

# Moran model

The Moran model describes the evolution of a collection of cells that is maintained at a constant population size of  $N$ . Thinking of the population genetics situation for which it was developed, we will often call the cells individuals. In comparing the results here with those given in the literature one must take into account that in genetics most organisms are diploid (have two copies of their DNA), so the population in the Moran model commonly consists of  $2N$  copies of a locus.

## 1 Neutral case

In the simplest version of the model (with no selection or mutation), the dynamics of the Moran model, which occur in continuous time, can be described as follows:

- Each individual is replaced at rate 1. That is, individual  $x$  lives for an exponentially distributed amount with mean 1 and then is “replaced.”
- To replace individual  $x$ , we choose an individual at random from the population (including  $x$  itself) to be the parent of the new individual.

Suppose now that each individual has one of two alleles  $A$  and  $a$ , and let  $X_t$  be the number of copies of  $A$ . The transition rates for  $X_t$  are

$$\begin{aligned} i \rightarrow i + 1 & \quad \text{at rate} \quad b_i = (N - i) \cdot \frac{i}{N} \\ i \rightarrow i - 1 & \quad \text{at rate} \quad d_i = i \cdot \frac{N - i}{N} \end{aligned} \tag{1} \quad \boxed{\text{Moranrates}}$$

where  $b$  is for birth and  $d$  is for death. In words,  $a$ 's are selected for possible replacement at total rate  $N - i$ . The number of  $A$ 's will increase if an  $A$  is chosen to be the parent of the new individual, an event of probability  $i/N$ . Similarly,  $A$ 's are selected for possible replacement at total rate  $i$ . The number of  $A$ 's will decrease if an  $a$  is chosen to be the parent of the new individual, an event of probability  $(N - i)/N$ . Note that  $b_i = d_i$ .

Let  $\tau = \min\{t : X_t = 0 \text{ or } X_t = N\}$  be the fixation time, i.e., the first time at which all individuals have the same type. Since it is possible to reach the absorbing states 0 and  $N$  starting from any interior state  $0 < i < N$  we have  $P_i(\tau < \infty) = 1$

Moranabs **Theorem 1.** *In the Moran model, the probability that  $A$  becomes fixed when there are initially  $i$  copies is  $i/N$ .*

*Proof.* The rates for up and down jumps are the same, so  $(d/dt)E_i X_t = 0$ , and hence  $E_i X_t$  is constant, i.e.,  $X_t$  is a martingale. Intuitively this implies that

$$i = E_i X_\tau = N P_i(X_\tau = N) \tag{2} \quad \boxed{\text{exitmart}}$$

To prove this we note that

$$i = E_i X_t = N P_i(X_\tau = N, \tau \leq t) + E_i(X_t; \tau > t)$$

Letting  $t \rightarrow \infty$  and noting  $P_i(\tau > t) \rightarrow 0$ ,  $|X_t| \leq N$  the desired result follows. □

Let  $T_k = \min\{t : X_t = k\}$  be the hitting time of  $k$ . Writing  $\bar{E}_i\tau = E_i(\tau|T_N < T_0)$ , we can state

**hitT** **Theorem 2.** *Let  $p = i/N$ . In the Moran model when  $N$  is large*

$$\bar{E}_i\tau \approx -\frac{N(1-p)}{p} \log(1-p) \quad (3) \quad \text{Ethitcond}$$

As  $p \rightarrow 0$ ,  $-\log(1-p)/p \rightarrow 1$ , so

$$\bar{E}_1\tau \sim N \quad (4) \quad \text{Ethitcond0}$$

*Proof.* Let  $S_j$  be the amount of time spent at  $j$  before time  $\tau$  and note that

$$E_i\tau = \sum_{j=1}^{N-1} E_iS_j \quad (5) \quad \text{ETfix}$$

Let  $N_j$  be the number of visits to  $j$ . Let  $q(j) = 2j(N-j)/N$  be the rate at which the chain leaves  $j$ . Since each visit to  $j$  lasts for an exponential amount of time with mean  $1/q(j)$ , we have

$$E_iS_j = \frac{1}{q(j)} E_iN_j \quad (6) \quad \text{NytoSy}$$

To compute  $E_iN_j$ , we begin by noting that

$$P_i(N_j \geq 1) = P_i(T_j < \infty)$$

Letting  $T_j^+ = \min\{t : X_t = j \text{ and } X_s \neq j \text{ for some } s < t\}$  be the time of the first return to  $j$ , we have for  $n \geq 1$

$$P_i(N_j \geq n+1 | N_j \geq n) = P_j(T_j^+ < \infty)$$

The last formula shows that, conditional on  $N_j \geq 1$ ,  $N_j$  has a geometric distribution with success probability  $P_j(T_j^+ = \infty)$ . Combining this with our formula for  $P_i(N_j \geq 1)$ , we have

$$E_iN_j = \frac{P_i(T_j < \infty)}{P_j(T_j^+ = \infty)} \quad (7) \quad \text{ExNy}$$

Since the average value of  $X_t$  is constant in time, the martingale argument in (2) shows that for  $0 \leq i \leq j$

$$i = jP_i(T_j < T_0) + 0 \cdot [1 - P_i(T_j < T_0)]$$

and solving gives

$$P_i(T_j < T_0) = \frac{i}{j} \quad P_i(T_j > T_0) = \frac{j-i}{j} \quad (8) \quad \text{PxTyltT0}$$

Similar reasoning shows that for  $j \leq i \leq N$ ,

$$i = jP_i(T_j < T_N) + N[1 - P_i(T_j < T_N)]$$

and solving gives

$$P_i(T_j < T_N) = \frac{N-i}{N-j} \quad P_i(T_j > T_N) = \frac{i-j}{N-j} \quad (9) \quad \text{PxTyltTN}$$

When the process leaves  $j$ , it goes to  $j - 1$  or  $j + 1$  with equal probability, so

$$\begin{aligned} P_j(T_j^+ = \infty) &= \frac{1}{2} \cdot P_{j+1}(T_j > T_N) + \frac{1}{2} \cdot P_{j-1}(T_j > T_0) \\ &= \frac{1}{2} \cdot \frac{1}{N-j} + \frac{1}{2} \cdot \frac{1}{j} = \frac{N}{2j(N-j)} \end{aligned}$$

Putting our results into (7) gives

$$E_i N_j = \begin{cases} \frac{i}{j} \cdot \frac{2j(N-j)}{N} & i \leq j \\ \frac{N-i}{N-j} \cdot \frac{2j(N-j)}{N} & j \leq i \end{cases}$$

Since  $q(j) = 2j(N-j)/N$ , (6) gives

$$E_i S_j = \begin{cases} \frac{i}{j} & i \leq j \\ \frac{N-i}{N-j} & j \leq i \end{cases} \quad (10) \quad \boxed{\text{ExSy}}$$

If we let  $h(i) = P_i(T_N < T_0)$  and let  $p_t(i, j)$  be the transition probability for the Moran model, then it follows from the definition of conditional probability and the Markov property that

$$\bar{p}_t(i, j) = \frac{P_i(X_t = j, T_N < T_0)}{P_i(T_N < T_0)} = p_t(i, j) \cdot \frac{h(j)}{h(i)}$$

Integrating from  $t = 0$  to  $\infty$ , we see that the conditioned chain has

$$\bar{E}_i S_j = \int_0^\infty \bar{p}_t(i, j) dt = \frac{h(j)}{h(i)} E_i S_j \quad (11) \quad \boxed{\text{ExSycond}}$$

$h(i) = i/N$ , so  $h(j)/h(i) = j/i$  and using the formula for  $E_i S_j$  given in (10), we have

$$\bar{E}_i S_j = \begin{cases} 1 & i \leq j \\ \frac{j}{i} \cdot \frac{N-i}{N-j} & j \leq i \end{cases} \quad (12) \quad \boxed{\text{ExSycneut}}$$

By the reasoning that led to (5),

$$\bar{E}_i \tau = \sum_{j=1}^{N-1} \bar{E}_i S_j = \sum_{j=i}^{N-1} 1 + \frac{N-i}{i} \cdot \sum_{j=1}^{i-1} \frac{j}{N-j}$$

The first sum is  $N - i$ . For the second we note that

$$\sum_{j=1}^{i-1} \frac{j}{N-j} = N \sum_{j=1}^{i-1} \frac{j/N}{1-j/N} \cdot \frac{1}{N} \approx N \int_0^p \frac{u}{1-u} du$$

where  $p = i/N$ . To evaluate the integral, we note that it is

$$= \int_0^p -1 + \frac{1}{1-u} du = -p - \log(1-p)$$

Combining the last three formulas gives

$$\begin{aligned}\bar{E}_i\tau &\approx N(1-p) + \frac{N(1-p)}{p}(-p - \log(1-p)) \\ &= -\frac{N(1-p)}{p}\log(1-p)\end{aligned}$$

which gives (3). □

## 2 Directional selection

In this section, we will introduce selection letting 1 and  $1 - s$  be the relative fitnesses of the two alleles,  $A$  and  $a$ . Let  $X_t$  be the number of  $A$ 's at time  $t$ . Thinking of the fitnesses as the probability that an offspring of that type is viable, we can formulate the transition rates of the Moran model with selection as

$$\begin{aligned} i \rightarrow i + 1 & \text{ at rate } b_i = (N - i) \cdot \frac{i}{N} \\ i \rightarrow i - 1 & \text{ at rate } d_i = i \cdot \frac{N - i}{N} \cdot (1 - s) \end{aligned} \quad (13) \quad \boxed{\text{sMoranrate}}$$

In words,  $a$ 's are selected for possible replacement at total rate  $N - i$ . The number of  $A$ 's will increase if an  $A$  is chosen to be the parent of the new individual, an event of probability  $i/N$ . The reasoning is similar for the second rate, but in this case the replacement only occurs with probability  $1 - s$ .

**Theorem 3.** *In the Moran model with selection  $s > 0$*

$$P_i(T_N < T_0) = \frac{1 - (1 - s)^i}{1 - (1 - s)^N} \quad (14) \quad \boxed{\text{fixselect}}$$

When  $i = 1$ , the numerator is just  $s$ . If selection is strong, i.e.,  $Ns$  is large, then  $(1 - s)^N \approx 0$  and the probability of fixation of a new mutant is just  $s$ . When  $Ns = O(1)$ ,  $(1 - s) \approx e^{-s}$ , so (14) can be written as

$$P_i(T_N < T_0) \approx \frac{1 - e^{-is}}{1 - e^{-Ns}} \quad (15) \quad \boxed{\text{fixselecta}}$$

This case in which  $s = O(1/N)$  is called the *weak selection regime*.

*Proof.* Let  $h(i) = P_i(T_N < T_0)$ . Births happen at rate  $b_i$  and deaths at rate  $d_i$ , so the probability a birth occurs before a death is  $b_i/(b_i + d_i)$  and we have

$$h(i) = \frac{b_i}{b_i + d_i} h(i + 1) + \frac{d_i}{b_i + d_i} h(i - 1)$$

Multiplying on each side by  $b_i + d_i$  and rearranging, we have

$$h(i + 1) - h(i) = \frac{d_i}{b_i} (h(i) - h(i - 1)) = (1 - s)(h(i) - h(i - 1))$$

Now  $h(0) = 0$ , so if we let  $c = h(1)$  and iterate, it follows that

$$(\star) \quad h(i + 1) - h(i) = c(1 - s)^i$$

Summing we have

$$h(j) = \sum_{i=0}^{j-1} c(1 - s)^i = c \frac{1 - (1 - s)^j}{s}$$

We must have  $h(N) = 1$  so  $c = s/(1 - (1 - s)^N)$  and the desired result follows.  $\square$

We can also prove the result using a more intuitive martingale argument.

*Another derivation of (14).* To motivate the computation, we begin by recalling the martingale proof of Theorem 1. Let  $\tau = T_0 \wedge T_N$ . When  $s = 0$ ,  $EX_t$  is constant in time, so we have

$$i = N \cdot P_i(X_\tau = N) + 0 \cdot P_i(X_\tau = 0)$$

Solving, we have  $P_i(X_\tau = N) = i/N$ .

When  $s > 0$ ,  $b_i/(b_i + d_i) = 1/(2 - s)$ . A little calculation shows that

$$\begin{aligned} (1-s)^{i+1} \frac{1}{2-s} + (1-s)^{i-1} \frac{1-s}{2-s} \\ = (1-s)^i \frac{1-s}{2-s} + (1-s)^i \frac{1}{2-s} = (1-s)^i \end{aligned}$$

so, in this case, the value of  $E(1-s)^{X_t}$  stays constant in time. Reasoning as before,

$$(1-s)^i = (1-s)^N P_i(X_\tau = N) + 1 \cdot [1 - P_i(X_\tau = N)]$$

Solving we have

$$P_i(X_\tau = N) = \frac{1 - (1-s)^i}{1 - (1-s)^N}$$

in agreement with (14). □

One can generalize Theorem 2 to compute the expected time to fixation in the model with selection. However to obtain more insight into what is happening during the fixation of a favorable allele, we will take a different approach.

**hitTs** **Theorem 4.** *In the Moran model with selection as  $N \rightarrow \infty$*

$$\bar{E}_1 \tau \sim \frac{2}{s} \log N$$

*Proof.* The key is to establish that there are three phases in the fixation process.

1. While the advantageous  $A$  allele is rare, the number of  $A$ 's can be approximated by a supercritical branching process.
2. While the frequency of  $A$ 's,  $u_A \in [\epsilon, 1 - \epsilon]$  there is very little randomness and  $u_A$  follows the solution of the logistic differential equation:  $du_A/dt = su_A(1 - u_A)$ .
3. While the disadvantageous  $a$  allele is rare, the number of  $a$ 's can be approximated by a subcritical branching process.

**Phase 1.** Let  $i$  be the number of  $A$ 's. If  $i/N$  is small, then the transition rates in (13) simplify:

$$\begin{aligned} i \rightarrow i + 1 & \text{ at rate } b_i \approx i \\ i \rightarrow i - 1 & \text{ at rate } d_i \approx (1-s)i \end{aligned}$$

This is a continuous time branching process in which each of the  $i$  individuals gives birth at rate 1 and dies at rate  $1 - s$ . Letting  $Z_t$  be the number of individuals at time  $t$ , it is easy to see from the description that

$$\frac{d}{dt}EZ_t = sEZ_t$$

so  $EZ_t = Z_0e^{st}$ . A result from the theory of branching processes, see Athreya and Ney (1972), shows that as  $t \rightarrow \infty$

$$e^{-st}Z_t \rightarrow W \tag{16}$$

bplimit

The limit  $W$  may be 0, and will be if the branching process dies out, that is, if  $Z_t = 0$  for some  $t$ . However, on the event that the process does not die out  $\Omega_\infty = \{Z_t > 0 \text{ for all } t\}$ , we have  $W > 0$ .

Let  $T_1$  be the first time that  $X_t = M = N/\log N$ . Using (16), we see that  $(e^{-st}Z_t|\Omega_\infty) \rightarrow \bar{W} = (W|W > 0)$  so if we condition on survival

$$\frac{N}{\log N} \approx \exp(sT_1)\bar{W}$$

and solving gives

$$T_1 \approx \frac{1}{s} \log \left( \frac{N}{\bar{W} \log N} \right) \approx \frac{1}{s} \log(N)$$

**Phase 2.** Let  $T_2$  be the first time that  $X_t = N - M$ , where  $M = N/\log N$ . As we will now show, during the second phase from  $T_1$  to  $T_2$  the process behaves like the solution of the logistic differential equation. Let  $X_t$  be the number of copies of the mutant allele at time  $t$ , and let  $Y_t^N = X_t/N$ .  $Y_t^N$  makes transitions as follows:

$$\begin{aligned} i/N &\rightarrow (i+1)/N && \text{at rate } b_i = N - i \cdot \frac{i}{N} \\ i/N &\rightarrow (i-1)/N && \text{at rate } d_i \approx (1-s)i \cdot \frac{N-i}{N} \end{aligned}$$

When  $Y_0^N = i/N = y$ , the infinitesimal mean

$$\frac{d}{dt}EY_t^N = b_i \cdot \frac{1}{N} + d_i \cdot \left(-\frac{1}{N}\right) = s \frac{N-i}{N} \cdot \frac{i}{N} = sy(1-y)$$

while the infinitesimal variance

$$\frac{d}{dt}E(Y_t^N - y_0)^2 = (b_i + d_i) \cdot \frac{1}{N^2} = (2-s) \frac{N-i}{N} \cdot \frac{i}{N} \cdot \frac{1}{N} \rightarrow 0$$

In this situation, results in Section 7.4 of Ethier and Kurtz (1986), show that as  $N \rightarrow \infty$ ,  $Y_t^N$  converges to  $Y_t$ , the solution of the logistic differential equation

$$dY_t = sY_t(1 - Y_t)$$

It is straightforward to check that the solution of this equation is

$$Y_t = \frac{1}{1 + Ce^{-st}}$$

where  $C = (1 - Y_0)/Y_0$ . In the case of interest,  $Y_0 = 1/\log(N)$ , so  $C \approx \log(N)$ . Thus  $Y_t = 1 - 1/(\log N)$  when

$$(\log N)e^{-t} = \frac{\log N}{\log N - 1} - 1 = \frac{1}{\log N - 1} \sim \frac{1}{\log N}$$

Solving, we find that  $T_2 - T_1 \approx 2 \log \log N$ .

**Phase 3.** To achieve fixation of the  $A$  allele mutation after time  $T_2$ , the  $M = N/(\log N)$   $a$  alleles must decrease to 0. The number of  $a$  alleles,  $Z_t$ , makes transitions

$$\begin{aligned} j &\rightarrow j + 1 && \text{at rate } d_{N-j} \approx (1 - s)j \\ j &\rightarrow j - 1 && \text{at rate } b_{N-j} \approx j \end{aligned}$$

That is,  $Z_t$  is a continuous time branching process in which each of the  $j$  individuals gives birth at rate  $(1 - s)$  and dies at rate 1. By arguments in phase 1,  $EZ_t = Z_0e^{-st}$  so it takes about  $(1/s) \log(2N)$  units of time to reach 0.

The times in the three phases were

Phase 1	$(1/s) \log(N)$
Phase 2	$\log \log(N)$
Phase 3	$(1/s) \log(N)$

and we have proved Theorem 4. □



### 3 Waiting for two mutations

Consider now a version of the Moran model in which initially all cells are type 0, and where in addition to the usual replacement dynamics, cells of type  $i - 1$  mutate to type  $i$  at rate  $u_i$ . In some treatments mutations are only allowed to occur at births, but this small detail makes very little difference to results, so we will take the mathematically simpler approach of having mutation as a separate process. In this section we are interested in  $\tau_2$  the time the first type 2 individual occurs. The first results in this direction are due to Nowak et al (2004) and Iwasa et al (2004,2005). One can find a nice account in Chapter 12 of Nowak (2006).

#### 3.1 Stochastic tunneling

One boring scenario for producing a type 2 is that a type 1 mutation occurs and fixes in the population, then a mutation to type 2 occurs. Writing  $a \ll b$  as short for  $a/b$  is small or more precisely the assumption that  $a_N/b_N \rightarrow 0$ , there is the following more interesting possibility

stunnel **Theorem 5.** *If  $1/\sqrt{u_2} \ll N \ll 1/u_1$  then as  $N \rightarrow \infty$*

$$P(\tau_2 > t/Nu_1\sqrt{u_2}) \rightarrow e^{-t}$$

To begin to explain the intuition that underlies this result, let  $\theta$  be the probability that a type 1 gives birth to a type 2 before its family line dies out. By considering what happens at the first event we see that

$$\theta = \frac{u_2}{u_2 + 2} + \frac{1}{u_2 + 2}(2\theta - \theta^2) \tag{17}$$

STmut2

To check this, it is convenient to write  $A$  for type 1 and  $B$  for type 2 then we have

$$\begin{aligned} A &\rightarrow 0 && \text{at rate } \frac{1 \cdot (N - 1)}{N} \approx 1 \\ A &\rightarrow 2A && \text{at rate } \frac{(N - 1) \cdot 1}{N} \approx 1 \\ A &\rightarrow B && \text{at rate } u_2 \end{aligned}$$

The mutation  $A \rightarrow B$  will occur first with probability  $u_2/(u_2 + 2)$  in which case success is assured (i.e., we will get a 2). Removal of the lone  $A$ ,  $A \rightarrow 0$ , will occur first with probability  $1/(u_2 + 2)$  in which case success is impossible. Finally,  $A \rightarrow 2A$  will occur first with probability  $1/(u_2 + 2)$  in which case success has probability  $1 - (1 - \theta)^2 = 2\theta - \theta^2$  since successes for the the two lineages is almost independent.

A little algebra converts (17) into  $\theta^2 + u_2\theta - u_2 = 0$  which has positive solution

$$\frac{-u_2 + \sqrt{u_2^2 + 4u_2}}{2} \approx \sqrt{u_2} \tag{18}$$

STmut2

since  $u_2^2 \ll u_2 \ll \sqrt{u_2}$  when  $u_2$  is small. While the number of 1's in the population remains  $o(N)$ , mutations to type 1 occur at rate  $Nu_1$ . By (27) the probability that a type 1 mutation

will give rise to a type 2 is  $\sim \sqrt{u_2}$ . Using Poisson thinning now we see that if  $\sigma_2$  is the time of the first type 1 mutation that gives rise to a type 2 then  $\sigma_2$  is approximately exponential with rate  $Nu_1\sqrt{u_2}$ .

Up to this point we have not used the assumptions of the theorem. To explain how they enter the picture, we note

1. The number of type 1's is a time change of a symmetric random walk, so if the number reaches  $M$  then there will be of order  $M^2$  births before the family of type 1's dies out. From this we see that the type 2 mutation will first occur in a family that reaches size  $O(1/\sqrt{u_2})$ . If we want our assumption about the number of type 1's up to  $\tau_2$  to be  $o(N)$  then we must have  $1/\sqrt{u_2} \ll N$ .

2. We have a limit theorem for  $\sigma_2$  but we want one for  $\tau_2$ , so we need to show that  $\tau_2 - \sigma_2$  can be neglected. To do this we note that Theorem 2 implies

$$E_1(T_M | T_M < T_0) \sim M$$

We have  $M = O(1/\sqrt{u_2})$  while  $E\sigma_2 = O(1/nu_1\sqrt{u_2})$  so for  $\tau_2 - \sigma_2 = o(E\sigma_2)$  we need  $Nu_1 \ll 1$ .

### 3.2 The assumption $Nu_1 \rightarrow 0$

Our next goal is to prove a result that is a little more general than Theorem 5 in that it allows  $Nu_1 \rightarrow \lambda > 0$ .

**Theorem 6.** *Suppose that  $Nu_1 \rightarrow \lambda \in [0, \infty)$ ,  $u_2 \rightarrow 0$ , and  $N\sqrt{u_2} \rightarrow \infty$  as  $N \rightarrow \infty$ . Then*

$$P(\tau_2 > t/Nu_1\sqrt{u_2}) \rightarrow \exp\left(-\int_0^t h(s) ds\right)$$

m2thm where  $h(s) = (1 - e^{-2s/\lambda})/(1 + e^{-2s/\lambda})$  if  $\lambda > 0$  and  $h(s) \equiv 1$  if  $\lambda = 0$ .

If we let  $X_1(t)$  be the number of type 1 individuals at time  $t$  then

$$P(\tau_2 > t) = E \exp\left(-u_2 \int_0^t X_1(s) ds\right) \tag{19} \span style="border: 1px solid black; padding: 2px;">expfort2$$

**Step 1.** *We can replace  $X_1(t)$  by a continuous-time critical branching process,  $Y(t)$ , with births and deaths at rate 1 and immigration at rate  $Nu_1$ .*

When  $X_1(t) = k$ , type 1 mutations occur at rate  $(N - k)u_1$ , while birth events in which a type 1 individual replaces a type 0 individual occur at rate  $k(N - k)/N$ , so we have jumps

$$\begin{aligned} k \rightarrow k + 1 & \quad \text{at rate } (k + Nu_1) \cdot \frac{N - k}{N} \\ k \rightarrow k - 1 & \quad \text{at rate } k \cdot \frac{N - k}{N} \end{aligned}$$

The branching process with immigration,  $Y(t)$ , has jumps

$$\begin{aligned} k &\rightarrow k + 1 && \text{at rate } k + Nu_1 \\ k &\rightarrow k - 1 && \text{at rate } k \end{aligned}$$

Comparing rates we see that the process  $\{X_1(t), t \geq 0\}$  is a time-change of  $\{Y(t), t \geq 0\}$ , in which time runs slower than in the branching process by a factor of  $(N - k)/N$ . That is if

$$T(t) = \int_0^t \frac{N - X_1(s)}{N} ds \leq t$$

then the two processes can be coupled so that  $X_1(t) = Y(T(t))$ , for all  $t \geq 0$ . The time change will have little effect as long as  $X_1(t)$  is  $o(N)$ .

**Step 2.** *On the relevant time scale, the number of 1s stays small with high probability.*

size

**Lemma 1.** *Fix  $t > 0$ ,  $\epsilon > 0$ , and let  $M_t = \max_{0 \leq s \leq t/(Nu_1\sqrt{u_2})} X_1(s)$ . We have*

$$\lim_{N \rightarrow \infty} P\left(M_t > \epsilon N\right) = 0.$$

*Proof.* Since in addition to the immigration, individuals give birth and die at the same rate, the process  $\{X_1(s), s \geq 0\}$  is a submartingale. Because the rate of type 1 mutations is always bounded above by  $Nu_1$ , we have  $EX_1(s) \leq Nu_1s$  for all  $s$ . By Doob's Maximal Inequality,

$$P(M_t > \epsilon N) \leq \frac{EX_1(t/(Nu_1\sqrt{u_2}))}{\epsilon N} \leq \frac{1}{\epsilon N} \cdot \frac{Nu_1t}{Nu_1\sqrt{u_2}},$$

which goes to zero as  $N \rightarrow \infty$ , since  $N\sqrt{u_2} \rightarrow \infty$ . □

**Step 3.** *A useful lemma.*

Steps 1 and 2 have shown that it is enough to prove the result for the branching process,  $Y(t)$ . Let  $Q$  denote the distribution of  $\{Y(t), t \geq 0\}$ , and let  $Q_1$  denote the law of the process starting from a single type 1 and modified to have no further mutations to type 1.

Q1toQ

**Lemma 2.** *The waiting time for the first type 2 in a system with type 1 mutations at rate  $Nu_1$  satisfies*

$$Q(\tau_2 \leq t) = 1 - \exp\left(-Nu_1 \int_0^t Q_1(\tau_2 \leq s) ds\right) \tag{20}$$

*Proof.* Type 1 mutations are a Poisson process with rate  $Nu_1$ . A point at time  $t - s$  is a success, i.e., produces a type 2 before time  $t$  with probability  $Q_1(\tau_2 \leq s)$ . By results for thinning a Poisson process, the number of successes by time  $t$  is Poisson with mean  $Nu_1 \int_0^t Q_1(\tau_2 \leq s) ds$ . The result follows from the observation that  $Q(\tau_2 \leq t)$  is the probability of at least one success in the Poisson process. □

**Step 4.** Compute  $g_2(t) = Q_1(\tau_2 \leq t)$ .

By considering what happens between time 0 and  $h$

$$g_2(t+h) = g_2(t)[1 - (2+u_2)h] + h[2g_2(t) - g_2(t)^2] + h \cdot 0 + u_2h \cdot 1 + o(h)$$

where the four terms correspond to nothing happening, a birth, a death, and a mutation of the original type 1 to type 2. Doing some algebra and letting  $h \rightarrow 0$

$$g_2'(t) = -u_2g_2(t) - g_2(t)^2 + u_2 \quad (21) \quad \boxed{\text{g2DE}}$$

If we let  $r_1 > r_2$  be the solutions of  $x^2 + u_2x - u_2 = 0$ , i.e.,

$$r_i = \frac{-u_2 \pm \sqrt{u_2^2 + 4u_2}}{2} \quad (22) \quad \boxed{\text{rireq}}$$

we can write this as  $g_2'(t) = -(g_2(t) - r_1)(g_2(t) - r_2)$ . A little calculus gives

$$g_2(t) = \frac{r_1(1 - e^{(r_2-r_1)t})}{1 - (r_1/r_2)e^{(r_2-r_1)t}}$$

Using the facts that  $r_1 - r_2 = \sqrt{u_2^2 + 4u_2} \sim 2\sqrt{u_2}$  and  $r_1/r_2 \rightarrow -1$  we see that if  $t\sqrt{u_2} \rightarrow s$  then

$$g_2(t) \sim \sqrt{u_2} \cdot \frac{1 - e^{-2s}}{1 + e^{-2s}} \quad (23) \quad \boxed{\text{g2t}}$$

Using (23) in Theorem 2 gives the result in Theorem 6.

### 3.3 The assumption $N\sqrt{u_2} \rightarrow \infty$

In the previous subsection we saw that the assumption  $Nu_1 \rightarrow 0$  was needed to be able to ignore the difference  $\tau_2 - \sigma_2$  in the limit theorem. The assumption  $N\sqrt{u_2} \rightarrow \infty$  implies that the 1's are  $o(N)$  until time  $\tau_2$ . In the other direction,

seqfix

**Theorem 7.** *If  $Nu_1 \rightarrow 0$  and  $N\sqrt{u_2} \rightarrow 0$  then  $\tau_2 \Rightarrow \text{exponential}(u_1) + \text{exponential}(Nu_2)$ , the sum of two independent exponentials.*

*Proof.* If  $N\sqrt{u_2} \ll 1$  then the probability of fixation  $1/N \gg \sqrt{u_2}$  the probability a type 1 mutant gives rise to a type 2 before its family does out. From this we see that with high probability a type 1 mutation destined for fixation will occur before the first type 2 mutation occurs. Type 1 mutations that fix occur at rate  $Nu_1 \cdot 1/N$ . By Theorem 2 the average waiting time for fixation conditioned that it occurs is  $\sim N \ll 1/u_1$  so this can be ignored. One the 1's fix the waiting time for the mutation to type 2 is  $\text{exponential}(Nu_2)$ .  $\square$

There is interesting behavior in borderline case between Theorem 7 and 5.

borderth

**Theorem 8.** *Suppose that  $Nu_1 \rightarrow 0$  and  $(Nu_1\sqrt{u_2})^2 \rightarrow \gamma > 0$ , and let*

$$\alpha = \sum_{k=1}^{\infty} \frac{\gamma^k}{(k-1)!(k-1)!} \bigg/ \sum_{k=1}^{\infty} \frac{\gamma^k}{k!(k-1)!} > 1 \quad (24) \quad \boxed{\text{alphadef}}$$

*then  $P(u_1\tau_2 > t) \rightarrow \exp(-\alpha t)$ .*

In this case the mutation to type 2 occurs with positive probability before fixation occurs, and at a time when the number of type 1's,  $X_1(t)$ , is  $O(N)$ . The keys to the analysis are

- If we start with  $X_1(0) = N\epsilon$  then  $N^{-1}X_1(Nt)$  converges to  $Y_t$  where  $Y_t$  is the Wright-Fisher diffusion with infinitesimal generator  $x(1-x)d^2/dx^2$ .
- If  $Y(0) = y$  and  $u(y)$  is the probability that starting from  $X_1(Nt) = Ny$  the process hits 0 before reaching 1 or generating a type 2 mutation satisfies

$$x(1-x)u''(x) - \gamma xu(x) \quad u(0) = u(1) = 1 \quad (25) \quad \boxed{\text{WFueq}}$$

The solution of (25) is

$$u(y) = c \sum_{k=1}^{\infty} \frac{\gamma^k}{k!(k-1)!} (1-y)^k$$

and the constant  $\alpha = u'(0)$ . The details are somewhat complicated so we refer the reader to Durrett, Schmidt, and Schweinsberg (2007)

### 3.4 Type 1 mutations are not neutral

We return to the tunneling regime but now assume that type 1's have fitness  $1+r$ .

**Theorem 9.** *If  $1/\sqrt{u_2} \ll N \ll 1/u_1$  and  $r = \rho\sqrt{u_2}$  then*

$$P(\tau_2 > t/Nu_1R\sqrt{u_2}) \quad \text{where} \quad R = \frac{1}{2} \left( \rho + \sqrt{\rho^2 + 4} \right)$$

Note that now the weak selection regime is  $r = O(\sqrt{u_2})$  rather than  $s = O(1/N)$  in (15). This is intuitive since the proof of Theorem ?? tells us that first type 2 arises in a type 1 family that reaches size  $1/\sqrt{u_2}$ .

Let  $\theta$  be the probability that a type 1 gives birth to a type 2 before its family line dies out. By considering what happens at the first event we see that

$$\theta = \frac{u_2}{u_2 + 2 + r} + \frac{1+r}{u_2 + 2 + r} (2\theta - \theta^2) \quad (26) \quad \boxed{\text{selmuteq}}$$

A little algebra converts (26) into

$$(1+r)\theta^2 + \theta(u_2 - r) - u_2 = 0$$

which has positive solution

$$\frac{-(u_2 - r) + \sqrt{(u_2 - r)^2 + 4(1+r)u_2}}{2} \approx R\sqrt{u_2} \quad (27) \quad \boxed{\text{selmut2}}$$

since  $r = \rho\sqrt{u_2} \gg u_2$ . The remainder of the proof is similar to that of Theorem 5.

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