FILE S4: COMPUTING SUMS OF ANCESTRAL PATHS

In this Supplementary File, we describe the calculation of $\phi_k^{k'}(\ell)$ using the sum of ancestral paths approach.

Calculation of $\phi_k^k(3)$: We begin by considering a simpler specific case, where $k = k'$ and $\ell = 3$. There are a total of $\binom{6}{3} = 20$ possible ancestral paths by which two individuals sampled from class k can coalesce in class $k-3$. These can be separated into four types, according to whether the two ancestral lineages were ever together in classes $k-1$ or $k-2$. We can list all paths of each type, using the notation that A is a mutation event in the first lineage, and B is a mutation event in the second lineage. We have

$$\underbrace{\begin{pmatrix} ABABAB \\ ABABBA \\ ABBAAB \\ ABBABA \\ BAABAB \\ BAABBA \\ BABAAB \\ BABABA \end{pmatrix}}_{\binom{2}{1}\binom{2}{1}\binom{2}{1}=8 \text{ ways}} \quad \underbrace{\begin{pmatrix} ABAABB \\ ABBBAA \\ BAAABB \\ BABBAA \end{pmatrix}}_{\binom{2}{1}(\binom{4}{2}-\binom{2}{1}\binom{2}{1})=4 \text{ ways}} \quad \underbrace{\begin{pmatrix} AABBAB \\ AABBBA \\ BBAAAB \\ BBAABA \end{pmatrix}}_{\binom{2}{1}(\binom{4}{2}-\binom{2}{1}\binom{2}{1})=4 \text{ ways}} \quad \underbrace{\begin{pmatrix} AAABBB \\ AABABB \\ BBBAAA \\ BBABAA \end{pmatrix}}_{\binom{6}{3}-\text{others}=4\text{ways}}.$$

The probabilities of all paths of a particular type are identical. We can calculate the probability of each of the four types of paths using the same logic as outlined in the main text. We find

$$P(AAABBBc) = I_x^{k-3}\frac{k(k-1)(k-2)}{8(2k-1)(2k-3)(2k-5)}\left(1-I_x^k\right), \tag{S.45}$$

$$P(AABBABc) = I_x^{k-3}\frac{k(k-1)(k-2)}{8(2k-1)(2k-3)(2k-5)}\left(1-I_x^k\right)\left(1-I_x^{k-1}\right), \tag{S.46}$$

$$P(ABAABBc) = I_x^{k-3}\frac{k(k-1)(k-2)}{8(2k-1)(2k-3)(2k-5)}\left(1-I_x^k\right)\left(1-I_x^{k-2}\right), \tag{S.47}$$

$$P(ABABABc) = I_x^{k-3}\frac{k(k-1)(k-2)}{8(2k-1)(2k-3)(2k-5)}\left(1-I_x^k\right)\left(1-I_x^{k-1}\right)\left(1-I_x^{k-2}\right). \tag{S.48}$$

Summing over all the possible paths, we find

$$\phi_k^k(3) = I_{k-3}\frac{\binom{k}{k-3}\binom{k}{k-3}}{\binom{2k}{6}}\left[1-\frac{\binom{2}{1}\binom{4}{2}}{\binom{6}{3}}I_{k-1}-\frac{\binom{2}{1}\binom{4}{2}}{\binom{6}{3}}I_{k-2}+\frac{\binom{2}{1}\binom{2}{1}\binom{2}{1}}{\binom{6}{3}}I_{k-1}I_{k-2}\right]. \tag{S.49}$$

We now pause to consider the form of the probabilities of each type of ancestral path. These probabilities differ only by factors of $(1-I_x^{k-i})$. One such factor arises each time the two ancestral lineages are together in class $k-i$. In other words, we can rewrite the probability of each path as the probability of an undistorted path (defined to be a path in which the contributions due to the possibility of coalescence in previous classes are neglected), times a correction for each class in which the two lineages are together:

$$P(AAABBBc) = P(\text{Undistorted Path}) \left(1 - I_x^k\right) \tag{S.50}$$

$$P(AABBABc) = P(\text{Undistorted Path}) \left(1 - I_x^k\right) \left(1 - I_x^{k-1}\right) \tag{S.51}$$

$$P(ABAABBc) = P(\text{Undistorted Path}) \left(1 - I_x^k\right) \left(1 - I_x^{k-2}\right) \tag{S.52}$$

$$P(ABABABc) = P(\text{Undistorted Path}) \left(1 - I_x^k\right) \left(1 - I_x^{k-1}\right) \left(1 - I_x^{k-2}\right). \tag{S.53}$$

By definition, the "undistorted path" probability is the probability neglecting the contributions due to the possibility of coalescence in previous steps, and is therefore the same for all paths. We have

$$P(\text{Undistorted Path}) = \frac{k(k-1)(k-2)k(k-1)(k-2)}{2k(2k-1)(2k-2)(2k-3)(2k-4)(2k-5)} I_x^{k-\ell} \tag{S.54}$$

$$= \frac{\frac{k!}{(k-3)!}\frac{k!}{(k-3)!}}{\frac{2k!}{(2k-6)!}} I_x^{k-\ell}. \tag{S.55}$$

Using these results, we can write $\phi_k^k(3)$ as

$$\phi_k^k(3) = [\#\text{ of Paths}]\, P(\text{Undistorted Path}) \left[F_k(1 - I_x^k) + F_{k,k-1}(1 - I_x^k)(1 - I_x^{k-1}) + F_{k,k-2}(1 - I_x^k)(1 - I_x^{k-2}) + F_{k,k-1,k-2}(1 - I_x^k)(1 - I_x^{k-1})(1 - I_x^{k-2})\right], \tag{S.56}$$

where we have defined $F_{\{a\}}$ to be the fraction of paths that are together in the set of classes $\{a\}$ (and are not together in any other class).

Calculation of $\phi_{k'}^k(\ell)$: We now use this approach to calculate the coalescence probability in the general case. The probability of any particular ancestral path from k and k' to $k-\ell$ is the product of the individual probabilities of each mutational step that makes up this path. Each such individual probability consists of three parts: a numerator, which depends only on the current class of the lineage that mutates, divided by a denominator, which depends only on the sum of the current set of classes for both lineages, times a correction factor of $(1 - I_x^{k-i})$ if the two lineages are in the same class at that step.

Although in each ancestral path the mutations will occur in a different order, all paths will ultimately consist of the same set of mutations ($k' \to k'-1 \to \ldots \to k-\ell$ and $k \to k-1 \to \ldots \to k-\ell$). Therefore, regardless of the path taken, the product of the numerators from each step will be identical. Similarly, the sum of the current set of classes will begin at $k'+k$, and decrement by one each time a deleterious mutation occurs, until both lineages are in the final class ($k'+k \to k'+k-1 \to \ldots \to 2k-2\ell$). Therefore, regardless of the path taken, the product of the denominators from each step will also be identical. Therefore, the paths will differ only by the correction factor $(1 - I_x^{k-i})$ for each class in which the two ancestral lineages are together. This means that, analogous to the case of $\phi_k^k(3)$ we described above, the probability of each path is the probability of an "undistorted path" times the appropriate correction factor. The probability of the undistorted path is

$$P(\text{Undistorted Path}) = \frac{k'(k'-1)\dots(k-\ell+1)k(k-1)\dots(k-\ell+1)}{(k'+k)(k'+k-1)\dots(2k-2\ell+1)} I_x^{k-\ell}. \tag{S.57}$$

We can now sum up all possible paths to obtain

$$\begin{aligned}\phi_{k'}^{k}(\ell) &= [\#\text{ of Paths}]\, P(\text{Undistorted Path}) \Bigg[F_\emptyset + \sum_{i=0}^{\ell} F_{k-i}(1-I_x^{k-i}) \\ &+ \sum_{i=0}^{\ell-1}\sum_{j>i}^{\ell} F_{k-i,k-j}(1-I_x^{k-i})(1-I_x^{k-j}) \\ &+ \sum_{i=0}^{\ell-2}\sum_{j>i}^{\ell-1}\sum_{m>j}^{\ell} F_{k-i,k-j,k-m}(1-I_x^{k-i})(1-I_x^{k-j})(1-I_x^{k-m}) + \dots \Bigg],\end{aligned} \tag{S.58}$$

where as before $F_{\{a\}}$ is the fraction of paths that are together in the set of classes $\{a\}$ (and are not together in any other class). Note that there are a total of $\ell+1$ terms in this equation, representing the possibility that the two lineages can be together in anywhere from 0 to ℓ of the classes. We can rearrange these terms to write

$$\begin{aligned}\phi_{k'}^{k}(\ell) &= [\#\text{ of Paths}]\, P(\text{Undistorted Path}) \Bigg[1 - \sum_{i=0}^{\ell} G_{k-i} I_x^{k-i} \\ &+ \sum_{i=0}^{\ell-1}\sum_{j>i}^{\ell} G_{k-i,k-j} I_x^{k-i} I_x^{k-j} \\ &- \sum_{i=0}^{\ell-2}\sum_{j>i}^{\ell-1}\sum_{m>j}^{\ell} G_{k-i,k-j,k-m} I_x^{k-i} I_x^{k-j} I_x^{k-m} + \dots \Bigg],\end{aligned} \tag{S.59}$$

where we have defined $G_{\{a\}}$ to be the fraction of paths that are together in *at least* the set of classes $\{a\}$.

We can evaluate each of these factors of G. For example, the fraction of paths that are together in class $k-i$ equals the number of ways for the two lineages to descend from classes k' and k to be together in class $k-i$, $\binom{k'-k+2i}{i}$, times the number of ways for the two lineages to descend from class $k-i$ to be together in class $k-\ell$, $\binom{2i-2\ell}{i-\ell}$, divided by the total number of ways for the two lineages to descend from classes k' and k to be together in $k-\ell$, $\binom{k'-k+2\ell}{\ell}$. Using this logic, we find

$$\begin{aligned}\phi_{k'}^{k}(\ell) &= [\#\text{ of Paths}]\, P(\text{Undistorted Path}) \\ &\times \left[1 - \sum_{i=0}^{\ell-1} \frac{\binom{k'-k+2i}{i}\binom{2\ell-2i}{\ell-i}}{\binom{k'-k+2\ell}{\ell}} I_x^{k-i} + \sum_{i=0}^{\ell-2}\sum_{j>i}^{\ell-1} \frac{\binom{k'-k+2i}{i}\binom{2j-2i}{j-i}\binom{2\ell-2j}{\ell-j}}{\binom{k'-k+2\ell}{\ell}} I_x^{k-i} I_x^{k-j} \dots \right].\end{aligned} \tag{S.60}$$

The total number of paths is $\binom{k'-k+2\ell}{\ell}$, so we finally find that the full probability of coalescence in class

$k-\ell$ is

$$\phi_k^{k'}(\ell) = I_x^{k-\ell}\frac{\binom{k'}{k-\ell}\binom{k}{k-\ell}}{\binom{k'+k}{k'-k+2\ell}}\left[1-\sum_{i=0}^{\ell-1}\frac{\binom{k'-k+2i}{i}\binom{2\ell-2i}{\ell-i}}{\binom{k'-k+2\ell}{\ell}}I_x^{k-i}+\right.$$
$$\left.\sum_{i=0}^{\ell-2}\sum_{j>i}^{\ell-1}\frac{\binom{k'-k+2i}{i}\binom{2j-2i}{j-i}\binom{2\ell-2j}{\ell-j}}{\binom{k'-k+2\ell}{\ell}}I_x^{k-i}I_x^{k-j}-\ldots\right]. \tag{S.61}$$

This is Eq. (56) from the main text. Note that it equals our non-conditional result for $P_c^{k,k'\to\ell}$ times a correction factor. There are a total of $\ell+1$ terms in this correction factor. This full correction factor can be arbitrarily complex for large ℓ, so we do not write out a general form here. However, it is straightforward to calculate for any values of k, k', and ℓ; a Mathematica script to do so is available on request.