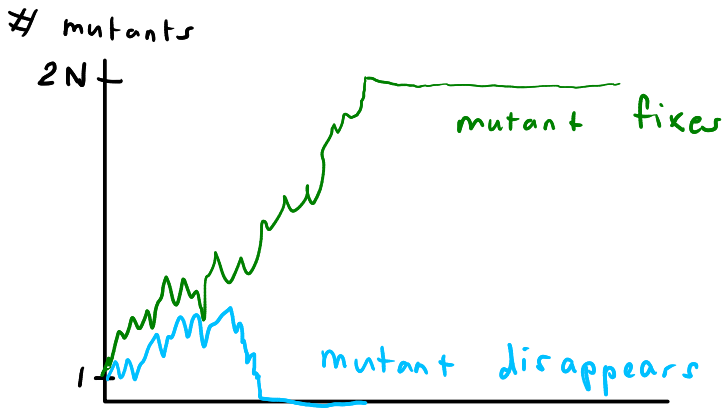


substitution rate

k = rate at which new mutants appear + fix

$$= \underbrace{2N\mu}_{\text{new mutants appears}} \; \pi_{fix}$$

π_{fix} → prob. of fixation

Consider a "micro" version of WF model:

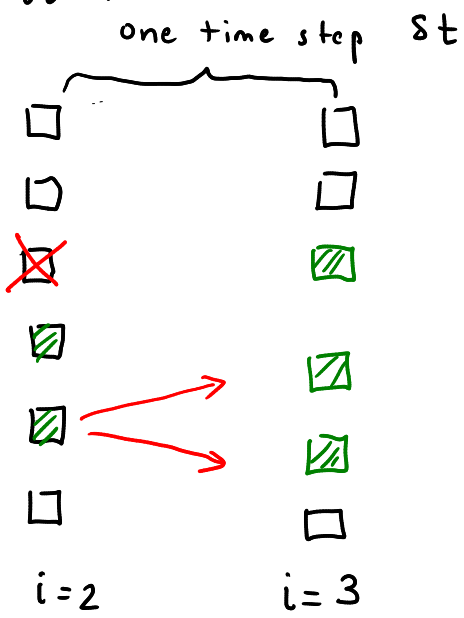
Moran model

pop. size $2N$

□ = non-mutant (wild type)

▨ = mutant

i = # mutants



every δt:

- one allele dies at random
- one gets chosen to reproduce + everyone else survives

⇒ same pop. size

reproduction step: either wild type or mutant gets a chance to reproduce first, moving sys. to next time step

g = repr. rate of wild type

f = repr. rate of mutant

wild type first: $\dfrac{g(2N-i)}{fi + g(2N-i)}$

i → # wild types

define:

$$s = \frac{f}{g} - 1$$

selection coefficient

$|s| \ll 1$ typically

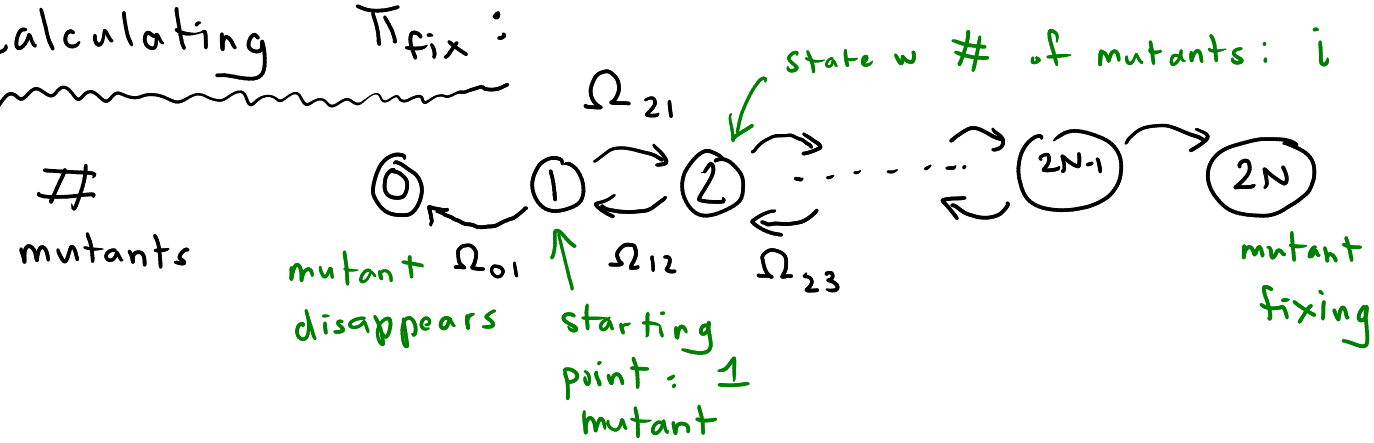
mutant first : $\dfrac{f_i}{f_i + g(2N-i)}$

$s > 0$: $f > g \Rightarrow$ beneficial mutant

$s = 0$: neutral mutant

$s < 0$: deleterious mutant

Calculating π_{fix}:



find π_i = prob. that mutant reaches 2N given start at i

we need $\pi_1 \equiv \pi_{fix}$ (start at $i=1$)

let's say current state is at $1 \le i \le 2N-1$:

$$i \to i+1: \quad \Omega_{i+1,i} = \underbrace{\frac{2N-i}{2N}}_{\text{prob. wild type dies}} \cdot \underbrace{\frac{f_i}{f_i + g(2N-i)}}_{\text{prob. mutant reproduces}}$$

$$i \to i-1: \quad \Omega_{i-1,i} = \underbrace{\frac{i}{2N}}_{\text{prob. mutant dies}} \cdot \frac{g(2N-i)}{f_i + g(2N-i)}$$

$$\Omega_{1,0} = 0 = \Omega_{2N-1,2N}$$

$i=0$ + $i=2N$ cannot escape

let's say i is $1 \le i \le 2N-1$:

before reaching $2N$ we have to pass thru either $i-1$ or $i+1$:

$$\pi_i = \begin{pmatrix}\text{prob. to}\\ \text{jump to } i-1\end{pmatrix} \pi_{i-1} + \begin{pmatrix}\text{prob. to}\\ \text{jump to } i+1\end{pmatrix} \pi_{i+1}$$

$$= \frac{\Omega_{i-1,i}}{\Omega_{i-1,i}+\Omega_{i+1,i}} \pi_{i-1} + \frac{\Omega_{i+1,i}}{\Omega_{i-1,i}+\Omega_{i+1,i}} \pi_{i+1}$$

$$= \frac{(1+s)}{(2+s)} \pi_{i+1} + \frac{1}{2+s} \pi_{i-1}$$

recursion relation

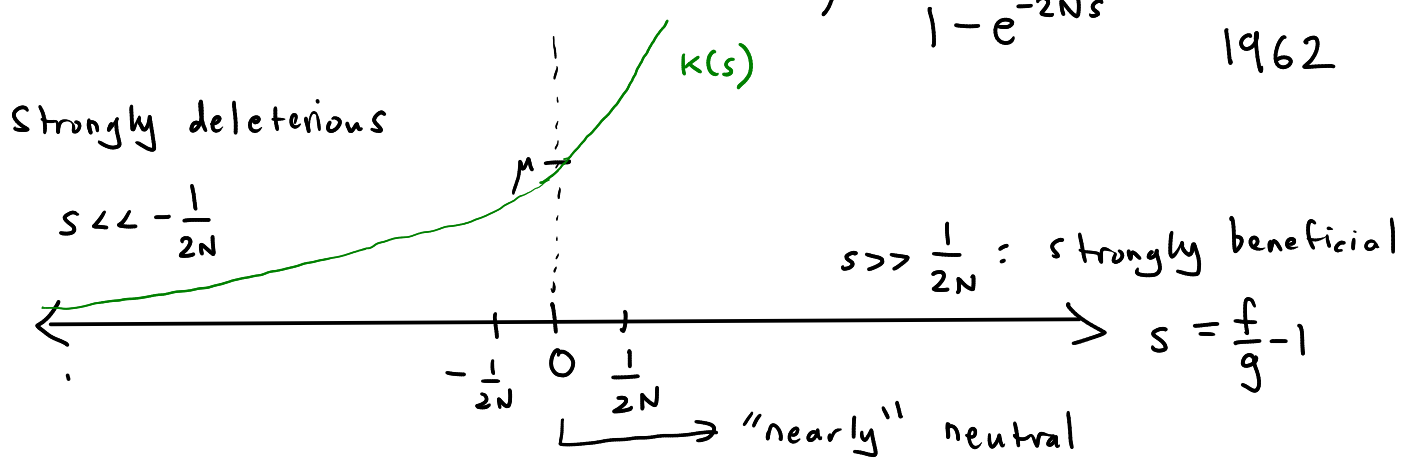
BC: $\pi_{2N} = 1$ $\quad \pi_0 = 0$ $\qquad |s| \ll 1$

Solution: $$\pi_i = \frac{1-(1+s)^{-i}}{1-(1+s)^{-2N}} \approx \frac{1-e^{-is}}{1-e^{-2Ns}}$$

$$\pi_{fix} = \pi_1 \approx \frac{1-e^{-s}}{1-e^{-2Ns}}$$

substitution rate $$k = 2N\mu \frac{1-e^{-s}}{1-e^{-2Ns}}$$

Motoo Kimura 1962



$|s| \ll \frac{1}{2N}$ $\quad k \approx 2N\mu \frac{1-(1-s)}{1-(1-2Ns)} = \mu$

$\Rightarrow$ nearly constant rate of subst. for neutral mutations indep. of N (Kimura, Ohta 1971): "molecular clock"