Benchmarking Pv3Rs

In this document, we investigate the runtime scaling of the `Pv3Rs`' main function, `compute_posterior`, with respect to the number of markers, the MOIs, and the number of episodes.

Caution: Running the RMarkdown script takes a few hours of compute time.

Setup

```
library(Pv3Rs)
library(tictoc)
library(MCMCpack)

# simulate allele frequencies for one marker
sim_fs_single <- function(n_a) {
  alleles <- letters[1:n_a] # n_a <= 26
  fs_unnamed <- as.vector(rdirichlet(1, alpha = rep(1, n_a)))
  setNames(fs_unnamed, alleles)
}

# simulate allele frequencies for multiple markers
# assumes each marker has the same number of alleles
sim_fs <- function(n_m, n_a) {
  markers <- paste0("m", 1:n_m) # marker names
  n_a_vec <- setNames(rep(n_a, n_m), markers)
  lapply(n_a_vec, sim_fs_single)
}

# simulate data for one marker, one episode
# sample without replacement to match desired MOI, so must have length(fs) >= MOI
sim_data_single <- function(fs_single, MOI) {
  sample(names(fs_single), MOI, prob=fs_single)
}

# simulate data for all markers, all episodes
sim_data <- function(MOIs, n_m, n_a) {
  fs <- sim_fs(n_m, n_a)
  y <- lapply(
    MOIs,
    function(MOI) lapply(fs, sim_data_single, MOI) # sample data for one episode
  )
  return(list(y=y, fs=fs))
}
```

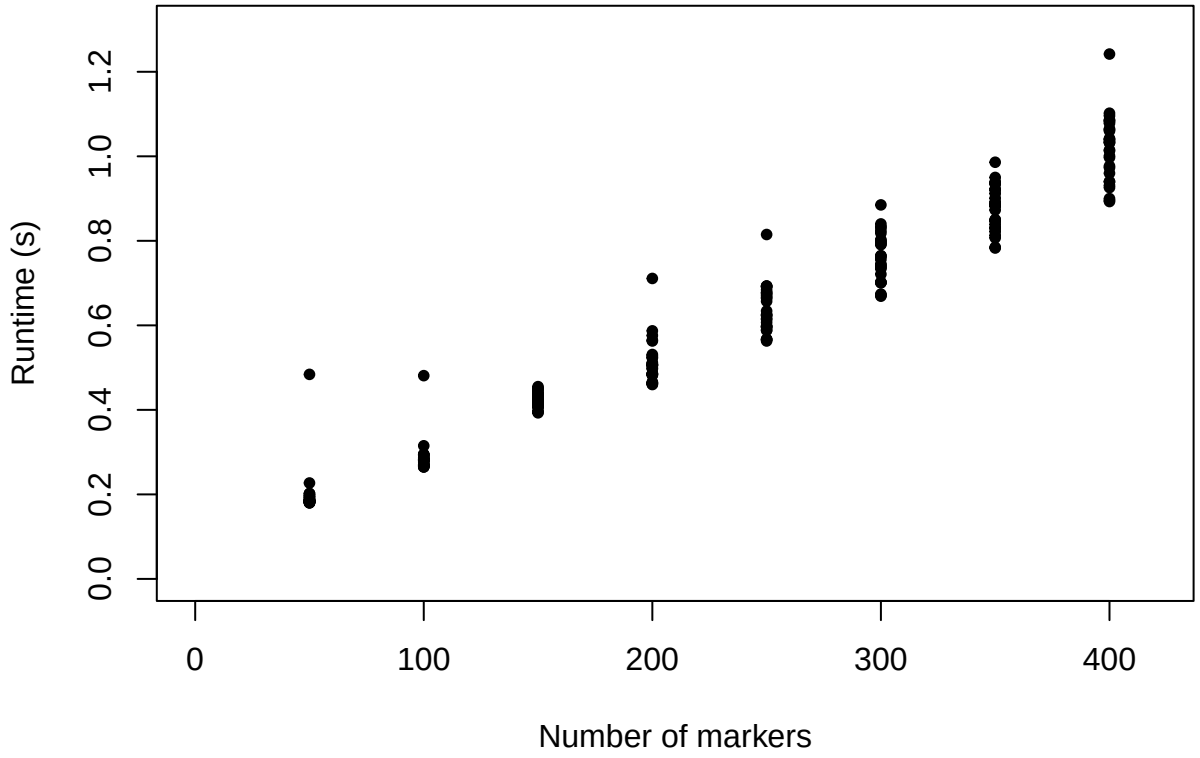
Runtime vs number of markers

We expect the runtime of `compute_posterior` to scale linearly with the number of markers due to the likelihood decomposition ([1], Section 3.4). We simulate genetic data spanning across 2 episodes both with MOI 2, and vary the number of markers between $50, 100, \ldots, 400$. Each marker is assumed to have 8 possible alleles.

```
set.seed(1)
n_markers <- 50*(1:8)
n_a <- 8
MOIs <- c(2, 2)
n_rep <- 30

data_by_m <- list()
for (n_m in n_markers) {
  data_by_m[[as.character(n_m)]] <- lapply(
    1:n_rep,
    function(x) sim_data(MOIs, n_m, n_a)
  )
}

time_by_m <- list()
for (n_m in n_markers) {
  tic(msg = paste0("Running n_m=", n_m))
  time_by_m[[as.character(n_m)]] <- sapply(
    data_by_m[[as.character(n_m)]],
    function(data) {
      tic("")
      suppressMessages(compute_posterior(data$y, data$fs))
      res <- toc(quiet=TRUE)
      res$toc - res$tic
    }
  )
  toc()
}
#> Running n_m=50: 5.937 sec elapsed
#> Running n_m=100: 8.609 sec elapsed
#> Running n_m=150: 12.711 sec elapsed
#> Running n_m=200: 15.345 sec elapsed
#> Running n_m=250: 19.128 sec elapsed
#> Running n_m=300: 22.771 sec elapsed
#> Running n_m=350: 26.322 sec elapsed
#> Running n_m=400: 30.541 sec elapsed
```

```
max_time <- max(sapply(time_by_m, max))
par(cex=1.0, mar=c(5, 4.5, 2, 1))
plot(
  NULL, type="n",
  xlim=c(0, 420),
  ylim=c(0, max_time*1.05),
  xlab="Number of markers",
  ylab="Runtime (s)"
)
for(n_m in n_markers) {
```

```
  points(rep(n_m, n_rep), time_by_m[[as.character(n_m)]], pch=20)
}
```



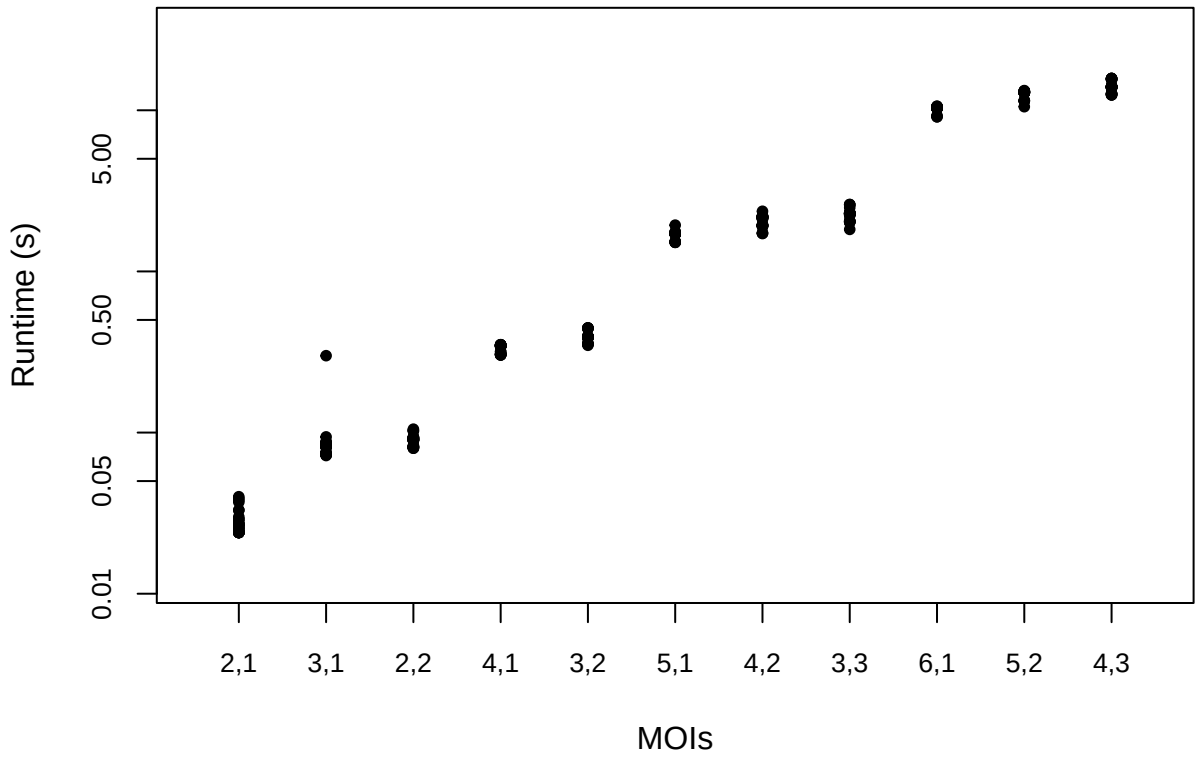
Runtime vs MOIs

As the number of MOIs increase, the runtime increases due to having more possibilities for allele assignment and more valid relationship graphs. We simulate genetic data consisting of 1 marker (8 alleles), spanning 2 episodes of various MOI combinations.

```
set.seed(1)
n_m <- 1
n_a <- 8
MOIs_comb <- list()
for(MOItot in 3:7) {
  for(MOI1 in (MOItot-1):1) {
    MOI2 <- MOItot-MOI1
    if(MOI1 >= MOI2) MOIs_comb <- c(MOIs_comb, list(c(MOI1, MOI2)))
  }
}
n_rep <- 30

data_by_MOI <- list()
for (MOIs in MOIs_comb) {
  data_by_MOI[[paste(MOIs, collapse=",")]] <- lapply(
```

```
    1:n_rep,
    function(x) sim_data(MOIs, n_m, n_a)
  )
}

time_by_MOI <- list()
for (MOIs in MOIs_comb) {
  MOIstr <- paste(MOIs, collapse=",")
  tic(msg = paste0("Running MOI=", MOIstr))
  time_by_MOI[[MOIstr]] <- sapply(
    data_by_MOI[[MOIstr]],
    function(data) {
      tic("")
      suppressMessages(compute_posterior(data$y, data$fs))
      res <- toc(quiet=TRUE)
      res$toc - res$tic
    }
  )
  toc()
}
#> Running MOI=2,1: 0.839 sec elapsed
#> Running MOI=3,1: 2.647 sec elapsed
#> Running MOI=2,2: 2.686 sec elapsed
#> Running MOI=4,1: 9.974 sec elapsed
#> Running MOI=3,2: 11.851 sec elapsed
#> Running MOI=5,1: 50.768 sec elapsed
#> Running MOI=4,2: 61.482 sec elapsed
#> Running MOI=3,3: 67.421 sec elapsed
#> Running MOI=6,1: 307.669 sec elapsed
#> Running MOI=5,2: 380.611 sec elapsed
#> Running MOI=4,3: 422.361 sec elapsed
```

```
min_time <- min(sapply(time_by_MOI, min))
max_time <- max(sapply(time_by_MOI, max))
n <- length(MOIs_comb)

par(cex=1.0, cex.axis=0.8, mar=c(5, 4.5, 2, 1))
plot(
  1, 1, type="n",
  xlim=c(0.5, n+0.5),
  ylim=c(min_time*0.5, max_time*2),
  xlab="MOIs",
  ylab="Runtime (s)",
  xaxt='n', log="y",
)
axis(
  side=1, at=1:n,
  sapply(MOIs_comb, paste, collapse=",")
)

for(i in 1:n) {
  points(rep(i, n_rep), time_by_MOI[[i]], pch=20)
}
```



Empirically, the runtime (note the log scale) has roughly exponentially scaling with respect to the total MOI. It is difficult to conclude an exact growth rate due to the small range of the total MOI. Given a fixed total MOI, the runtime is slightly shorter (see printed output of total runtime) if the maximum MOI is larger. This can be explained by the following observations:

- A larger maximum MOI leads to more pairs of genotypes that cannot be clones. This leads to less valid relationship graphs to enumerate.
- Allele assignment for the largest MOI is always fixed. A smaller minimum MOI leads to less allele assignment possibilities to be considered.

Runtime vs number of episodes

Here we investigate two separate cases:

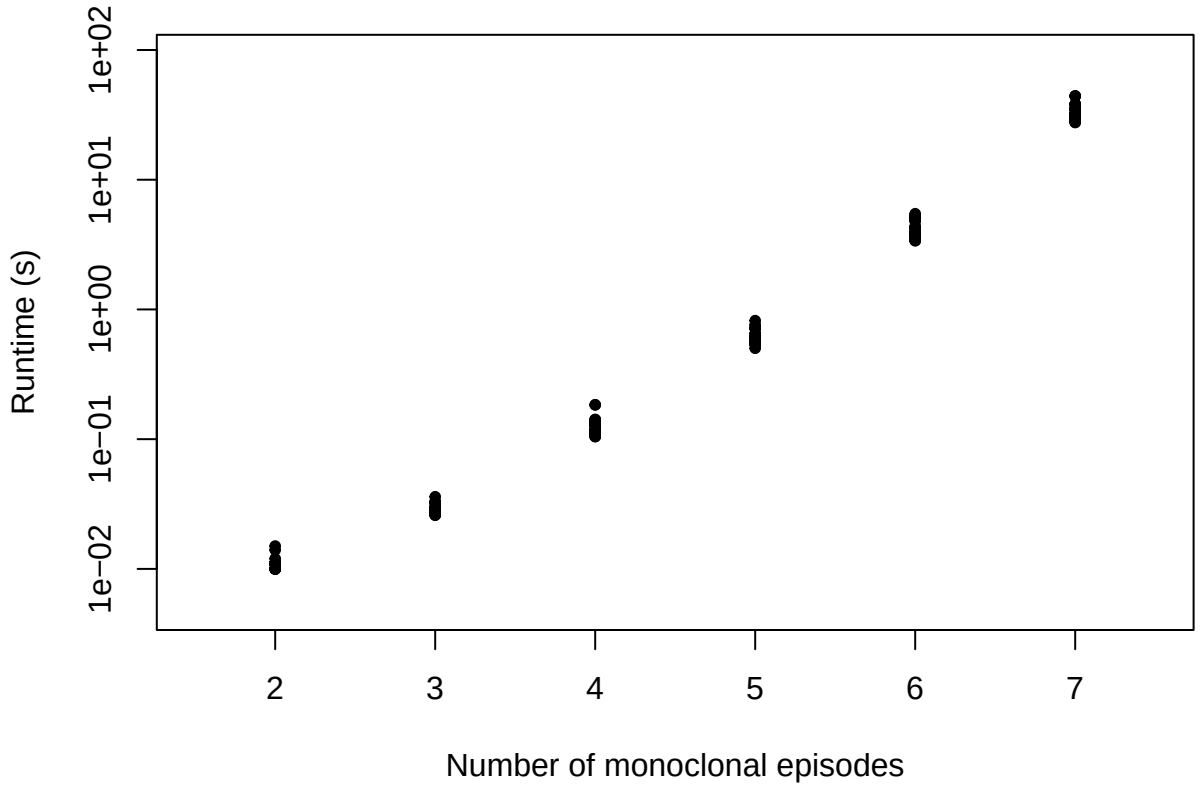
- increasing the number of episodes with 1 genotype per episode, and
- increasing the number of episodes with a fixed total MOI.

1 genotype per episode

We simulate genetic data consisting of 1 marker (8 alleles), with 1 genotype per episode for various numbers of episodes.

```
set.seed(1)
n_m <- 1
n_a <- 8
n_epis <- 2:7
n_rep <- 30

data_by_epi <- list()
for (epi in n_epis) {
  data_by_epi[[as.character(epi)]] <- lapply(
    1:n_rep,
    function(x) sim_data(rep(1, epi), n_m, n_a)
  )
}

time_by_epi <- list()
for (epi in n_epis) {
  tic(msg = paste0("Running epi=", epi))
  time_by_epi[[as.character(epi)]] <- sapply(
    data_by_epi[[as.character(epi)]],
    function(data) {
      tic("")
      suppressMessages(compute_posterior(data$y, data$fs))
      res <- toc(quiet=TRUE)
      res$toc - res$tic
    }
  )
  toc()
}
#> Running epi=2: 0.329 sec elapsed
#> Running epi=3: 0.864 sec elapsed
#> Running epi=4: 3.805 sec elapsed
#> Running epi=5: 18.757 sec elapsed
#> Running epi=6: 126.427 sec elapsed
#> Running epi=7: 1008.11 sec elapsed
```

```
min_time <- min(sapply(time_by_epi, min))
max_time <- max(sapply(time_by_epi, max))

par(cex=1.0, mar=c(5, 4.5, 2, 1))
plot(
  1, 1, type="n",
  xlim=c(1.5, 7.5),
  ylim=c(min_time*0.5, max_time*2),
  xlab="Number of monoclonal episodes",
  ylab="Runtime (s)",
  log="y",
)

for(epi in n_epis) {
  points(rep(epi, n_rep), time_by_epi[[as.character(epi)]], pch=20)
}
```



With one genotype per episode, the runtime (note the log scale) scales super-exponentially with respect to the number of episodes (or equivalently, the total MOI). In fact, the number of relationship graphs with n episodes with 1 genotype per episode is given by

$$R_n = \sum_{k=1}^{n} S(n,k) B_k,$$

where $S(n_k)$ are Stirling numbers of the second kind and B_k are Bell numbers. We provide the derivation in the Appendix, where we also show that $\log R_n \sim n \log n$.

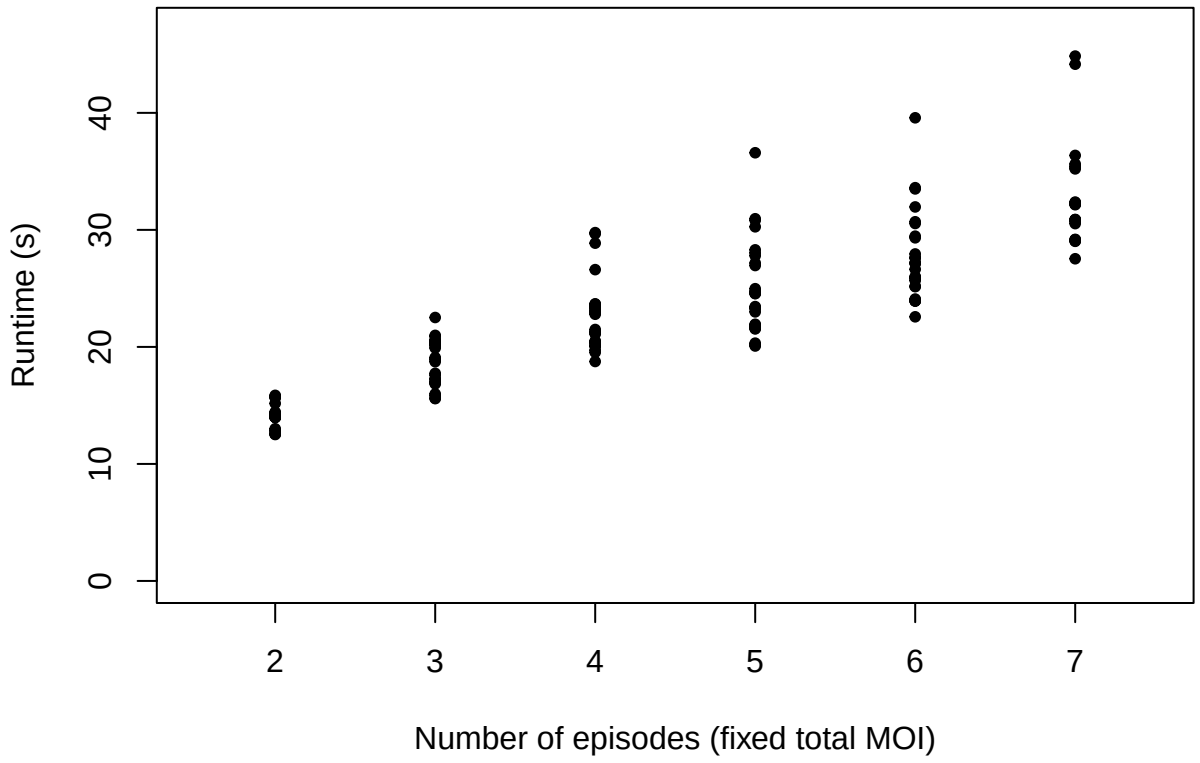
Fixed total MOI

We simulate genetic data consisting of 1 marker (8 alleles), for various numbers of episodes with a fixed total MOI of 7. See printed output below for the sequence of MOIs considered.

```
set.seed(1)
n_m <- 1
n_a <- 8
maxepi <- 7 # fixed total MOI
n_rep <- 30

MOI_fix_comb <- list()
for(epi in 2:maxepi) {
  m <- maxepi %/% epi
  rem <- maxepi %% epi
  MOI_fix_comb <- c(MOI_fix_comb, list(c(rep(m+1, rem), rep(m, epi-rem))))
```

```
}

data_by_MOI_fix <- list()
for (MOIs in MOI_fix_comb) {
  data_by_MOI_fix[[paste(MOIs, collapse=",")]] <- lapply(
    1:n_rep,
    function(x) sim_data(MOIs, n_m, n_a)
  )
}

time_by_MOI_fix <- list()
for (MOIs in MOI_fix_comb) {
  MOIstr <- paste(MOIs, collapse=",")
  tic(msg = paste0("Running MOI=", MOIstr))
  time_by_MOI_fix[[MOIstr]] <- sapply(
    data_by_MOI_fix[[MOIstr]],
    function(data) {
      tic("")
      suppressMessages(compute_posterior(data$y, data$fs))
      res <- toc(quiet=TRUE)
      res$toc - res$tic
    }
  )
  toc()
}
#> Running MOI=4,3: 422.496 sec elapsed
#> Running MOI=3,2,2: 567.92 sec elapsed
#> Running MOI=2,2,2,1: 679.498 sec elapsed
#> Running MOI=2,2,1,1,1: 745.38 sec elapsed
#> Running MOI=2,1,1,1,1,1: 820.083 sec elapsed
#> Running MOI=1,1,1,1,1,1,1: 973.633 sec elapsed
```

```
min_time <- min(sapply(time_by_MOI_fix, min))
max_time <- max(sapply(time_by_MOI_fix, max))

par(cex=1.0, mar=c(5, 4.5, 2, 1))
plot(
  1, 1, type="n",
  xlim=c(1.5, maxepi + 0.5),
  ylim=c(0, max_time*1.05),
  xlab="Number of episodes (fixed total MOI)",
  ylab="Runtime (s)",
)

for(epi in 2:maxepi) {
  points(rep(epi, n_rep), time_by_MOI_fix[[epi-1]], pch=20)
}
```



With the total MOI fixed, the runtime does not increase as drastically with the number of episodes. However, more episodes still lead to more valid relationship graphs as there are less pairs of intra-episode genotypes which cannot be clones, explaining the increase in runtime.

Appendix

To derive a formula for R_n, the number of relationship graphs for n episodes with 1 genotype per episode, we treat a relationship graph as a nested partition. The clonal relationships in a relationship graph induce a partition of all genotypes into subsets, where all genotypes within the same subset are clones of each other. We call such a subset a 'clonal cell'. The sibling relationships in a relationship graph induce a partition of all clonal cells into subsets, such that any two genotypes from the same subset that are not clones of each other must be siblings. Recall that Stirling numbers of the second kind $S(n,k)$ count the number of ways to partition n objects into k subsets, whereas the Bell numbers B_k count the number of ways to partition k objects (into any number of subsets). Letting k denote the number of clonal cells, we have

$$R_n = \sum_{k=1}^{n} S(n,k) B_k.$$

To establish the asymptotics of R_n, we first note that $R_n \geq S(n,n)B_n = B_n$. It is well known that $\log B_n \sim n \log n$. If we additionally have that $R_n \leq n^n$, it then follows that $\log R_n \sim n \log n$. The rest of this appendix is devoted to proving that $R_n \leq n^n$ is indeed true. Let $\mathcal{H}_n$ be the set of all functions h that map elements of $\{1,\ldots,n\}$ to $\{1,\ldots,n\}$. Since $|\mathcal{H}_n| = n^n$, it suffices to show that there is an injection from the set of all relationship graphs (with n genotypes) to $\mathcal{H}_n$.

Consider the following mapping of a relationship graph to a function h: Given a relationship graph, label the genotypes from 1 to n, and label the clonal cells from 1 to k. For each $k' = 1,\ldots,k$, let $c_{k'}$ denote

the smallest genotype label in clonal cell k'. For each genotype i in clonal cell k' that is not $c_{k'}$, we define $h(i) = c_{k'}$. It remains to define the values of $h(c_1), \ldots, h(c_k)$. The sibling relationships induce a partition of $\{1, \ldots, k\}$ into subsets of clonal cells. Let $\{x_1, \ldots, x_m\}$ be such a subset, where $1 \leq x_1 \leq \cdots \leq x_m \leq k$. For each $m' = 1, \ldots, m$, we define $h(c_{x_{m'}}) = h(c_{x_{m'+1}})$, where subscripts of x are taken modulo m. We repeat the same for all subsets of the partition induced by sibling relationships, which completes the definition of the mapping. Informally, we select one genotype from each clonal cell to be a representative. The function h maps non-representative genotypes to their corresponding representatives, and maps representative genotypes to representative genotypes, such that each subset induced by the sibling relationships corresponds to a cycle induced by h.

It remains to show that this mapping is indeed an injection. Consider two different relationship graphs g_1 and g_2, corresponding to the functions h_1 and h_2 under the mapping above. We seek to show that $h_1 \neq h_2$. Suppose that the genotypes i and i' have a different relationship under g_1 and g_2. It suffices to consider the following two cases:

Case 1: Genotypes i and i' are strangers under g_1, but not under g_2. Given a function h obtained from the mapping of a relationship graph and a genotype j, let $\text{sink}(j; h)$ denote the set of genotype labels that appear infinitely many times in the sequence $(j, h(j), h(h(j)), \ldots)$. It follows that $\text{sink}(i; h) \neq \text{sink}(i'; h)$ if and only if genotypes i and i' are strangers. Therefore, we must have $h_1 \neq h_2$.

Case 2: Genotypes i and i' are siblings under g_1, but clones under g_2. Given a function h obtained from the mapping of a relationship graph and a genotype j, let $\text{sink}_1(j; h)$ be the genotype label $\text{sink}(j; h)$ that occurs first in the sequence $(j, h(j), h(h(j)), \ldots)$. It follows that $\text{sink}_1(i; h) = \text{sink}_1(i'; h)$ if and only if genotypes i and i' are clones (or $i = i'$, which is irrelevant). Therefore, we must have $h_1 \neq h_2$.

This completes the proof that $\log R_n \sim n \log n$.

References

[1] Taylor AR, Foo YS, White MT. (2022). Plasmodium vivax relapse, reinfection and recrudescence estimation using genetic data. medRxiv preprint medRxiv:2022.11.23.22282669. https://doi.org/10.1101/2022.11.23.22282669