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NEIGHBORHOODS OF PHYLOGENETIC TREES: EXACT AND ASYMPTOTIC COUNTS*

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Abstract. A central theme in phylogenetics is the reconstruction and analysis of evolutionary trees from a given set of data. To determine the optimal search methods for reconstructing trees, it is crucial to understand the size and structure of the neighborhoods of trees under tree rearrangement operations. The diameter and size of the immediate neighborhood of a tree have been well-studied; however, little is known about the number of trees at distance two, three, or (more generally) k from a given tree. In this paper we provide a number of exact and asymptotic results concerning these quantities and identify some key aspects of tree shape that play a role in determining these quantities. We obtain several new results for two of the main tree rearrangement operations—nearest neighbor interchange and subtree prune and regraft—as well as for the Robinson–Foulds metric on trees.

Key words. phylogenetic tree, splits, Robinson–Foulds metric, tree rearrangements, asymptotics

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1. Introduction.

Phylogenetics is the study of evolutionary relationships between species. These relationships are represented as phylogenetic trees, where the leaves correspond to extant species and the interior vertices correspond to ancestral species. A branch between two species in a tree indicates an evolutionary relationship between them [24, 13]. Central to phylogenetics is the problem of finding the optimal tree to fit a given data set, with the aim of determining the evolutionary history of the species being studied. However, the number of possible phylogenetic trees grows rapidly with the number of leaves, so for data sets with a large number of leaves, the optimal tree is commonly found by searching the set of phylogenetic trees (tree space) via tree rearrangement operations [19, 26]. Tree rearrangement operations are also used to compare phylogenetic trees by looking at the distance (smallest number of tree rearrangement operations) between the trees. These could be trees obtained from the same data set using different search methods or from different data sets on the same set of species [10, 9].

In order to effectively search tree space using tree rearrangement operations, it is crucial to understand the size and structure of the neighborhood of (i.e., the set of trees obtained from) a phylogenetic tree under these operations. In this paper, we investigate the size of the neighborhoods of trees arising from two commonly used tree rearrangement operations: nearest neighbor interchange (NNI) and subtree prune and regraft (SPR), as well as the Robinson–Foulds (RF) distance. Figure 1 shows examples of the RF, NNI, and SPR distances between trees. Expressions for the number of trees

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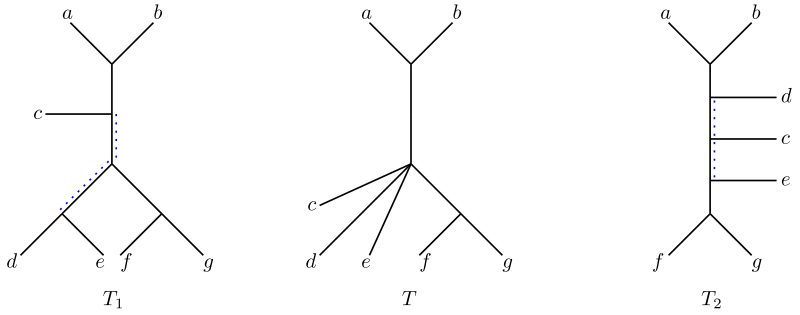

FIG. 1. *Here, T_1 and T_2 are unrooted binary phylogenetic trees with seven leaves. They are* (i) *distance two apart under the RF metric,* (ii) *distance two apart under the NNI metric, and* (iii) *distance one apart under the SPR metric. The (nonbinary) phylogenetic tree T is obtained from T_1 or T_2 by contracting the two internal edges indicated by dotted lines.*

at distance one or two from a given tree under RF, distance one, two, or three under NNI, and distance one under SPR and tree bisection and reconnection (TBR) are already known [5, 22, 1, 17]. We provide new asymptotic expressions for the number of trees at distance k from a given tree under NNI and the RF distance. We also show that unlike NNI and RF, the number of trees at distance two from a given tree under SPR is dependent on the shape of the tree and cannot be expressed solely in terms of the number of leaves and cherries of the tree.

The literature on the structure of tree neighborhoods and tree space includes results regarding the smallest number of NNI operations required to reach every tree in the set [14, 7], and the characterization of the splits appearing in trees within a certain distance of a given tree under various distance measures including RF, NNI, SPR, and TBR [3]. Here, we provide asymptotic results for the number of binary (fully resolved) trees that are a specified (small) distance from a given binary tree under the RF metric. Recently, Bryant and Steel [5] established the asymptotics at the other end of the distribution. They showed that the proportion of binary trees that are at nearly maximal distance from each other follows a Poisson distribution whose mean depends on the proportion of leaves of the given tree that lie in a cherry (a path of length two where both endpoints are leaves of the tree). Using the expressions for the sizes of the first and second neighborhoods, we provide an exact count for the number of pairs of binary phylogenetic trees with n leaves that share a first neighbor under NNI and RF.

1.1. Notation. A (unrooted) *phylogenetic tree* on a set X is a tree T for which X is the set of leaves (vertices of degree one) and each nonleaf vertex is unlabeled and of degree at least three. An edge that is incident with a leaf is called a *pendant* edge; otherwise it is an *internal* edge. If each nonleaf vertex has degree three, we say that T is *binary* (most of this paper deals with binary phylogenetic trees).

Two phylogenetic trees T_1 and T_2 are regarded as *equal* (written $T_1 = T_2$) if they have the same leaf labels and are isomorphic by a map that preserves the leaf labeling. In this paper we will use the term "tree" to refer to an unrooted binary phylogenetic tree unless otherwise stated. We let $B(X)$ be the set of all unrooted binary phylogenetic trees on leaf set X, and $B(n) = B(\{1, 2, \ldots, n\})$. Let $b(n) = |B(n)|$ and note that $|B(X)| = b(n)$ for any set X of size n.

The following lemma gives two well-known expressions, one for the number of internal edges in a binary tree and one for $b(n)$ (see [24] for more detail).

LEMMA 1.1.
(i) *Let $T \in B(X)$, $n = |X| \geq 3$. Then T has $n-3$ internal edges.*
(ii) *For all $n \in \mathbb{Z}^+$, $n \geq 3$, we have $b(n) = \frac{(2n-4)!}{(n-2)!2^{n-2}}$.*

A *cherry* in a tree T is a path of length two in which both endpoints are leaves of T. For example, in Figure 1, T_1 has three cherries, while T_2 has two.

2. Summary of main results. In this paper we consider three metrics on $B(n)$: RF, NNI, and SPR, defined in sections 3, 4, and 5, respectively. Given one of these three metrics δ_θ, $\theta \in \{\text{RF, NNI, SPR}\}$, on $B(n)$, the kth *neighborhood* of a tree T, denoted $N_\theta^k(T)$, is given by

$$N_\theta^k(T) = \{T' \in B(n) : \delta_\theta(T, T') = k\}$$

for $k \geq 1$. A tree $T' \in N_\theta^k(T)$ is called a k^{th} *neighbor* of T.

We now outline our main results. The first result describes the number of kth neighbors of a tree (for fixed k) for RF and NNI and can be summarized as follows.

THEOREM 2.1. *Let $T \in B(n)$ ($n \geq 4$). Then for each fixed $k \in \mathbb{Z}^+$, and for each $\theta \in \{RF, NNI\}$ we have*

$$|N_\theta^k(T)| = \frac{2^k n^k}{k!}\left(1 + c_{T,k}^\theta n^{-1} + O(n^{-2})\right), \tag{2.1}$$

where $|c_{T,k}^\theta| = \Theta(k^2)$ (explicit upper and lower bounds on $c_{T,k}^\theta$ are provided in the relevant sections).

Our second main result concerns the size of $N_\theta^k(T)$ for $k = 2$. First, note that the case $k = 1$ is uninteresting since for any tree $T \in B(n)$, $|N_\theta^1(T)| = p_\theta(n)$, for a (known) polynomial function p_θ of n (equal to $2n - 6$ for NNI and RF, and to $2(n-3)(2n-7)$ for SPR).

For NNI and RF it is known that $|N_\theta^2(T)| = 2n^2 + O(n)$ (this follows also from Theorem 2.1), and the $O(n)$ term is easily described in both cases (it depends on the the shape of T only via the number of its cherries). For SPR we show that

$$|N_{SPR}^2(T)| = Cn^4 + O(n^3),$$

and we show that the coefficient C depends on the shape of T. Thus, unlike NNI and SPR, the shape of the tree plays a role in the highest-order term in the second neighborhood. Moreover, $C = C_T$ can take different values even for trees that have the same number of cherries (the quantity that, with n, fully determines the size of $|N_\theta^2(T)|$ for NNI and RF). For NNI and RF we also provide an explicit description of the number of pairs of trees that are distance two apart.

A further result for RF provides a (nonasymptotic) universal bound which shows that nearly all trees are at near maximal distance from any given phylogenetic tree under RF.

3. Robinson–Foulds metric. Let T be a phylogenetic tree. Then a bipartition $\{L_1, L_2\}$ of $\mathcal{L}(T)$ is a *split* of T if there exists an edge $e \in E(T)$ such that $T \setminus e$ has components T_1 and T_2 with $\mathcal{L}(T_1) = L_1$ and $\mathcal{L}(T_2) = L_2$. We define $S(T, e) = \{L_1, L_2\}$ as the split of T *associated with* e. A split $S(T, e)$ is *trivial* if e is a pendant edge of T. We define $\Sigma(T) = \{S(T, e)$: where e is an internal edge of $T\}$ as the set of all nontrivial splits of T. Two trees T_1 and T_2 are *equal* if and only if $\Sigma(T_1) = \Sigma(T_2)$ [6].

Given two phylogenetic trees, T_1 and T_2, the *RF distance* between T_1 and T_2 is defined by

$$\delta_{RF}(T_1, T_2) = \frac{1}{2}|\Sigma(T_1) - \Sigma(T_2)| + \frac{1}{2}|\Sigma(T_2) - \Sigma(T_1)|,$$

Alternatively, the RF distance between T_1 and T_2 can be seen as the minimum m for which there exist $E_1 \subseteq E(T_1)$ and $E_2 \subseteq E(T_2)$, where $|E_1| = |E_2| = m$, such that $T_1/E_1 = T_2/E_2$. This is illustrated in Figure 1, where $\delta_{RF}(T_1, T_2) = 2$.

The kth *RF neighborhood* of a tree $T \in B(n)$ is the set of trees in $B(n)$ that are exactly RF distance k from T. In terms of edge contraction, this neighborhood consists of all trees $T' \in B(n)$ such that the minimum j for which we could contract j edges of T and j edges of T' and obtain the same (nonbinary) tree, is k.

The RF distance was originally introduced by Bourque [2] and was generalized by Robinson and Foulds [23]. Unlike the metrics induced by NNI and SPR that we will see in later sections, the RF distance between two trees is computationally easy to calculate. (Day [11] provided a linear-time algorithm.) We now consider the first, second, and kth RF neighborhoods of an unrooted binary phylogenetic tree. Let $T \in B(n)$, where $n \geq 3$. Then

(i) $|N^1_{RF}(T)| = 2(n-3)$, and

(ii) $|N^2_{RF}(T)| = 2n^2 - 8n + 6c - 12$, where c is the number of cherries of T.

This expression for the size of the first RF neighborhood is commonly known, and as we will see later, it is the same as the size of the first NNI neighborhood, found by Robinson [22]. The expression for the size of the second RF neighborhood appears in section 4.2 of [5].

Much of the literature on the RF distance has focused on calculating the RF distance between two trees and on the distribution of the distances between trees. Bryant and Steel [5] gave a polynomial-time algorithm for finding the distribution of trees around a given tree T and showed that this distribution can be approximated by a Poisson distribution determined by the proportion of leaves of T that are in cherries. Hendy, Little, and Penny [15] used generating function techniques to calculate the probability that two trees, selected uniformly at random from $B(n)$, are RF distance m from each other.

While the sizes of the first and second RF neighborhoods are known, the sizes of higher neighborhoods are not known in general. Although N^2_{RF} depends on the shape of T (via c), for $k = 1, 2$ we can write $N^k_{RF} = \frac{2^k n^k}{k!}(1 + O(n^{-1}))$. Our main result in this section (Theorem 3.1) provides a generalization of this asymptotic equality to all values of $k \geq 1$.

THEOREM 3.1. *Let $T \in B(n)$ $(n \geq 4)$. For each fixed $k \in \mathbb{Z}^+$,*

$$N^k_{RF}(T) = \frac{2^k n^k}{k!}\left(1 + C_{T,k} n^{-1} + O(n^{-2})\right), \tag{3.1}$$

$$\textit{where} \quad -\frac{5k^2 + 7k}{4} \leq C_{T,k} \leq 4k^2 - 7k.$$

The proof of Theorem 3.1 comprises two steps. First, we determine the number of binary phylogenetic trees whose splits differ from $\Sigma(T)$ by exactly the k splits associated with a given subset of k internal edges of T. We then determine the number of subsets of k internal edges in T by considering three cases:

1. The k edges are pairwise nonadjacent.
2. Exactly two of the k edges are adjacent.
3. More than two of the k edges are adjacent.

The term of order n^k in (3.1) is completely determined by case 1 above, while the term of order n^{k-1} is determined by cases 1 and 2. Case 3 only contributes terms of order n^{k-2} or lower.

Neighbors with different splits over k given edges. Let Σ_k be a given set of k splits of $T \in B(n)$ $(k \geq 1)$. We define

$$\Delta(T, \Sigma_k) = |\{T' \in B(n) : (\Sigma(T) - \Sigma_k) \subset \Sigma(T')\}|$$

as the number of trees containing the splits $\Sigma(T) - \Sigma_k$ and

$$\mathring{\Delta}(T, \Sigma_k) = |\{T' \in B(n) : (\Sigma(T) \cap \Sigma(T')) = \Sigma(T) - \Sigma_k\}|$$

as the number of trees containing the splits $\Sigma(T) - \Sigma_k$ and no other splits of T.

In Lemma 3.2 we obtain an expression for $\Delta(T, \Sigma_k)$ and show that once T and Σ_k are specified, $\mathring{\Delta}(T, \Sigma_k)$ is independent of n.

LEMMA 3.2. *Let $T \in B(n)$ $(n \geq 4)$, let $e_1, \ldots, e_k$ $(1 \leq k \leq n-3)$ be distinct internal edges of T, and let Σ_k be the set of k splits of T associated with these edges. Define F to be the subgraph of T consisting of the edges $e_1, \ldots, e_k$. Then we have the following:*

(i)

$$\Delta(T, \Sigma_k) = \prod_{m=1}^{k} \left(\frac{(2m+2)!}{(m+1)!2^{m+1}} \right)^{c_m},$$

where c_m is the number of components of F with exactly m edges.

(ii) *Let $T' \in B(s)$ $(s \geq k+3)$, and let F' be the subgraph of T' consisting of distinct internal edges $e'_1, \ldots, e'_k$ of T'. Let Σ'_k be the set of k splits of T' associated with these edges. If F' is isomorphic to F, then*

$$\mathring{\Delta}(T', \Sigma'_k) = \mathring{\Delta}(T, \Sigma_k).$$

In other words, the number of trees containing the splits $\Sigma(T) - \Sigma_k$ and no other splits of T is not dependent on n.

Proof.

(i) Let $C_1, \ldots, C_\ell$ be the components of F. Given a component C_i with m edges, let A_i be the subtree of T consisting of the corresponding m edges of F in T and their adjacent edges. Then A_i has $m+3$ leaves. We want to find $\Delta(A_i, \Sigma_i)$, where Σ_i is the set of splits associated with the internal edges of A_i. (Note that this is the same as the number of trees that are at most RF distance m from A_i.) Clearly $\Delta(A_i, \Sigma_i) = |B(|\mathcal{L}(A_i)|)| = |B(m+3)|$, as it is the number of trees in $B(m+3)$ that have at least zero splits in common with A_i. By Lemma 1.1,

$$|B(m+3)| = \frac{(2(m+3)-4)!}{((m+3)-2)!2^{(m+3)-2}} = \frac{(2m+2)!}{(m+1)!2^{m+1}}.$$

We can apply this principle to each component of F. The results for each component are independent of those for the other components of F. Therefore, we can take the product to obtain

$$\Delta(T, \Sigma_k) = \prod_{i=1}^{\ell} \Delta(A_i, \Sigma_i) = \prod_{m=1}^{k} \left(\frac{(2m+2)!}{(m+1)!2^{m+1}} \right)^{c_m}.$$

(ii) This is similar to (i), except that we now restrict our attention to $\mathring{\Delta}(T, \Sigma_k)$, that is, those trees in $\Delta(T, \Sigma_k)$ that do not contain any of the splits in Σ_k. Similarly to (i), we have

$$\mathring{\Delta}(T, \Sigma_k) = \prod_{i=1}^{\ell} \mathring{\Delta}(A_i, \Sigma_i). \tag{3.2}$$

Note that for each subtree A_i, some of the trees counted by $\Delta(A_i, \Sigma_i)$ have splits in common with A_i and hence are not counted by $\mathring{\Delta}(A_i, \Sigma_i)$. Clearly, $\mathring{\Delta}(A_i, \Sigma_i)$ is dependent on the shape and size of A_i, which itself depends on the choice of the k edges of T and not on the shape or number of leaves of T. Therefore, since $F' = F$, we have

$$\mathring{\Delta}(T', \Sigma'_k) = \prod_{i=1}^{\ell} \mathring{\Delta}(A_i, \Sigma_i) = \mathring{\Delta}(T, \Sigma_k).$$

∎

We now consider expressions for $\Delta(T, \Sigma'_k)$ and $\mathring{\Delta}(T, \Sigma'_k)$, where Σ'_k is the set of splits associated with k distinct, pairwise nonadjacent internal edges of T.

LEMMA 3.3. *Let $T \in B(n)$ ($n \geq 4$) and let Σ'_k ($1 \leq k \leq n-3$) be the set of splits associated with distinct, pairwise nonadjacent internal edges $e_1, \ldots, e_k$ of T. Then*

(i) $\Delta(T, \Sigma'_k) = 3^k$, *and*

(ii) $\mathring{\Delta}(T, \Sigma'_k) = 2^k$.

Proof. Part (i) follows directly from Lemma 3.2, so it remains to establish part (ii). For some i, $1 \leq i \leq k$, let A_i be the subtree of T consisting of edge e_i and its adjacent edges in T. Then A_i has four leaves, so $\Delta(A_i, S(A_i, e_i)) = |B(4)| = 3$. However, one of these three trees is A_i. The remaining two trees each have a single internal edge, and the split associated with this edge is not $S(A_i, e_i)$. Hence $\mathring{\Delta}(A_i, S(A_i, e_i)) = 2$, and by (3.2), $\mathring{\Delta}(T, \Sigma'_k) = 2^k$. ∎

Now that we have investigated the case where the k internal edges are pairwise nonadjacent, we consider an adjacent pair of internal edges.

LEMMA 3.4. *Let $T \in B(n)$ ($n \geq 5$), and let Σ_2 be the set of splits associated with two adjacent internal edges of T. Then $\mathring{\Delta}(T, \Sigma_2) = 10$.*

Proof. Let $\Sigma_2 = \{S(T, e_1), S(T, e_2)\}$, where e_1 and e_2 are adjacent internal edges of T. The set of trees counted by $\Delta(T, \Sigma_2)$ includes trees which have one or more of the splits in Σ_2 in common with T. Therefore, to obtain $\mathring{\Delta}(T, \Sigma_2)$, we subtract from $\Delta(T, \Sigma_2)$ the number of trees in $B(n)$ that have exactly one split different to T associated with either e_1 or e_2, or the same splits as T. Hence

$$\mathring{\Delta}(T, \Sigma_2) = \Delta(T, \Sigma_2) - \mathring{\Delta}(T, S(T, e_1)) - \mathring{\Delta}(T, S(T, e_2)) - 1.$$

Therefore, by Lemma 3.2, if e_1 and e_2 are adjacent, then $\mathring{\Delta}(T, \Sigma_k) = 15 - 5 = 10$. ∎

The number of subsets of k internal edges.

LEMMA 3.5. *Let $T \in B(n)$ ($n \geq 4$). Then we have the following:*

(i) *The number of sets of k distinct, pairwise nonadjacent internal edges $e_1, \ldots, e_k$ in T ($1 \leq k \leq n-3$), denoted $A_{T,k}$, satisfies*

$$\frac{1}{k!}n^k - \frac{k(5k+1)}{2k!}n^{k-1} + O(n^{k-2}) \leq A_{T,k} \leq \frac{1}{k!}n^k - \frac{k(k+2)}{k!}n^{k-1} + O(n^{k-2}).$$

(ii) *The number of sets of k distinct internal edges $e_1, \ldots, e_k$ in T ($2 \le k \le n-3$) where exactly two edges are adjacent, denoted $B_{T,k}$, satisfies*

$$\frac{1}{2(k-2)!}n^{k-1} + O(n^{k-2}) \le B_{T,k} \le \frac{2}{(k-2)!}n^{k-1} + O(n^{k-2}).$$

(iii) *The number of sets of k distinct internal edges $e_1, \ldots, e_k$ ($3 \le k \le n-3$) in T where more than two edges are adjacent is $O(n^{k-2})$.*

Proof.

(i) We calculate the bounds by considering the best and worst case scenarios for the choice of each edge. There are $n-3$ choices for the first edge e_1. There are at most $(n-3)-2$ choices for e_2 (this can occur when e_1 has exactly one adjacent internal edge in T). There are then at most $(n-3)-4$ choices for e_3 (this can occur when e_1 and e_2 each have exactly one adjacent internal edge in T), and so on. Therefore

$$\begin{aligned} A_{T,k} &\le \frac{1}{k!}(n-3)(n-3-2)(n-3-2(2))\cdots(n-3-2(k-1)) \\ &= \frac{1}{k!}n^k - \frac{1}{k!}n^{k-1}\sum_{i=0}^{k-1}(3+2i) + O(n^{k-2}) \\ &= \frac{1}{k!}n^k - \frac{k(k+2)}{k!}n^{k-1} + O(n^{k-2}). \end{aligned}$$

On the other hand, there are at least $(n-3)-5$ choices for e_2 (this can occur when e_1 has four adjacent internal edges in T). There are then at least $(n-3)-10$ choices for e_3 (this can occur when e_1 and e_2 each have four adjacent internal edges in T), and so on. Therefore

$$\begin{aligned} A_{T,k} &\ge \frac{1}{k!}(n-3)(n-3-5)(n-3-5(2))\cdots(n-3-5(k-1)) \\ &= \frac{1}{k!}n^k - \frac{1}{k!}n^{k-1}\sum_{i=0}^{k-1}(3+5i) + O(n^{k-2}) \\ &= \frac{1}{k!}n^k - \frac{k(5k+1)}{2k!}n^{k-1} + O(n^{k-2}). \end{aligned}$$

(ii) We will prove this in the same way as (i), assuming without loss of generality that e_1 and e_2 are the adjacent pair of edges. There are $n-3$ choices for e_1. There are at most four choices for e_2 (this can occur if e_1 has four adjacent internal edges in T). For e_3, there are at most $(n-3)-3$ choices (this can occur if e_1 and e_2 each have two adjacent pendant edges in T). The remaining edges follow in the same way as in (1). Therefore

$$\begin{aligned} B_{T,k} &\le \frac{4}{2(k-2)!}(n-3)(n-6)(n-6-2(1))\ldots(n-6-2(k-3)) \\ &= \frac{2}{(k-2)!}n^{k-1} + O(n^{k-2}). \end{aligned}$$

On the other hand, there is at least one choice for e_2 (this can occur if e_1 has exactly one adjacent internal edge in T). For e_3, there are at least $(n-3)-7$ choices (this can occur if e_1 and e_2 each have no adjacent pendant edges in T). The remaining edges are chosen in the same way as in (1). Hence

$$B_{T,k} \geq \frac{1}{2(k-2)!}(n-3)(n-10)(n-10-5(1))\dots(n-10-5(k-3))$$
$$= \frac{1}{2(k-2)!}n^{k-1} + O(n^{k-2}).$$

(iii) Let F be the subgraph of T consisting of the edges $e_1, \dots, e_k$. Then F has $m \leq k-2$ components. Suppose we first choose m internal edges of T corresponding to one edge in each component of F. By (i), the number of such choices is $O(n^m)$, as each of these edges will contribute a linear factor to the total number of ways of choosing the k edges. However, the remaining $k-m \geq 2$ edges must be chosen from edges that are adjacent to those already chosen. The number of these choices depends only on the number and location of the edges already chosen and not on n. Hence the number of possible sets is $O(m)$, where $m \leq k-2$. ∎

Note that in the proof of Lemma 3.5, it may not be possible to maximize (or minimize) the number of choices for each individual edge in T; however, this is not a problem as we only require bounds on the number of choices of the k edges of T.

From Lemmas 3.2, 3.3, and 3.4, we know the number of binary phylogenetic trees whose splits differ from those of $T \in B(n)$ by exactly k splits over a given set of k edges. From Lemma 3.5, we have the number of subsets of k internal edges. We are now in a position to prove Theorem 3.1.

Proof of Theorem 3.1. We break down the calculation of the size of the kth RF neighborhood of T into two steps. We consider the number of trees whose splits differ from those of T by exactly the k splits corresponding to a given set of k distinct internal edges of T. We then consider the number of ways these k edges can be chosen in T. By Lemma 3.2, given T and a set of k distinct internal edges of T with associated split set Σ_k, the number of trees with the splits $\Sigma(T) - \Sigma_k$ and none of the splits in Σ_k ($\mathring{\Delta}(T, \Sigma_k)$) is independent of n. Hence, only the number of ways of choosing the k edges in T is dependent on n.

By Lemma 3.5, when we count the number of ways of choosing k distinct internal edges of T, the case where the k edges are pairwise nonadjacent (case 1 from the beginning of this section) gives a term of order n^k and a term of order n^{k-1}. The case where exactly two of the k edges are adjacent (case 2) produces a term of order n^{k-1} but does not have a term of order n^k. If more than two of the k edges are adjacent (case 3), then the highest order term is $O(n^{k-2})$.

Now we consider the number of trees whose splits differ from those of T by exactly the k splits corresponding to a given set of k distinct internal edges of T. From the information above, the only two cases we need to consider are those where the k edges are pairwise nonadjacent, or exactly two of the k edges are adjacent. By Corollary 3.3, the case where all edges are pairwise nonadjacent produces 2^k kth RF neighbors with splits that differ from the splits of T over precisely the k given internal edges. In the case where exactly two edges are adjacent, the $k-1$ pairwise nonadjacent edges give 2^{k-2} kth RF neighbors, by Corollary 3.3. By Lemma 3.4, the adjacent pair of edges results in 10 neighbors. Hence, in total, there are $10 \cdot 2^{k-2}$ kth RF neighbors. Therefore, by Lemma 3.5,

$$|N^k_{RF}(T)| \geq \left(\frac{1}{k!}n^k - \frac{k(5k+1)}{2k!}n^{k-1}\right)2^k + 10\left(\frac{1}{2(k-2)!}n^{k-1}\right)2^{k-2} + O(n^{k-2})$$
$$= \frac{2^k}{k!}n^k - \frac{5k^2+7k}{4k!}2^k n^{k-1} + O(n^{k-2}).$$

$$|N_{RF}^k(T)| \le \left(\frac{1}{k!}n^k - \frac{k(k+2)}{k!}n^{k-1}\right)2^k + 10\left(\frac{2}{(k-2)!}n^{k-1}\right)2^{k-2} + O(n^{k-2})$$
$$= \frac{2^k}{k!}n^k + \frac{4k^2-7k}{k!}2^k n^{k-1} + O(n^{k-2}).$$

3.1. Shared splits. We end this section by presenting a simple and general upper bound on the proportion of binary trees that share at least k nontrivial splits with a given tree on the same leaf set. The relevance of this result for biology is that it shows that a "random" binary tree (selected with uniform probability) has a low probability of sharing more than a few splits with a given tree, regardless of the number of leaves (species) involved and the topology of the given tree. For example, the probability of sharing three nontrivial splits is at most 0.02.

Let T_0 be a phylogenetic tree (not necessarily binary) with n leaves, and let $\pi_k(T_0)$ be the proportion of trees in $B(n)$ that share at least k nontrivial splits with T_0 (note that T_0 does not have to be a binary tree). Thus, $\pi_k(T_0)$ is the proportion of binary phylogenetic trees T for which

$$d_{RF}(T, T_0) \le \frac{1}{2}(|i_0| + n - 3 - 2k),$$

where i_0 is the number of internal edges of T_0. In general, $\pi_k(T_0)$ will depend on properties of the tree T_0; however, the next theorem provides a universal upper bound on π_k that applies for any choice of T_0 and is independent of the number of internal edges in T, and even of n.

THEOREM 3.6. *For any phylogenetic tree T_0 with n leaves, the proportion, $\pi_k(T_0)$, of trees in $B(n)$ that share at least k nontrivial splits with T_0 satisfies*

$$\pi_k(T_0) \le \frac{1}{2^k k!}$$

for all $k = 1, 2, \ldots, i_0$ and $\pi_k(T_0) = 0$ for all $k > i_0$, where i_0 is the number of internal edges of T_0.

Proof. Let $N_k(T_0)$ be the number of trees in $B(n)$ that share at least k nontrivial splits with T_0. Let $\Sigma_0 = \Sigma(T_0)$, the set of nontrivial splits of T_0. We have

$$N_k(T_0) = \left|\bigcup_{\Sigma\subseteq\Sigma_0:|\Sigma|=k} \{T \in B(n) : \Sigma \subseteq \Sigma(T)\}\right|.$$

Therefore, by the union bound, $N_k(T_0)$ is bounded above by the sum of $|\{T \in B(n) : \Sigma \subseteq \Sigma(T)\}|$ over all subsets Σ of Σ_0 of size k. Since there are precisely $\binom{|i_0|}{k}$ terms in this sum, we obtain

$$N_k(T_0) \le \binom{i_0}{k} \cdot M, \tag{3.3}$$

where $M = \max\{|\{T \in B(n) : \Sigma \subseteq \Sigma(T)\}| : \Sigma \subseteq \Sigma_0, |\Sigma| = k\}$. Now, for a subset Σ of Σ_0 let T_Σ be the unique nonbinary phylogenetic tree that has Σ as its set of nontrivial splits (i.e., the tree obtained from T_0 by contracting each internal edge of T_0 that is not associated with a split in Σ). Let $\mathring{V}(T_\Sigma)$ denote the set of interior vertices of T_Σ. Then

$$|\{T \in B(n) : \Sigma \subseteq \Sigma(T)\}| = \prod_{v\in V_{\text{int}}(T_\Sigma)} b(\deg(v)). \tag{3.4}$$

Now, for each vertex $v \in \mathring{V}(T_\Sigma)$, we have $\deg(v) \geq 3$. Moreover, when $|\Sigma| = k$, a simple counting argument shows that

$$|\mathring{V}(T_\Sigma)| = k+1 \quad \text{and} \quad \sum_{v \in \mathring{V}(T_\Sigma)} \deg(v) = n+2k. \tag{3.5}$$

Leaving trees for a moment, consider the optimization problem of maximizing $\prod_{i=1}^{N} b(n_i)$, subject to the constraints that $n_1, n_2, \ldots, n_N$ are integers, each taking a value of at least 3, and with a sum equal to $R \geq 3N$. It follows from the faster-than-exponential growth of the function b that the maximum possible value is $b(R-3(N-1))$ (Lemma 5 of [25]). Taking $N = k+1$ and $R = n+2k$ (from (3.5)), so that $R-3(N-1) = n-k$, we see from (3.4) that $|\{T \in B(n) : \Sigma \subseteq \Sigma(T)\}| \leq b(n-k)$ for any $\Sigma \subseteq \Sigma_0$ with $|\Sigma| = k$. In other words, from (3.3),

$$N_k(T_0) \leq \binom{i_0}{k} b(n-k).$$

Consequently, $\pi_k(T_0) = N_k(T_0)/b(n) = \binom{i_0}{k} b(n-k)/b(n) \leq \binom{n-3}{k} b(n-k)/b(n)$, where the last inequality holds because $i_0 \leq n-3$. Finally, notice that we can write

$$\binom{n-3}{k} b(n-k)/b(n) = \frac{1}{k!} \cdot \prod_{j=0}^{k-1} \frac{n-j-3}{2n-2j-5},$$

and each of the k terms in the product is strictly less than $\frac{1}{2}$. This completes the proof. ∎

4. Nearest neighborhood interchange metric. We begin by defining some terms used throughout this and subsequent sections.

Let $T \in B(n)$. The *distance* between two vertices $x, y \in V(T)$, denoted $d_T(x,y)$, is the length of the shortest $(x-y)$-path in T. We define the *distance* between two vertex sets of T, $U = \{u_1, u_2, \ldots\}$ and $V = \{v_1, v_2, \ldots\}$ to be $d_T(U,V)$, where

$$d_T(U,V) = \min\{d_T(u_i, v_j) : 1 \leq i \leq |U|, 1 \leq j \leq |V|\}.$$

The distance between a subtree T' of T and a set of vertices $V \subseteq V(T)$ is $d_T(V(T'), V)$, simplified to $d_T(T', V)$.

If a subtree T' of T has exactly one vertex of degree two (sometimes called the *root* of T'), it is a *pendant subtree*. Unless otherwise specified, from here on all subtrees in this paper are assumed to be maximal, pendant subtrees. An edge e of T is *incident* to subtree T' if e is not an edge of T' and is incident to the root of T'.

Let $e = \{x, y\}$ be an interior edge of T, and let A_1 and A_3 be subtrees of T that are distance one from e and distance three apart (see Figure 2). Then A_1 and A_3 are *swappable* across e. Let vertex z_1 adjacent to x be the root of A_1, and z_3 adjacent to y be the root of A_3. An *NNI operation* on T is performed by deleting the edges $\{x, z_1\}$ and $\{y, z_3\}$, and inserting edges $\{x, z_3\}$ and $\{y, z_1\}$. We will also refer to this process as *swapping* the subtrees A_1 and A_3 *across* e. The resulting tree is a *first NNI neighbor* of T. To make it clear which edge of a tree T two subtrees are swapped across in an NNI operation on T, we will refer to such an operation as an *NNI operation on edge e in T*.

The two distinct first NNI neighbors resulting from an NNI operation on edge e in T can be seen in Figure 2. We have four subtrees A_1, A_2, A_3, and A_4 that are all

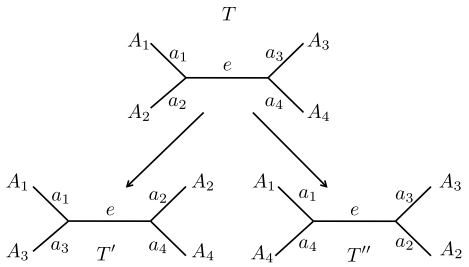

FIG. 2. *The two first NNI neighbors of T resulting from an NNI operation on the edge e.*

distance one from e in T. To obtain T' from T we swap subtrees A_2 and A_3, and to obtain T'' we swap subtrees A_2 and A_4. Note that swapping subtrees A_1 and A_4 in T produces a tree isomorphic to T'. Although there are four different pairs of subtrees that could be swapped across e, there are only two distinct first neighbors that can be obtained from NNI operations on e.

We see in Figure 2 that in T' and T'', all four subtrees A_1, A_2, A_3, and A_4 are distance one from e. Given a labeling of the edges of the original tree T, we preserve this labeling by assigning the label a_i to the edge incident to subtree A_i in T and in the two first NNI neighbors of T resulting from an NNI operation on edge e. Note that T can also be obtained from T' by an NNI operation, which we call the *inverse* of the operation used to obtain T' from T.

Consider a graph G in which each vertex represents a tree in $B(n)$ and there is an edge between the vertices representing trees T_1 and T_2 if they are first NNI neighbors. The *NNI distance* between T_1 and T_2, $\delta_{NNI}(T_1, T_2)$, is the distance between the two vertices representing trees T_1 and T_2 in G.

The size of $N^k_{NNI}(T)$ for small values of k is given as follows. Let $T \in B(n)$ have T cherries. Then

(i) $|N^1_{NNI}(T)| = 2(n-3)$,
(ii) $|N^2_{NNI}(T)| = 2n^2 - 10n + 4c$, and
(iii) $|N^3_{NNI}(T)| = \frac{4}{3}n^3 - 8n^2 - \frac{70}{3}n + 8cn + 12p_3(T) + 164$,

where $p_3(T)$ is the number of internal paths of length three in T. These results for the first and second NNI neighborhoods were shown by Robinson [22]. It is interesting to compare these with the corresponding results for the RF distance. In both cases, the first neighborhood is dependent only on the number of leaves, while the second neighborhood is determined by the number of leaves and cherries. In fact, the size of the first NNI neighborhood is the same as the size of the first RF neighborhood. Robinson [22] also found an upper bound on the size of the third NNI neighborhood of a binary phylogenetic tree. Using this result one can derive our exact formula for the size of the third NNI neighborhood given above (for details, see [12]).

As mentioned previously, tree rearrangement operations are also used to compare trees produced by different tree reconstruction methods, or trees obtained from different data sets. This can be achieved by determining the NNI distance (the smallest number of operations) between the two trees. DasGupta et al. [9] showed that the problem of computing the NNI distance between two trees in $B(n)$ is NP-complete. Culik and Wood [8] found an upper bound of $4n\log(n)$ on the NNI distance between two trees in $B(n)$, which was later improved to $n\log(n)$ by Li, Tromp, and Zhang [20].

It is also useful to understand the structure of $B(n)$ and the first and second NNI neighborhoods of a tree (e.g., how the first NNI neighbors of a tree relate to each

other). A *walk* in a graph G is a sequence of vertices and edges, in which the vertices are not necessarily distinct. Consider a graph G in which each vertex represents a tree in $B(n)$ and there is an edge between the vertices representing trees T_1 and T_2 if they are first NNI neighbors. Bryant [4] noted that the length of the shortest walk that visits every vertex of G was unknown. Gordon, Ford, and St. John [14] provided a constructive proof that this walk is a Hamiltonian path (a path that visits every vertex of G exactly once). Therefore by a series of NNI operations beginning from a tree $T \in B(n)$, it is possible to visit each tree in $B(n)$ exactly once. We refer to this series of NNI operations as an *NNI walk*. In section 5, we investigate the structure of $B(n)$ by determining the number of pairs of trees that share a first NNI neighbor (the number of pairs of trees that are within NNI distance two of each other).

4.1. Asymptotic result. Our main result for this section is the asymptotic expression for the size of the kth NNI neighborhood of a binary tree given in Theorem 4.1.

THEOREM 4.1. *Let $T \in B(n)$ $(n \geq 4)$. Then for each fixed $k \in \mathbb{Z}^+$,*

$$|N^k_{NNI}(T)| = \frac{2^k n^k}{k!}\left(1 + D_{T,k}n^{-1} + O(n^{-2})\right), \tag{4.1}$$

$$\textit{where} \quad -\frac{3k(k+1)}{2} \leq D_{T,k} \leq 3k(k-2).$$

We will prove Theorem 4.1 at the end of section 4.1. As in the proof of Theorem 3.1, we consider the number of kth NNI neighbors resulting from NNI operations on a given set of k internal edges. From Lemma 3.5, we know the number sets of k internal edges of T. Combining these gives us the total number of kth NNI neighbors. The four different cases that are relevant are as follows:

1. The k edges are distinct and pairwise nonadjacent.
2. The k edges are distinct and exactly two are adjacent.
3. The k edges are distinct and more than two are adjacent.
4. The k edges are not all distinct.

These are the same cases as for RF, with the additional possibility that the k edges are not all distinct (case 4). In (4.1) of Theorem 4.1, the term of order n^k is completely determined by case 1, whereas the term of order n^{k-1} is determined by cases 1 and 2. Cases 3 and 4 only contribute to terms of order n^{k-2} or lower.

Throughout this section we consider the trees resulting from a series of NNI operations beginning with a tree $T \in B(n)$. Let $NNI(T; e_1, e_2, \ldots, e_k) \subseteq \cup_{j=0}^{k} N^j_{NNI}(T)$ be the set of trees that can be obtained by performing an NNI operation on internal edge e_1 in T to give T_1, followed by an NNI operation on internal edge e_2 in T_1 to give T_2, and so on until we have completed k NNI operations. Note that if $T' \in NNI(T; e_1, \ldots, e_k)$, T' is not necessarily a kth NNI neighbor of T. It may instead be a jth NNI neighbor of T for some $j < k$ $(j \in \mathbb{N})$.

The proof of Theorem 4.1 relies on Lemma 3.5 and two additional technical lemmas, which we state here without proof (proofs for these can be found [12]).

LEMMA 4.2. *Let $T \in B(n)$ $(n \geq 4)$.*

(i) *For any given set of k distinct, pairwise nonadjacent internal edges $(1 \leq k \leq n-3)$, there are 2^k kth neighbors of T resulting from NNI operations on this sequence of edges in any order.*

(ii) *For any given set of k distinct internal edges $(2 \leq k \leq n-2)$ where exactly one pair is adjacent, there are 2^{k+1} kth neighbors of T resulting from NNI operations on this sequence edges in any order.*

(iii) *For a given T and a given sequence of k (not necessarily distinct) edges of T ($k \geq 1$), the number of kth NNI neighbors resulting from NNI operations on this sequence edges in any order is constant with respect to n.*

LEMMA 4.3. *Let $T \in B(n)$ ($n \geq 4$), and let $e_1, \ldots, e_k$ ($k \geq 2$) be internal edges of T. Suppose that $e_m = e_j$ for some m, j, where $1 \leq m < j \leq k$. Let*

$$P = NNI(T; e_1, \ldots, e_m, e_{m+1}, \ldots, e_{j-1}, e_j, \ldots, e_k),$$
$$Q = NNI(T; e_1, \ldots, e_{m-1}, e_{m+1}, \ldots, e_{j-1}, e_j, \ldots, e_k),$$
$$R = NNI(T; e_1, \ldots, e_{m-1}, e_{m+1}, \ldots, e_{j-1}, e_{j+1}, \ldots, e_k).$$

Suppose that the edges $e_{m+1}, \ldots, e_{j-1}$ are nonadjacent to e_m. If the operation on edge e_j is the inverse of the operation on edge e_m, then $P = R$; otherwise, $P = Q$.

Proof of Theorem 4.1. We break down the calculation of the size of the kth NNI neighborhood of T into two steps. First we consider the number of kth NNI neighbors resulting from k NNI operations on a given sequence of k edges of T. We then consider the number of ways these k edges can be chosen in T. By Lemma 4.2, the number of kth NNI neighbors of a given tree T resulting from operations on a given sequence of k edges is not dependent on n. Hence, only the number of ways of choosing these k edges is dependent on n. We consider two cases.

First, assume that the k edges are all distinct, and consider the number of ways they can be chosen in T. By Lemma 3.5 the case where the k edges are pairwise nonadjacent (case 1 from the beginning of this subsection) gives a term of order n^k and a term of order n^{k-1}. The case where exactly two of the k edges are adjacent (case 2) produces a term of order n^{k-1}, but not a term of order n^k. If more than two of the k edges are adjacent, then the highest order term is $O(n^{k-2})$.

Now suppose that the k edges are not all distinct. By Lemma 3.5, if $k-1$ of the k edges are distinct and pairwise nonadjacent, the highest order term is $O(n^{k-1})$. However, by Lemma 4.3, the trees produced by this are not kth NNI neighbors of T. By Lemma 3.5, if more than two of the k edges are the same or if more than two are adjacent, the highest order term is $O(n^{k-2})$.

In the case where the edges are pairwise nonadjacent, by Lemma 4.2, there are 2^k kth NNI neighbors of T resulting from NNI operations on a given set of k edges. In the case where exactly two edges are adjacent there are 2^{k+1} resulting kth NNI neighbors. Hence by Lemma 3.5,

$$\begin{aligned} |N^k_{NNI}(T)| &\geq \left(\frac{1}{k!}n^k - \frac{k(5k+1)}{2k!}n^{k-1}\right)2^k + \frac{1}{2(k-2)!}n^{k-1}2^{k+1} + O(n^{k-2}) \\ &= \frac{2^k}{k!}n^k - \frac{3k(k+1)}{2k!}2^k n^{k-1} + O(n^{k-2}); \end{aligned}$$

$$\begin{aligned} |N^k_{NNI}(T)| &\leq \left(\frac{1}{k!}n^k - \frac{k(k+2)}{k!}n^{k-1}\right)2^k + \frac{2}{(k-2)!}n^{k-1}2^{k+1} + O(n^{k-2}) \\ &= \frac{2^k}{k!}n^k + \frac{3k(k-2)}{k!}2^k n^{k-1} + O(n^{k-2}). \end{aligned}$$

∎

We can see that this result is very similar to the size of the kth RF neighborhood, as $D_{T,k}$ and $C_{T,k}$ are both quadratic in k.

4.2. Pairs of trees with shared neighbors. We end this section by providing an expression for the number of pairs of binary phylogenetic trees with n leaves that share a first NNI or RF neighbor, or equivalently, the number of pairs of trees that are within at most distance two of each other.

Our calculation involves summing the size of the first and second neighborhoods of a tree, over all binary phylogenetic trees, and discounting any duplicate trees. However, the size of the second neighborhood for both NNI and RF is dependent on the number of cherries, by Bryant and Steel [5] and Robinson [22]. Therefore it is necessary to know the number of binary phylogenetic trees with n leaves and c cherries, which we will denote here by $b(n, c)$. Hendy and Penny [16] found an expression for $b(n, c)$, which they proved using induction on the number of leaves. Here we present a constructive proof of their result.

PROPOSITION 4.4. *For all* $n \geq 4$,

$$b(n,c) = \frac{n!(n-4)!}{c!(c-2)!(n-2c)!2^{2c-2}}$$

for $2 \leq c \leq \frac{n}{2}$, *and* $b(n, c) = 0$ *otherwise.*

Proof. The number of ways to choose the $2c$ leaves from $[n]$ to form the c cherries of T is $\binom{n}{2c}$, and the number of ways to pair these $2c$ leaves up into a set of c (unordered) pairs is $\frac{(2c)!}{c!2^c}$. Thus there are

$$M = \frac{n!}{c!(n-2c)!2^c}$$

ways to select the c cherries from $[n]$. Let Y be any one choice of such c pairs. There are $b(c)$ trees in $B(Y)$ and any tree in $B(n, c)$ is obtained by (i) selecting the set of pairs Y (in M ways), (ii) selecting a tree T_Y in $B(Y)$ (in $b(c)$ ways), and (iii) attaching each of the remaining $n - 2c$ leaves of $[n]$ to one of the $2c - 3$ edges of $T \in B(Y)$ (so as not to create any further cherries). To count cases for step (iii), recall that $\binom{r+s-1}{r}$ is the number of ways to place r unlabeled objects into s labeled bins, and $r!$ is the number of ways to assign r distinct labels bijectively to r unlabeled objects. Applying this to the $s = 2c - 3$ edges of T_Y and to the $r = n - 2c$ leaves to be attached to the edges of this tree, the number of ways to perform step (iii) is $(n-2c)!\binom{(n-2c)+(2c-3)-1}{n-2c} = \frac{(n-4)!}{(2c-4)!}$. Notice that different choices of Y (or a different choice of T_Y) lead to a different set of trees, so the total number of trees in $B(n)$ with c cherries is the product over the three counts for steps (i), (ii), and (iii) above, namely,

$$M \cdot b(c) \cdot \frac{(n-4)!}{(2c-4)!},$$

which simplifies to the expression in Proposition 4.4. ∎

We can now use this result to find the number of pairs of binary phylogenetic trees in $B(n)$ that are within at most distance two of each other under NNI and RF. For $\theta \in \{NNI, RF\}$, let $N_\theta^{\leq 2}(n) = \{(T, T') : T, T' \in B(n), d_\theta(T, T') \leq 2\}$.

COROLLARY 4.5. *Let* $n \geq 3$, *Then*

(i) $|N_{NNI}^{\leq 2}(n)| = \sum_{c=2}^{\lfloor \frac{n}{2} \rfloor} b(n,c)(n^2 - 4n + 2c - 3)$,

(ii) $|N_{RF}^{\leq 2}(n)| = \sum_{c=2}^{\lfloor \frac{n}{2} \rfloor} b(n,c)(n^2 - 3n + 3c - 9)$,

where $b(n, c)$ *is given by Proposition* 4.4.

Proof.

(i) For $T \in B(n)$, with c cherries the number of first and second NNI neighbors is

$$\begin{aligned} N_{NNI}(T) + N^2_{NNI}(T) &= 2(n-3) + 2n^2 - 10n + 4c \\ &= 2n^2 - 8n + 4c - 6. \end{aligned}$$

To find the number of pairs of trees in $B(n)$ that are within NNI distance two, we simply sum the number of first and second neighbors over all trees in $B(n)$ and then halve the result as each pair will be counted twice. So,

$$\begin{aligned} |N^{\leq 2}_{NNI}(n)| &= \frac{1}{2}\sum_{c=2}^{\lfloor \frac{n}{2} \rfloor} b(n,c)(2n^2 - 8n + 4c - 6) \\ &= \sum_{c=2}^{\lfloor \frac{n}{2} \rfloor} b(n,c)(n^2 - 4n + 2c - 3). \end{aligned}$$

(ii) For each unrooted binary tree T, the number of first and second RF neighbors is

$$\begin{aligned} N_{RF}(T) + N^2_{RF}(T) &= 2(n-3) + 2n^2 - 8n + 6c - 12 \\ &= 2n^2 - 6n + 6c - 18. \end{aligned}$$

Therefore

$$\begin{aligned} |N^{\leq 2}_{RF}(n)| &= \frac{1}{2}\sum_{c=2}^{\lfloor \frac{n}{2} \rfloor} b(n,c)(2n^2 - 6n + 6c - 18) \\ &= \sum_{c=2}^{\lfloor \frac{n}{2} \rfloor} b(n,c)(n^2 - 3n + 3c - 9). \end{aligned}$$

∎

5. Subtree prune and regraft. In this section, we show that unlike RF and NNI, the size of the second SPR neighborhood of a tree $T \in B(n)$ is not uniquely determined by the number of leaves and cherries of T.

An *SPR operation* on a tree $T \in B(n)$ is defined by the following process:

1. Choose an edge $e = \{u, v\} \in E(T)$ and delete it, leaving two components T_u (containing the vertex u) and T_v (containing the vertex v).
2. Choose an edge $f \in E(T_v)$ and subdivide f with a new vertex w to obtain two edges f_1 and f_2. The vertex w has degree two.
3. Insert the edge $g = \{w, u\}$ and suppress the vertex v to obtain a binary tree $T' \in B(n)$.

Essentially, we *prune* the subtree T_u and *regraft* it onto edge f. We refer to e as the *cut edge* and f as the *join edge* of the SPR operation (see Figure 3). The tree T' is a *first SPR neighbor* of T. We will use the notation $SPR(T, (e, f))$ to refer to the tree obtained by an SPR operation on tree T with cut edge e and join edge f. Note that if $d_T(e, f) = 1$, then T' is a first NNI neighbor of T [24].

Consider a graph G in which each vertex represents a tree in $B(n)$ and there is an edge between the vertices representing trees T_1 and T_2 if they are first SPR neighbors. The *SPR distance* between T_1 and T_2, $\delta_{SPR}(T_1, T_2)$, is the distance between the two vertices representing T_1 and T_2 in G.

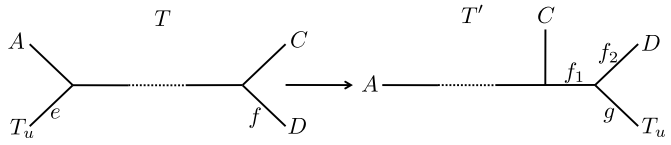

FIG. 3. *An example of an SPR operation with cut edge e and join edge f.*

For a tree $T \in B(n)$, the size of the first SPR neighborhood is given by

$$|N^1_{SPR}(T)| = 2(n-3)(2n-7).$$

This was determined by Allen and Steel [1]. No other SPR neighborhood sizes are currently known.

In relation to the structure of the SPR neighborhood, Carceres et al. [7] provided tight bounds on the length of the shortest NNI walk that visits all trees in the first SPR neighborhood of a tree T. Allen and Steel [1] found upper and lower bounds for the maximum SPR distance between any two trees in $B(n)$.

As with NNI and RF, the size of the first SPR neighborhood of a tree depends only on the number of leaves in the tree. However, unlike NNI and RF, the size of the second SPR neighborhood of a tree cannot be expressed solely in terms of the number of leaves and cherries of the tree. In this section we show that these two parameters are not sufficient to determine even the highest order term of the size of the second SPR neighborhood. At the end of this section we prove our main results, which are presented in Theorems 5.1 and 5.2.

THEOREM 5.1. *Let $T \in B(n)$.*

(i) *If T is a caterpillar, then*

$$|N^2_{SPR}(T)| = \frac{1}{2}n^4 + O(n^3).$$

(ii) *If T is a balanced tree, then*

$$|N^2_{SPR}(T)| = \frac{1}{3}n^4 + O(n^3).$$

Theorem 5.1 shows that, unlike RF or NNI, the coefficient of the leading power of n in the size of the second neighborhood for SPR does not just depend on n. For RF and NNI we saw that the number of cherries fully determines the second neighborhood size, and so perhaps the extreme difference in the number of cherries between caterpillar trees (which have only two) and balanced trees (which have $n/2$) is the reason for this difference in the coefficient of n^4. This turns out not to be the case. We consider two different structures of an unrooted binary tree T with $n = 3m$ ($m \geq 3$) leaves and three cherries. These two tree structures (Type I and Type II) can be seen in Figures 4 and 5, respectively. Similar to Theorem 5.1, we show that trees of Type I and Type II also have a different highest order term in the expression for the size of the second SPR neighborhood. This result is presented in Theorem 5.2.

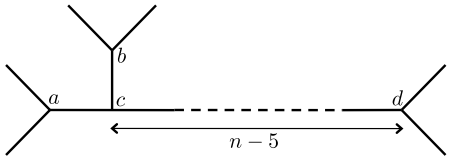

FIG. 4. *A Type* I *tree with three cherries and* $n = 3m$ *leaves* ($m \geq 3$).

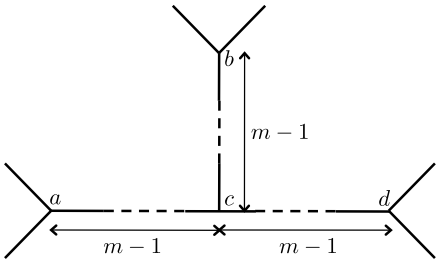

FIG. 5. *A Type* II *tree with three cherries and* $n = 3m$ *leaves* ($m \geq 3$).

THEOREM 5.2. *Let* T_1 *and* T_2 *be unrooted binary trees with* $n = 3m$ *leaves* ($m \geq 3$) *and three cherries, and suppose that* T_1 *is of Type* I *and* T_2 *is of Type* II. *Then*

$$|N^2_{SPR}(T_1)| = \frac{1}{2}n^4 + O(n^3) \text{ and}$$
$$|N^2_{SPR}(T_2)| = \frac{23}{54}n^4 + O(n^3).$$

5.1. Proof of Theorems 5.1 and 5.2. We will use the notation

$$SPR(T, (c_1, j_1), (c_2, j_2), \ldots, (c_k, j_k))$$

to denote the tree obtained by k successive SPR operations starting with tree T, where c_1 and j_1 in T are the cut and join edges, respectively, of the first operation, c_2 and j_2 in $SPR(T, (c_1, j_1))$ are the cut and join edges of the second operation, and so on. When $k = 2$, we refer to the two operations that result in the set of trees $SPR(T, (c_1, j_1), (c_2, j_2))$ as a *pair of SPR operations*. It is worth noting that some of these cut and join edges may not be edges of T if they are created by one of the SPR operations. However, the results in this section will require only sets of "well-separated" edges, where the cut and join edges are pairwise at least distance three apart, so that all of the edges $c_1, \ldots, c_k$ and $j_1, \ldots, j_k$ are edges of T.

First, we determine an upper bound on the size of the second SPR neighborhood. This follows directly from the expression for the size of the first SPR neighborhood given by Allen and Steel [1].

COROLLARY 5.3. *Let* $T \in B(n)$ ($n \geq 3$). *Then*

$$|N^2_{SPR}(T)| \leq 4(n-3)^2(2n-7)^2 = O(n^4).$$

The first step in proving Theorems 5.1 and 5.2 is to determine whether all pairs of SPR operations contribute to the term of order n^4 in the expression for the size of the second SPR neighborhood of a tree.

Let $T \in B(n)$ and let

$$\mathbb{T}(T) = \{(c_1, c_2, j_1, j_2) : c_1, j_1 \in E(T), c_1 \neq j_1; c_2, j_2 \in E(SPR(T, (c_1, j_1))), c_2 \neq j_2\}.$$

This is the set of all possible choices for the four cut and join edges of two SPR operations starting with tree T.

Let $\mathbb{S}(T)$ be the subset of $\mathbb{T}(T)$, where $c_2, j_2 \in E(T)$ and the four edges c_1, j_1, c_2, j_2 are pairwise at least distance three apart in T.

The following lemma shows that in order to prove Theorems 5.1 and 5.2, it suffices to consider only pairs of SPR operations with cut and join edges in $\mathbb{S}(T)$.

LEMMA 5.4. *Let $T \in B(n)$. Then*

$$|\mathbb{S}(T)| = \frac{2}{3}n^4 + O(n^3),$$

$$|\mathbb{T}(T) - \mathbb{S}(T)| = O(n^3).$$

Proof. For sufficiently large values of n, it is possible to choose the edges c_1, j_1, c_2, and j_2 in T such that $(c_1, c_2, j_1, j_2) \in \mathbb{S}(T)$. To determine the size of $\mathbb{S}(T)$, we count the number of sets of four internal edges of T, where all pairs of edges in the set are at least distance three apart. There are $2n-3$ choices for edge c_1, since this is the number of edges in T (this follows from Lemma 1.1). The maximum number of choices for j_1 is $(2n-3-7)$ (this can occur if c_1 is a pendant edge). The minimum number of choices for edge j_1 is $(2n-3-29)$ (this can occur if c_1 is an internal edge). The maximum number of choices for c_2 is $(2n-3-7-6)$ (this can occur if c_1 and j_1 are both pendant edges). The minimum number of choices for c_2 is $(2n-3-2(29))$ (this can occur if both c_1 and j_1 are internal edges). A similar process determines upper and lower bounds on the number of choices for edge j_2. We divide by the number of ways to order the four edges. Therefore

$$|\mathbb{S}(T)| \geq \frac{1}{4!}(2n-3)(2n-3-29)(2n-3-2(29))(2n-3-3(29)) = \frac{2}{3}n^4 + O(n^3) \text{ and}$$

$$|\mathbb{S}(T)| \leq \frac{1}{4!}(2n-3)(2n-3-7)(2n-3-7-6)(2n-3-7-2(6)) = \frac{2}{3}n^4 + O(n^3).$$

We now consider $\mathbb{T}(T) - \mathbb{S}(T)$. Determining $|\mathbb{T}(T) - \mathbb{S}(T)|$ is similar to determining $|\mathbb{S}(T)|$; however, for at least one of the four cut and join edges, instead of counting the number of edges at least distance three from those already chosen, we count the number within distance two of those already chosen and therefore obtain a constant factor instead of a linear factor. Let M be a maximal subset of the edges $\{c_1, c_2, j_1, j_2\}$ such that the edges in M are pairwise distance at least three apart in T, where $|M| = m < 4$. Suppose we first choose the edges in M. From the argument above we can see that the number of such choices is $O(n^m)$. The remaining $4 - m \geq 1$ edges must be chosen from edges within distance two of those already chosen. The number of these choices depends only on the number and location of the m edges already chosen, and not on n. Hence

$$|\mathbb{S}(T)| = \frac{2}{3}n^4 + O(n^3), \text{ and } |\mathbb{T}(T) - \mathbb{S}(T)| = O(n^3). \qquad \square$$

The proof of Theorem 5.1 requires three additional technical lemmas, which we state here without proof (proofs for these can be found in [12]).

LEMMA 5.5. *Let $T \in B(n)$, and suppose that we have trees $T' = SPR(T, (c_1, j_1))$ and $T'' = SPR(T, (c_1, j_1), (c_2, j_2))$, where $(c_1, c_2, j_1, j_2) \in \mathbb{S}(T)$. Suppose that the edges j_2, c_1, c_2, and j_1 lie on a path in T in this order. Then*

(i) *$T'' \notin N_{SPR}(T)$, and*

(ii) *for all other choices of edges $(c_1', c_2', j_1', j_2') \in \mathbb{S}(T)$, where $(c_1', c_2', j_1', j_2') \neq (c_1, c_2, j_1, j_2)$, we have*

$$T'' \neq SPR(T, (c_1', j_1'), (c_2', j_2')).$$

LEMMA 5.6. *Let $T \in B(n)$ and suppose that we have trees $T' = SPR(T, (c_1, j_1))$ and $T'' = SPR(T, (c_1, j_1), (c_2, j_2))$, where $(c_1, c_2, j_1, j_2) \in \mathbb{S}(T)$. Suppose that there is no path in T in which the edges j_2, c_1, c_2, and j_1 lie in this order. Then*

(i) *$T'' \notin N_{SPR}(T)$, and*

(ii) *for all choices of edges $(c_1', c_2', j_1', j_2') \in \mathbb{S}(T)$, $(c_1', c_2', j_1', j_2') \neq (c_1, c_2, j_1, j_2)$, we have*

$$T'' = SPR(T, (c_1', j_1'), (c_2', j_2'))$$

if and only if $(c_1', c_2', j_1', j_2') = (c_2, c_1, j_2, j_1)$.

LEMMA 5.7. *For $n \geq 4$ we have the following:*

(i) *A caterpillar with n leaves has $4(n-k)$ paths of length k for $3 \leq k \leq n-1$.*

(ii) *Let*

$$f(k) = \begin{cases} 3\left(2^{\frac{k}{2}-1}\right)\left(n - 2^{\frac{k}{2}}\right), & k \text{ even}; \\ 2^{\frac{k+1}{2}}\left(n - 3\left(2^{\frac{k-3}{2}}\right)\right), & k \text{ odd}. \end{cases}$$

A balanced tree with $n = 2^i$ leaves ($i \geq 2$) has $f(k)$ paths of length k for $3 \leq k \leq 2i-1$, and a balanced tree with $n = 3 \cdot 2^i$ leaves ($i \geq 1$) has $f(k)$ paths of length k for $3 \leq k \leq 2(i+1)$.

Proof of Theorem 5.1. Suppose that T has a path P of length k, $k \geq 13$. Fix the two pendant edges of P as j_2 and j_1 so that j_2 is the first edge in P and j_1 is the kth edge in P. All pairs of the edges j_2, c_1, c_2, and j_1 must be distance three or more apart and in the order given. So $d_T(c_1, j_2) \geq 3$ and $d_T(c_1, j_1) \geq 7$. If c_1 is the mth edge in P, then $5 \leq m \leq k-8$. Now if c_2 is the jth edge in P, then $m+4 \leq j \leq k-4$, so there are $(k-4) - (m+4) + 1 = k - m - 7$ possible choices for the location of c_2. Finally, it does not matter at which endpoint of P we begin counting. So the number of ways of arranging the four edges on this path is

$$R_k = 2\sum_{m=5}^{k-8}(k - m - 7) = (k-11)(k-12).$$

Let $P(T)$ be the number of ways that the edges j_2, c_1, c_2, and j_1 can appear in a path in a T in the order given.

(i) By Lemma 5.7, T has $4(n-k)$ paths of length k for $k \geq 3$. Hence for a caterpillar,

$$P(T) = \sum_{k=13}^{n-1} 4(n-k)(k-11)(k-12) \tag{5.1}$$

$$= \frac{1}{3}n^4 + O(n^3). \tag{5.2}$$

We know by Lemmas 5.5 and 5.6 that if we count the number of ways to choose the edges $(c_1, c_2, j_1, j_2) \in \mathbb{S}(T)$, then in the cases not counted by $P(T)$, we count every second neighbor twice. For the cases that are counted by $P(T)$ we do not obtain any duplicate trees. Therefore by Lemma 5.4,

$$\begin{aligned}|N^2_{SPR}(T)| &= \frac{1}{2}\left(\frac{2}{3}n^4 + O(n^3) - P(T)\right) + P(T)\\ &= \frac{1}{2}\left(\frac{2}{3}n^4 + P(T)\right) + O(n^3)\\ &= \frac{1}{2}\left(\frac{2}{3}n^4 + \frac{1}{3}n^4\right) + O(n^3) = \frac{1}{2}n^4 + O(n^3).\end{aligned}$$

(ii) Similarly for a balanced tree T with $n = 3(2)^i$ leaves ($i \geq 1$), we can sum over even and odd path lengths (see Lemma 5.7) to obtain

$$\begin{aligned}P(T) &= \sum_{k=13}^{n-1} P_k(T)(k-11)(k-12)\\ &= \sum_{m=7}^{\log_2(\frac{n}{3})+1} \left(3\left(2^{m-1}\right)(n-2^m)(2m-11)(2m-12)\right)\\ &\quad + \sum_{m=7}^{\log_2(\frac{n}{3})+1} \left(2^m\left(n-3\left(2^{m-2}\right)\right)(2m-12)(2m-13)\right)\\ &= \frac{8}{\ln(2)^2}n^2\ln(n)^2 + O(n^2\ln(n))\\ &= O(n^2\ln(n)^2) = O(n^3),\end{aligned}$$

where $P_k(T)$ is the number of distinct paths of length k in T. If T is a balanced tree with $n = 2^i$ leaves ($i \geq 2$), then instead we have

$$\begin{aligned}P(T) &= \sum_{m=7}^{\log_2(\frac{n}{4})+1} \left(3\left(2^{m-1}\right)(n-2^m)(2m-11)(2m-12)\right)\\ &\quad + \sum_{m=7}^{\log_2(\frac{n}{4})+2} \left(2^m\left(n-3\left(2^{m-2}\right)\right)(2m-12)(2m-13)\right)\\ &= \frac{8}{\ln(2)^2}n^2\ln(n)^2 + O(n^2\ln(n)) = O(n^3).\end{aligned}$$

Therefore, for any balanced tree T,

$$|N^2_{SPR}(T)| = \frac{1}{2}\left(\frac{2}{3}n^4 + P(T)\right) + O(n^3) = \frac{1}{3}n^4 + O(n^3).$$

∎

This shows that the size of the second SPR neighborhood of a tree cannot be uniquely determined by the number of leaves of the tree. We now prove Theorem 5.2, which shows that the number of leaves and cherries is insufficient.

Proof of Theorem 5.2. Suppose that $n = 3m$ and $c = 3$, where $m \geq 7$. Consider the tree T_1 of Type I, with n leaves and c cherries (see Figure 4). For any pair of

vertices x, y, let C_{xy} be the caterpillar formed by the path between vertices x and y in T_1 and all of the edges incident to vertices on that path. Let a, b, and d be the roots of the three cherries of T_1 such that $d_{T_1}(a, b) = 2$. Let c be the vertex in T_1 that is not adjacent to a leaf. Both of the caterpillars C_{ad} and C_{bd} have $n - 1$ leaves. If we find $P(C_{ad})$ and $P(C_{bd})$, then we will have found every way of choosing the edges c_1, c_2, j_1, and j_2 so that all four edges are on a path in the order j_2, c_1, c_2, j_1. Eliminating double counting, we have

$$P(T_1) = P(C_{ad}) + P(C_{bd}) - P(C_{cd}) = 2P(C_{ad}) - P(C_{cd}),$$

where $P(T_1)$ is the number of ways that the edges j_2, c_1, c_2, and j_1 can appear in a path in T_1 in the order given. We do not consider the caterpillar C_{ab} because it is too short to have any paths of length 13 or more. So by (5.2),

$$P(T_1) = \frac{2}{3}(n-1)^4 - \frac{1}{3}(n-2)^4 + O(n^3) = \frac{1}{3}n^4 + O(n^3).$$

Now let T_2 be the tree of Type II with n leaves, c cherries, and maximum path length $2m$ (see Figure 5). Let a, b, and d be the roots of the three cherries of T_2, and let c be the vertex in T_2 that is not adjacent to a leaf. By the same process as above,

$$P(T_2) = P(C_{ad}) + P(C_{bd}) + P(C_{ab}) - P(C_{ac}) - P(C_{bc}) - P(C_{cd}) = 3P(C_{ad}) - 3P(C_{ac}).$$

Now C_{ad} has $2m + 1$ leaves and C_{ac} has $m + 2$ leaves, so

$$\begin{aligned} P(T_2) &= (2m+1)^4 - (m+2)^4 + O(n^3) \\ &= \left(\frac{2}{3}n + 1\right)^4 - \left(\frac{1}{3}n + 2\right)^4 + O(n^3) \\ &= \frac{5}{27}n^4 + O(n^3). \end{aligned}$$

Therefore $|N^2_{SPR}(T_1)| = \frac{1}{2}n^4 + O(n^3)$ and $|N^2_{SPR}(T_2)| = \frac{23}{54}n^4 + O(n^3)$. ∎

Since T_1 and T_2 have the same number of leaves and cherries, it is clear that other properties of the tree T would be required to get an exact formula for the highest order term of $|N^2_{SPR}(T)|$.

6. Concluding comments. In this paper, we derived new results for the sizes of the first and second RF neighborhoods of an unrooted binary tree, and we extended the result of Robinson [22] for the third NNI neighborhood of an unrooted binary tree (see Appendix A in [12]). In addition, we calculated new asymptotic results for the sizes of the kth RF and NNI neighborhoods of a binary phylogenetic tree. We also found an upper bound on the proportion of binary trees that share at least k nontrivial splits with a given tree on the same leaf set and found an expression for the number of pairs of binary trees that share a first neighbor under the RF and NNI metrics.

In our results for the size of the kth RF and NNI neighborhoods of an unrooted binary tree T (Theorems 3.1 and 4.1), the term of order n^{k-1} contains a parameter dependent on T and k. We have calculated bounds on the value of this parameter: for RF, $-\frac{5k^2+7k}{4} \le C_{T,k} \le 4k^2 - 7k$; for NNI, $\frac{-3k(k+1)}{2} \le D_{T,k} \le 3k(k-2)$. These bounds are not strict, so it would be interesting to investigate ways of improving them. A natural question is whether both positive and negative values of $C_{T,k}$ and $D_{T,k}$ are possible for any given value of k, and if so, whether we can find examples of such trees.

We showed that in contrast to RF and NNI, the size of the second SPR neighborhood is not solely dependent on the number of leaves and cherries of the tree. Humphries and Wu [17] showed that for TBR even the first neighborhood depends on variables other than the number of leaves and cherries.

Throughout this paper, we have considered neighborhoods of unrooted binary trees under the three metrics: RF, NNI, and SPR. There are, however, many other metrics that can be used to compare trees and which would be interesting to investigate. For example, Humphries and Wu [17] found an expression for the size of the first TBR neighborhood of a tree that depends on variables other than the number of leaves and cherries. Moulton and Wu [21] recently defined a new metric d_p, which is similar to the TBR metric. (The same metric was also independently defined by Kelk and Fischer [18].) Using the result of Humphries and Wu [17], Moulton and Wu [21] calculated the size of the first neighborhood of an unrooted binary tree under this metric.

Given the difficulty of calculating the size of the second SPR neighborhood, it is possible that similar problems would arise in calculating the size of the second neighborhood under TBR or d_p. However, this would be interesting to investigate, and it may be possible to find the size of the second TBR or d_p neighborhood of a particular type of tree, such as a caterpillar or a balanced tree.

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