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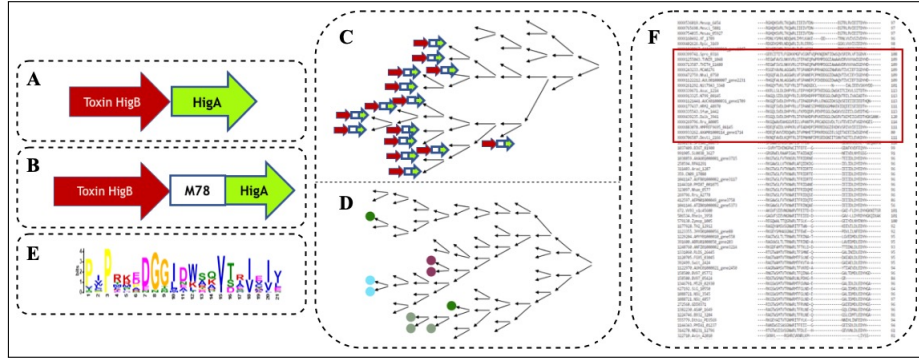


Figure S3 Application of RSAM-finder to the identification of two distinct chromosomal-invasion patterns of the *higBA* TA. (A) Two-component variant identified by Q_1 , consisting of the toxin *higB* (red) and its antitoxin *higA* (green), and characterized by a fast duplication rate. (B) Three-component variant of *higBA* identified by Q_2 , characterized by a slow duplication rate and far-reaching horizontal transfers. Predicted RSAM consists of a short insertion sequence in *higB* (shown in E) and the fusion of the antitoxin *higA* with an M78 peptidase domain. (C) Top-ranking subtree of the *higB* toxin gene tree identified by Q_2 . Leaves corresponding to instances of the three-component toxin system are marked. (D) Top-ranking subtree of the *higB* gene tree identified by Q_1 . Vertices marked with circles of the same color represent multiple copies of the gene in the same species. (E) A motif logo for the insertion sequence mentioned in B. (F) The multiple alignment of the *higB* protein sequences, illustrating the insertion sequence (highlighted by red rectangle).

18 G , S and σ (Fig. S2.C'), the tubes illustrate the edges of S , and each edge of G is embedded
 19 inside the tube (edge of S) to which it is mapped by γ . Then, $\Sigma = \{u_9, u_4\}$, $\Delta = \{u_7\}$ and
 20 $\Theta = \{u_6\}$. Moreover, $\Xi = \{(u_6, u_4)\}$.

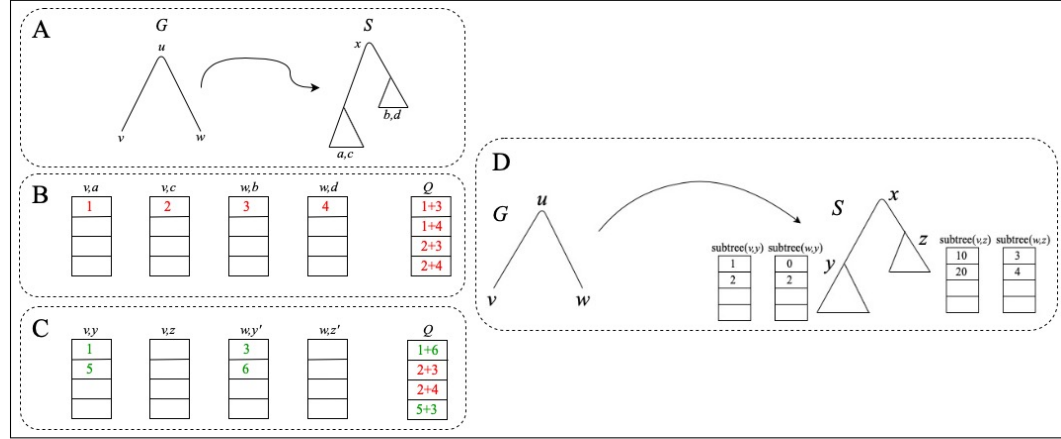
21 S2 Pseudocode of Algorithms for Hypergraph Construction

22 In Fig. 1 in Section 1, the hypernode $(u_5, x_5, 1)$ is annotated with score 1 and event 'S'. To
 23 extract the best solution from the hypergraph, we begin with the first (i.e. top-ranking) slot
 24 in the root of the hypergraph (which is $(u_5, x_5, 1)$ in the figure), and then follow the incoming
 25 hyperedges in top-down order. In the figure, the best solution is (1) in part C. To extract it
 26 from the hypergraph in part B, we map u_5 to x_5 with cost 1 and a speciation event. Then,
 27 by first following the hyperedges incoming to $(u_5, x_5, 1)$, we derive the mapping of u_3 to x_1
 28 and of u_4 to x_3 , and by secondly following the hyperedges incoming to $(u_3, x_1, 1)$, we also
 29 derive the mapping of u_1 to x_1 and of u_2 to x_2 .

30 The second best solution ((2) in part C) is extracted in the same manner—now, we start
 31 with the hypernode $(u_5, x_5, 2)$ rather than $(u_5, x_5, 1)$, and again follow incoming hyperedges
 32 in a top-down order until we reach the leaves. Similarly, we can extract all three non-nil
 33 solutions among the 4-best solutions (illustrated in part C). As before, the outer tubes
 34 illustrate the edges of S , and the edges of G are embedded inside based on the reconciliation.

36 S2.1 An Efficient Hypergraph Construction

37 An overview of our efficient algorithm can be found in Section 5.1. Here, we present the
 38 pseudocode for this algorithm.



■ **Figure S4** (A),(B) and (C) Demonstration of subroutine 1 of the naive algorithm. (Subroutines 2 and 3 are similar.) (D) The computation in line 21 of the efficient algorithm for hypergraph construction.

In this appendix we use the notation imin , defined as follows: Let X and Y be sets, and consider a function $f : X \rightarrow Y$, and an index $i \in \{1, \dots, |X|\}$. Then, $\text{imin}_{x' \in X} f(x') \triangleq f(x)$ where x is an element in X such that there are exactly i elements $x' \in X$ satisfying $f(x') \leq f(x)$. In case f is not an injective function, hence there multiple choices for x , we break ties arbitrarily.

Efficient DP Algorithm for Constructing the Hypergraph

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1: for  $u \in V(G)$ ,  $x \in V(S)$ ,  $1 \leq i \leq k$  do
2:   Set  $c(u, x, i)$ ,  $p_\Sigma(u, x, i)$ ,  $p_\Delta(u, x, i)$ ,  $p_\Theta(u, x, i)$ ,  $\text{subtree}(u, x, i)$  and  $\text{incomp}(u, x, i)$  to  $\infty$ 
3: end for
4: for  $u \in L(G)$  do
5:   Add  $(u, \sigma(u))$  to the supernode set of the hypergraph
6:    $\text{event}(u, \sigma(u), 1) \leftarrow \text{leaf}$   $c(u, \sigma(u), 1) \leftarrow 0$   $\text{subtree}(u, \sigma(u), 1) \leftarrow 0$ 
7:   for  $i$  from 2 to  $k$  do
8:      $\text{event}(u, x, i) \leftarrow \text{NaN}$   $c(u, x, i) \leftarrow \infty$ 
9:   end for
10: end for
11: for  $u \in I(G)$  with children  $v, w$  in postorder do
12:   for  $x \in V(S)$  in postorder do
13:     for  $i$  from 1 to  $k$  do
14:       if  $x \in L(S)$  then
15:          $p_\Sigma(u, x, i) = \infty$ 
16:          $p_\Delta(u, x, i) \leftarrow c_\Delta + \text{imin}_{1 \leq j, r \leq k} \{c(v, x, j) + c(w, x, r)\}$ 
17:         if  $x$  is not the root of  $S$  then
18:            $p_\Theta(u, x, i) \leftarrow c_\Theta + \text{imin}_{1 \leq j, r \leq k} \begin{cases} \text{subtree}(v, x, j) + \text{incomp}(w, x, r), \\ \text{subtree}(w, x, j) + \text{incomp}(v, x, r) \end{cases}$ 
19:       end if
20:     else  $x \in I(S)$  with children  $y, z$ 
21:        $p_\Sigma(u, x, i) \leftarrow \text{imin}_{1 \leq j, r \leq k} \begin{cases} \text{subtree}(v, y, j) + \text{subtree}(w, z, r), \\ \text{subtree}(w, y, j) + \text{subtree}(v, z, r) \end{cases}$ 

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9:4 RSAM-finder (Supplementary Materials)

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$$p_{\Delta}(u, x, i) \leftarrow c_{\Delta} + i \min_{1 \leq j, r \leq k} \begin{cases} \text{subtree}(v, y, j) + \text{subtree}(w, z, r), \\ \text{subtree}(w, y, j) + \text{subtree}(v, z, r), \\ \text{subtree}(v, y, j) + \text{subtree}(w, y, r), \\ \text{subtree}(v, z, j) + \text{subtree}(w, z, r), \\ c(v, x, j) + c(w, x, r), \\ c(v, x, j) + \text{subtree}(w, z, r), \\ c(w, x, j) + \text{subtree}(v, y, r), \\ c(v, x, j) + \text{subtree}(w, y, r), \\ c(w, x, j) + \text{subtree}(v, z, r) \end{cases}$$

$$p_{\Theta}(u, x, i) \leftarrow c_{\Theta} + i \min_{1 \leq j, r \leq k} \begin{cases} \text{subtree}(v, x, j) + \text{incomp}(w, x, r), \\ \text{subtree}(w, x, j) + \text{incomp}(v, x, r) \end{cases}$$

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88 We proceed with a few clarifications of the pseudocode.

89 **Initialization: Lines 1-10.** We initialize all lists to contains only scores of ∞ (lines 1-3).
90 Then, the lists associated with a matching between leaves that complies with σ —that is,
91 supernodes of the form $(u, \sigma(u))$ for some $u \in V(G)$ —are inserted into the hypergraphs, and
92 their topmost items are updated with a leaf event, cost 0 and **subtree** 0 (because the cost of
93 the best solutions mapping a gene to its species has the cost 0).

94 **Division into First and Second Phases: Lines 11-36.** For each vertex $u \in I(G)$ in
95 postorder (line 11), we have two phases, on which we elaborate below. In the first phase
96 (lines 12-31), we consider each vertex $x \in V(S)$ in postorder and perform most computations,
97 and in the second phase (lines 32-35) we consider each vertex $x \in V(S)$ in postorder and
98 compute the lists of **incomp**.

99 **Recursive Formulas for p_{Σ} , p_{Δ} and p_{Θ} : Lines 13-27.** In this part of the first phase, we
100 find the k -best costs for mapping the subtree of G rooted in u to the subtree of S rooted in x
101 for each possible event (speciation, duplication or horizontal transfer), based on computations
102 done in previous iterations or the initialization. The recursive formulas for these computations
103 are directly given in the pseudocode.

104 In Fig. S4.D, we demonstrate the construction of $p_{\Sigma}(u, x, i)$ for $i \in \{1, \dots, k\}$. Given
105 $u \in V(G)$ and $x \in V(S)$, we need to map the subtree of u to the subtree of x according to

the restrictions of a speciation event. Thus, we need to map the left and right children of u to some vertices in the subtrees of the left and right (or, alternatively, right and left) children of x , respectively. In the previous (naive) algorithm, this was done by simply always iterating over all the vertices in these subtrees and thereby finding the best scores. Here, we only need to look at two pairs of lists, $\{\text{subtree}(v, y), \text{subtree}(w, z)\}$ and $\{\text{subtree}(v, z), \text{subtree}(w, y)\}$, in order to find the best scores. Even though the best sum is $\text{subtree}(v, y, 1) + \text{subtree}(w, y, 1) = 1$, it does not correspond a valid solution (since then v and w are mapped to the same subtree). Here, the best sum corresponding to a valid solution is $\text{subtree}(v, y, 1) + \text{subtree}(w, z, 1) = 4$, where v is mapped to some y' in the subtree rooted in y , and similarly w is mapped to some z' in the subtree rooted in z .

Updating c and subtree in First Phase: Lines 29-30. First, in line 29, we immediately find k -best costs for mapping the subtree of u to the subtree of x (i.e. we compute $c(u, x)$) by selecting k -best costs from the list that is the combination of $p_\Sigma(u, x)$, $p_\Delta(u, x)$ and $p_\Theta(u, x)$. Notice that in this line, we also add the appropriate vertices and hyperedges to the hypergraph, in the exact same way in which it was done in the naive algorithm. $\text{event}(u, x, i)$ is defined by the source list ($p_\Sigma(u, x)$, $p_\Delta(u, x)$ or $p_\Theta(u, x)$) it came from. As before, if the combined list is shorter than k , we add hypernodes with $\text{event} = \text{Nan}$ and $\text{cost} = \infty$. Secondly, in line 30, we find k -best costs for mapping the subtree of u to the subtree of some vertex x' in the subtree of x (i.e. we compute $\text{subtree}(u, x)$) by selecting k -best costs from the list defined as follows. In case $x \in I(S)$, then this list is the combination of $c(u, x)$, $\text{subtree}(u, y)$ and $\text{subtree}(u, z)$, where y and z are the children of x in S . Otherwise, this list is simply $c(u, x)$.

Updating incomp in Second Phase: Lines 32-35. To compute the lists of the form $\text{incomp}(u, \cdot)$, in the second phase we iterate over all vertices $x \in I(S)$ with children y and z in *preorder*. We note that now the traversal of S is in preorder rather than postorder because the computation of a list $\text{incomp}(u, a)$ for a vertex $a \in V(S)$ that is not the root of S relies on having already computed the list $\text{incomp}(u, b)$ where b is the parent of a in S . Specifically, for a vertex $x \in I(S)$ with children y and z , we compute the list $\text{incomp}(u, y)$ by selecting k -best costs from the list that is the combination of $\text{incomp}(u, x)$ and $\text{subtree}(u, z)$, and symmetrically for $\text{incomp}(u, z)$ (swapping the roles of y and z).

Time Complexity and Correctness. We now turn to prove Observation 2 and Lemma 1.

Proof of Observation 2. For each pair of vertices $u \in V(G)$ and $x \in V(S)$, we construct a tuple of lists $(p_\Sigma(u, x), p_\Delta(u, x), p_\Theta(u, x), \text{subtree}(u, x), \text{incomp}(u, x))$. From the pseudocode, it is clear that the computation of each one of these lists is done in time $O(k)$. Thus, we have that the total running time is $O(m \cdot n \cdot k)$. ◀

Proof of Lemma 1. We can focus on proving that for every pair of vertices $u \in V(G)$ and $x \in V(S)$, and every index $i \in \{1, \dots, k\}$, if there exists an i^{th} best DLT scenario mapping the subtree of G rooted in u to the subtree of S rooted in x , then the hypernode (u, x, i) is inserted into the hypergraph \mathcal{H} under construction with association to this scenario. In this lemma, the proof of this claim is done in conjunction with the proof that for every pair of vertices $u \in V(G)$ and $x \in V(S)$, and every index $i \in \{1, \dots, k\}$, the following equalities hold.

■ $\text{subtree}(u, x, i)$ is the i^{th} best cost of a DLT scenario mapping the subtree of G rooted in u to some subtree of S whose root is a vertex y that is a descendant of x .

150 ■ $\text{incomp}(u, x, i)$ is the i^{th} best cost of a DLT scenario mapping the subtree of G rooted in
 151 u with some subtree of S whose root is a vertex y that is incomparable to x .

152 The proof is by induction on the order of computation.

153 In particular, $\text{table}_1(u_1, x_1) < \text{table}_2(u_2, x_2)$ where $\text{table}_1, \text{table}_2 \in \{\text{c}, \text{subtree}, \text{incomp}\}$ if one
 154 of the following conditions holds:

- 155 ■ u_1 is visited before u_2 in the postorder traversal of G .
- 156 ■ $u_1 = u_2$, $\text{table}_1, \text{table}_2 \in \{\text{c}, \text{subtree}\}$, and x_1 is visited before x_2 in the *postorder* tra-
 157 versal of S .
- 158 ■ $u_1 = u_2$, $x_1 = x_2$, $\text{table}_1 = \text{c}$ and $\text{table}_2 = \text{subtree}$.
- 159 ■ $u_1 = u_2$, $\text{table}_1 = \text{subtree}$ and $\text{table}_2 = \text{incomp}$.
- 160 ■ $u_1 = u_2$, $\text{table}_1 = \text{table}_2 = \text{incomp}$, and x_1 is visited before x_2 in the *preorder* traversal of
 161 S .

162 The basis of the induction comprises of the computation of hypernodes of the form (u, x, i)
 163 where $u \in L(G)$. To prove its correctness, consider such a hypernode (u, x, i) . If $i = 1$, then
 164 the algorithm inserts the hypernode $(u, x, 1)$ (whose event is *leaf*) with score 0 and *subtree*
 165 value 0; otherwise, the algorithm does not insert the hypernode—more precisely, it inserts a
 166 place-holder (whose event is *NaN*) with score ∞ and *subtree* value ∞ . In both cases, *incomp*
 167 value remains ∞ as in its creation. The correctness of these operations directly follows from
 168 the definitions of *subtree* and *incomp*, and the fact that the only possible DLT scenario in
 169 this case maps u to x , and the score of this match is 0.

170 For the inductive step, we consider some pair of vertices $u \in I(G)$ and $x \in V(S)$ along
 171 with a table $\text{table} \in \{\text{c}, \text{subtree}, \text{incomp}\}$, and prove that the values in *table* of the supernode
 172 (u, x) are computed correctly. For the inductive assumption, suppose that for every triple
 173 (table', u', x') ordered before (table, u, x) , the values in *table'* of (u', x') have already been
 174 computed correctly.

175 First, consider the case where $\text{table} = \text{subtree}$. By the pseudocode, $\text{subtree}(u, x)$ consists
 176 of the k -best scores from the lists $\text{c}(u, x)$, $\text{subtree}(u, y)$ (if x is not a leaf) and $\text{subtree}(u, z)$ (if
 177 x is not a leaf). Observe that these three lists have already been computed. Thus, by the
 178 inductive hypothesis, $\text{c}(u, x)$ consists of the (scores of the) k -best DLT scenarios mapping
 179 the subtree of G rooted in u to the subtree of S rooted in x (where u and x are matched
 180 to each other), $\text{subtree}(u, y)$ consists of the (scores of the) k -best DLT scenarios mapping
 181 the subtree of G rooted in u to the subtree of S rooted in some descendant of y (if x is not
 182 a leaf), and $\text{subtree}(u, z)$ consists of the (scores of the) k -best DLT scenarios mapping the
 183 subtree of G rooted in u to the subtree of S rooted in some descendant of z (if x is not a
 184 leaf). Notice that a DLT scenario maps the subtree of G rooted in u to the subtree of S
 185 rooted in some descendant of x if and only if it is a DLT scenario that maps the subtree
 186 of G rooted in u to one of the following subtrees: (i) the subtree of S rooted in x (where u
 187 and x are matched); (ii) a subtree of S rooted in some descendant of y (if x is not a leaf);
 188 (iii) a subtree of S rooted in some descendant of z (if x is not a leaf). Thus, it follows that
 189 $\text{subtree}(u, x)$ is computed correctly.

190 Second, consider the case where $\text{table} = \text{incomp}$. By the pseudocode, if x is the root of
 191 S , then $\text{incomp}(u, x)$ does not contain any item (having score different from ∞) as in its
 192 creation, which is correct because in this case, there exists no vertex incomparable to x
 193 and hence we cannot map one of the children of u as required in the definition of the DLT
 194 scenarios that correspond to $\text{incomp}(u, x)$. Therefore, now suppose that x is not the root of
 195 S , and let p denote the parent of x in S , and s denote the sibling of x in S (i.e. the other
 196 child of p in S). Then, by the pseudocode, $\text{incomp}(u, x)$ consists of the k -best scores from the

197 lists $\text{incomp}(u, p)$ and $\text{subtree}(u, s)$. Observe that these two lists have already been computed.
 198 Thus, by the inductive hypothesis, $\text{incomp}(u, p)$ consists of the (scores of the) k -best DLT
 199 scenarios mapping the subtree of G rooted in u to the subtree of S rooted in some vertex
 200 incomparable to p , and $\text{subtree}(u, s)$ consists of the (scores of the) k -best DLT scenarios
 201 mapping the subtree of G rooted in u to the subtree of S rooted in some descendant of s .
 202 Notice that a DLT scenario maps the subtree of G rooted in u to a subtree of S rooted in
 203 some vertex incomparable to x if and only if it is a DLT scenario that maps the subtree
 204 of G rooted in u to one of the following subtrees: (i) a subtree of S rooted in some vertex
 205 incomparable to p ; (ii) a subtree of S rooted in some descendant of s . Thus, it follows that
 206 $\text{incomp}(u, x)$ is computed correctly.

207 Third, consider the (last) case where $\text{table} = c$. By line 29 of the pseudocode, $c(u, x)$
 208 consists of the k -best scores from the lists $p_\Sigma(u, x)$, $p_\Delta(u, x)$ and $p_\Theta(u, x)$. Thus, to prove
 209 the correctness of the computation of $c(u, x)$, it suffices to prove that the following statement
 210 holds: $p_\Sigma(u, x)$, $p_\Delta(u, x)$ and $p_\Theta(u, x)$ consist of k -best DLT scenarios mapping the subtree of
 211 G rooted in u to the subtree of S rooted in x under the constraint that the event corresponding
 212 to the matching of u and x is speciation, duplication and horizontal transfer, respectively.

213 Towards the proof of the statement, consider the list $p_\Sigma(u, x)$. If $x \in L(S)$, then because
 214 $u \in I(G)$, there does not exist a DLT scenario mapping the subtree of G rooted in u to the
 215 subtree of S rooted in x under the constraint that the event corresponding to the matching
 216 of u and x is speciation, and hence the assignment of ∞ to every element $p_\Sigma(u, x, i)$ of the
 217 list is correct. Now, suppose that $x \in I(S)$. Then, by the pseudocode, $p_\Sigma(u, x)$ consists of
 218 the k -best scores present in the following multisets: $\{\text{subtree}(v, y, j) + \text{subtree}(w, z, j) \mid 1 \leq$
 219 $j, r \leq k\}$ and $\{\text{subtree}(w, y, j) + \text{subtree}(v, z, j) \mid 1 \leq j, r \leq k\}$. Observe that the lists
 220 $\text{subtree}(v, y)$, $\text{subtree}(w, z)$, $\text{subtree}(w, y)$ and $\text{subtree}(v, z)$ have already been computed. Thus,
 221 by the inductive hypothesis, $\text{subtree}(v, y)$ (resp., $\text{subtree}(w, z)$, $\text{subtree}(w, y)$ and $\text{subtree}(v, z)$)
 222 consists of the (scores of the) k -best DLT scenarios mapping the subtree of G rooted in
 223 v (resp., w , w and v) to a subtree of S rooted in some descendant of y (resp., z , y and z).
 224 Notice that a DLT scenario maps the subtree of G rooted in u to a subtree of S rooted in x
 225 under the constraint that the event corresponding to the matching of u and x is speciation if
 226 and only if it is a DLT scenario that matches u and x , maps the subtree of G rooted in v to
 227 a subtree of S rooted in a descendant of one child (y or z) of x , and the subtree of G rooted
 228 in w to a subtree of S rooted in a descendant of the other child of x . Thus, it follows that
 229 $p_\Sigma(u, x)$ is computed correctly.

230 Now, consider the list $p_\Delta(u, x)$. In case $x \in I(S)$, let y and z denote its children.
 231 By the pseudocode, $p_\Delta(u, x)$ consists of the k -best scores obtained by adding c_Δ to the
 232 costs present in the following multisets, where only the first one is relevant in case $x \in$
 233 $L(S)$: $\{c(v, x, j) + c(w, x, r) \mid 1 \leq j, r \leq k\}$, $\{c(v, x, j) + \text{subtree}(w, z, r) \mid 1 \leq j, r \leq k\}$,
 234 $\{c(w, x, j) + \text{subtree}(v, y, r) \mid 1 \leq j, r \leq k\}$, $\{c(v, x, j) + \text{subtree}(w, y, r) \mid 1 \leq j, r \leq k\}$,
 235 $\{c(w, x, j) + \text{subtree}(v, z, r) \mid 1 \leq j, r \leq k\}$, $\{\text{subtree}(v, y, j) + \text{subtree}(w, z, r) \mid 1 \leq j, r \leq k\}$,
 236 $\{\text{subtree}(w, y, j) + \text{subtree}(v, z, r) \mid 1 \leq j, r \leq k\}$, $\{\text{subtree}(v, y, j) + \text{subtree}(w, y, r) \mid 1 \leq$
 237 $j, r \leq k\}$ and $\{\text{subtree}(v, z, j) + \text{subtree}(w, z, r) \mid 1 \leq j, r \leq k\}$. Observe that the lists
 238 $c(v, x)$, $c(w, x)$, $\text{subtree}(w, y)$, $\text{subtree}(v, z)$, $\text{subtree}(w, z)$ and $\text{subtree}(v, y)$ have already been
 239 computed. Thus, by the inductive hypothesis, we have that (i) $c(v, x)$ (resp., $c(w, x)$) consists
 240 of the (scores of the) k -best DLT scenarios mapping the subtree of G rooted in v (resp., w)
 241 to the subtree of S rooted in x , and (ii) $\text{subtree}(v, y)$ (resp., $\text{subtree}(w, z)$, $\text{subtree}(w, y)$ and
 242 $\text{subtree}(v, z)$) consists of the (scores of the) k -best DLT scenarios mapping the subtree of G
 243 rooted in v (resp., w , w and v) to the subtree of S rooted in some descendant of y (resp.,
 244 z , y and z). Notice that a DLT scenario maps the subtree of G rooted in u to a subtree of S

rooted in x under the constraint that the event corresponding to the matching of u and x is duplication if and only if it is a DLT scenario that matches u and x , maps the subtree of G rooted in v to a subtree of S rooted in a descendant of x (which can be x itself), and the subtree of G rooted in w to a subtree of S rooted in a descendant of x (which can be x itself). Thus, it follows that $p_{\Delta}(u, x)$ is computed correctly.

Lastly, consider the list $p_{\Theta}(u, x)$. If x is the root of S , then there does not exist a DLT scenario mapping the subtree of G rooted in u to the subtree of S rooted in x under the constraint that the event corresponding to the matching of u and x is horizontal transfer (because there is no vertex incomparable to x to whom one of the children of u should be mapped), and hence it is correct that each element $p_{\Theta}(u, x, i)$ remains with the assignment of ∞ as it was created. Now, suppose that x is not the root of S . Then, by the pseudocode, $p_{\Theta}(u, x)$ consists of the k -best scores present in the following multisets: $\{\text{subtree}(v, x, j) + \text{incomp}(w, x, r) \mid 1 \leq j, r \leq k\}$ and $\{\text{subtree}(w, x, j) + \text{incomp}(v, x, r) \mid 1 \leq j, r \leq k\}$. Observe that the lists $\text{subtree}(v, x)$, $\text{subtree}(w, x)$, $\text{incomp}(w, x)$ and $\text{incomp}(v, x)$ have already been computed. Thus, by the inductive hypothesis, we have that (i) $\text{subtree}(v, x)$ (resp., $\text{subtree}(w, x)$) consists of the (scores of the) k -best DLT scenarios mapping the subtree of G rooted in v (resp., w) to a subtree of S rooted in some descendant of x (which can be x itself), and (ii) $\text{incomp}(v, x)$ (resp., $\text{incomp}(w, x)$) consists of the (scores of the) k -best DLT scenarios mapping the subtree of G rooted in v (resp., w) to a subtree of S rooted in some vertex incomparable to x . Notice that a DLT scenario maps the subtree of G rooted in u to a subtree of S rooted in x under the constraint that the event corresponding to the matching of u and x is horizontal transfer if and only if it is a DLT scenario that matches u and x , maps the subtree of G rooted in one of the children of u (v or w) to a subtree of S rooted in a descendant of x (which can be x itself), and the subtree of G rooted in the other child of u to a subtree of S rooted in a vertex incomparable to x . Thus, it follows that $p_{\Sigma}(u, x)$ is computed correctly. \blacktriangleleft

S3 Assigning Probabilities

Proof of Lemma 3. We will verify a stronger property than the one in the statement of the lemma: For every vertex u in the Gene tree G , it holds that

$$\sum_{x, i: (u, x, i) \in V(\mathcal{H})} w(u, x, i) = 1.$$

Before we verify this property, observe that when u is a leaf, then $c(u, x, 1) = 0$ for the unique vertex x that is compatible with u , and $c(u, x, i) = \infty$ (which means that $D(u, x, i) = \emptyset$ and hence $w(u, x, i) = 0$) for any other pair (x, i) . Thus, the stronger property implies the correctness of the weaker statement regarding leaves.

To prove the (stronger) property above, we use induction. In the basis, u is the root of the Gene tree G . Then, we have that $\sum_{x, i: (u, x, i) \in V(\mathcal{H})} w(u, x, i) = \sum_{i \in \{1, 2, \dots, k\}} w(r, i) = 1$, and therefore the property holds. Now, suppose that u is not the root of G , and that the property holds for each of its ancestors. Let v be the parent of u in \mathcal{H} . Then, we have that

$$\begin{aligned} \sum_{x, i: (u, x, i) \in V(\mathcal{H})} w(u, x, i) &= \sum_{x, i: (u, x, i) \in V(\mathcal{H})} \sum_{y, j: (v, y, j) \in D(u, x, i)} w(v, y, j) \\ &= \sum_{y, i: (v, y, i) \in V(\mathcal{H})} w(v, y, i) = 1. \end{aligned}$$

Here, the first equality followed directly from the definition of weights. The second equality followed from the fact that each hypernode (v, y, i) (for any y and i) that has positive weight

is derived from exactly one hypernode (u, x, j) (for some specific x and j). (However, each hypernode (u, x, j) can be used to derive several hypernodes (v, y, i) .) The last equality followed from the inductive hypothesis. This completes the proof. ◀

S4 Deferred Text

Fig. 1 demonstrates the second stage of the $((\{HT\}, \text{red}, \text{True}), (\{S, D, HT\}, \text{black}, \text{False}))$. The figure is an example of one possible reconciliation, and here we seek a vertex of the Gene tree the has a one child with lot of red-to-red horizontal transfers below it, and the other with a lot of black events. For convenience, we marked a vertex of the species tree, but it actually is the gene tree vertex which was mapped to it in the reconciliation.

S4.1 Stage 3.1: Coloring the Species and Gene Trees (Optional)

Our framework can be used for searching *different* evolutionary patterns. *Some* sought patterns might involve a phenotype of the species. Therefore, we assume that (as a part of the input), each leaf of the Species tree S *might* have a color (red or black) to represent its phenotype. In this paper, we use colors as *habitat identifiers*. More precisely, we say that a leaf $\ell \in L(S)$ has an *environmental habitat* (soil, water, plants, etc.) if $\text{black}(\ell) = 1$ and $\text{red}(\ell) = 0$, and a *living habitat* (human, animal) if $\text{black}(\ell) = 0$ and $\text{red}(\ell) = 1$.

The goal here is to assign to each vertex $x \in V(S)$ a color $\text{red}(x), \text{black}(x) \in \mathbb{N}_0$ as explained below.²

Computational of the Assignment. Recall that as part of the input, we are given a function $\text{colors} : L(S) \rightarrow \Upsilon$ where $\Upsilon = \{\text{red}, \text{black}\}$. Initially, for each leaf $x \in L(S)$, we define $\text{red}(x) = 1$ and $\text{black}(x) = 0$ if x is red (i.e. $\text{colors}(x) = \text{red}$), and $\text{red}(x) = 0$ and $\text{black}(x) = 1$ otherwise. Now, in postorder, for each internal vertex $x \in V(S)$ with children y and z , compute: $\text{red}(x) = \text{red}(y) + \text{red}(z)$, and $\text{black}(x) = \text{black}(y) + \text{black}(z)$.

Additionally, we use $\sigma : L(G) \rightarrow L(S)$ to color the vertices of the Gene tree G as follows. Initially, for each leaf $u \in L(G)$, we define $\text{red}(u) = 1$ and $\text{black}(u) = 0$ if $\text{colors}(\sigma(u)) = \text{red}$, and $\text{red}(u) = 0$ and $\text{black}(u) = 1$ otherwise. Now, in postorder, for each internal vertex $x \in V(S)$ with children y and z , compute: $\text{red}(x) = \text{red}(y) + \text{red}(z)$, and $\text{black}(x) = \text{black}(y) + \text{black}(z)$.

S4.1.1 Colored Pattern

When providing a pattern P with colors, we need to define the sought pattern. First, we will need some definitions,

Definitions. For each node $(u, x, i) \in V(\mathcal{H})$ define $\text{red}(u, x, i) = \text{red}(x)$, $\text{black}(u, x, i) = \text{black}(x)$, $\text{totalL}(u, x, i) = \text{red}(x) + \text{black}(x)$. We define $\text{Pr}[\text{red}] = \frac{\text{number of red leaves in } S}{|L(S)|}$, and, similarly $\text{Pr}[\text{black}] = \frac{\text{number of black leaves in } S}{|L(S)|}$.

For a node $(u, x, i) \in V(\mathcal{H})$, we say the it is “mostly red” if it holds that

$$\sum_{r=\text{red}(u, x, i)}^{\text{totalL}(u, x, i)} \binom{\text{totalL}(u, x, i)}{r} \cdot \text{Pr}[\text{red}]^r \cdot \text{Pr}[\text{black}]^{\text{totalL}(u, x, i)-r} \leq p,$$

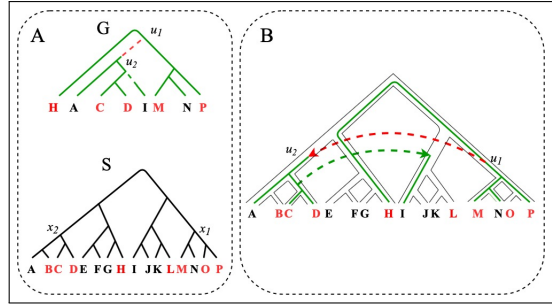
² The standard notation \mathbb{N}_0 denotes $\mathbb{N} \cup \{0\}$ where \mathbb{N} is the set of natural numbers.

and is “mostly black” if it holds that

$$\sum_{r=\text{red}(u,x,i)}^{\text{totalL}(u,x,i)} \binom{\text{totalL}(u,x,i)}{r} \cdot \Pr[\text{red}]^r \cdot \Pr[\text{black}]^{\text{totalL}(u,x,i)-r} \geq 1 - p,$$

where p is a predefined probability threshold. Intuitively, the formulas above are measuring how much a node in the hypergraph is a mapping between a Gene tree vertex $u \in V(G)$ and a Species tree vertex $x \in V(S)$, such that x is rooting a homogeneous (with respect to the colors) subtree. As the value p is smaller, we restrict the subtrees we define as “mostly red” (resp. “mostly black”) to be more homogeneous.

For each $\text{EV} \in \{\text{S}, \text{D}, \text{HT}\}$, $\text{color} \in \{\text{red}, \text{black}\}$ and $\text{distance} \in \{\text{True}, \text{False}\}$, the pattern $(\text{EV}, \text{colors}, \text{distance})$ is a hypernode (u, x, i) with children (v, y, j) and (w, z, r) (by children we mean that $(u, x, i) \in \text{D}(v, y, j)$ and $(u, x, i) \in \text{D}(w, z, r)$, as defined on Section 5.2), such that both (v, y, j) and (w, z, r) are “mostly color”.



■ **Figure S5** An illustration of (HT, red, False) pattern

For example, Figure S5 demonstrates the pattern (HT, red, False) inside a reconciliation (part B). The colors of the species are the colors of the text, this is $\text{color}(B) = \text{color}(C) = \text{color}(D) = \text{color}(H) = \text{color}(L) = \text{color}(M) = \text{color}(O) = \text{color}(P) = \text{red}$ and $\text{color}(A) = \text{color}(E) = \text{color}(F) = \text{color}(G) = \text{color}(I) = \text{color}(J) = \text{color}(K) = \text{color}(N) = \text{black}$. We illustrate one optimal solution for the input (part A). Note that this is not the hypergraph, see Figure S2 for more details about the representation. The bold red horizontal transfer edge is an edge that satisfies our requirements: a calculation for being “mostly red” for $(u_1, x_1, 1)$ is $\sum_{r=3}^4 \binom{4}{r} \cdot \left(\frac{1}{2}\right)^r \cdot \left(\frac{1}{2}\right)^{4-r} = 0.3125 < 0.5$ and for $(u_2, x_2, 1)$ is the same. Thus, for $p = 0.5$ the hypernode representing the match between u_1 and x_1 will be considered as a pattern satisfying our requirements. On the other hand, the black bold horizontal transfer is not satisfying the requirements, and will not be reported as interesting. In all of our results, we use $p = 0.05$.

S4.2 Stage 3.2

For each defined pattern $P = (\text{EV}, \text{color}, \text{distance})$, let $\text{counter}_P : V(G) \rightarrow \mathbb{R}^+$ be a counter, initialized by 0. For each $u \in I(G)$ let v, w be its right and left children. Let $\mathcal{I}_u = \{(u, x, i) \in V(\mathcal{H}) : (u, x, i) \text{ is marked as interesting with respect to } P\}$. This is, for each vertex $x \in V(S)$ and $i \in \{1, \dots, k\}$ such that $(u, x, i) \in V(\mathcal{H})$ was marked as interesting in stage 1 with respect to pattern P , $(u, x, i) \in \mathcal{I}_u$. Let

$$\text{counter}_P(u) = \text{counter}_P(v) + \text{counter}_P(w) + \sum_{(u,x,i) \in \mathcal{I}_u} w(u, x, i)$$

where $w(u, x, i)$ are the probabilities assigned in Section 5.2. Intuitively, for each vertex $u \in V(G)$ we calculate its probability to be interesting, with respect to the patterns we defined. In order to avoid a bias, we normalise each value by the number of edges in the subtree root in the vertex times k , which is an upper bound on the number of possible patterns in all the solutions. That is, for each vertex $u \in V(G)$ and pattern P , let $\text{counter}_P(u) = \frac{\text{counter}_P(u)}{|E(G_u)| \cdot k}$.

S5 Methods

S5.1 Simulator and Algorithm Implementation

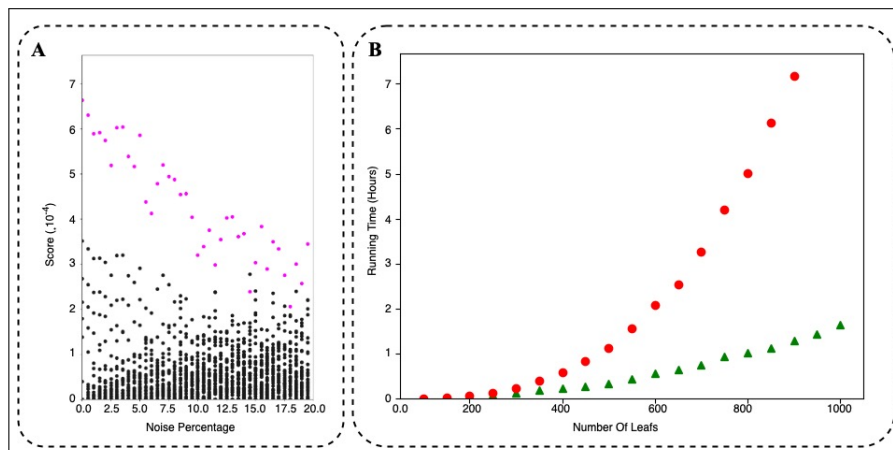
The simulator and our algorithm were implemented in Python, using NetworkX package, DendroPy [?] and ETE Toolkit [?]. Visualisation of the trees and plots were created using Matplotlib and Seaborn tools.

In order to further test our approach, we generate a random binary tree. The generation of a random binary tree is done in a top down manner: A list of vertices is maintained, initialized by the root. In each step, we choose randomly the leftmost or the rightmost item of the list, pop it, add two vertices (its children) to the right of the list. In order to unbalance the tree, we choose randomly 25% of the vertices, and connect the subtree rooted in them to a random leaf. First we duplicate this random tree and call one copy G and the other S . The function $\sigma : L(G) \rightarrow L(S)$ is the matching between each leaf in G to its copy in S , and the function $\text{color} : L(S) \rightarrow \{\text{red}, \text{black}\}$ is a random binary function. All of the simulations use the pattern $(\{\text{HT}\}, \text{red}, \text{True})$, in which we seek a subtree that is enriched in red-to-red horizontal transfer events. (For more details, see Section 5.3). In order to create the pattern in the random trees, we pick a random vertex $u \in V(G)$, and change the function $\sigma : L(G) \rightarrow L(S)$ for vertices $w \in G_u$ in a way that will create a Horizontal transfer event. Assume we pick a vertex $w \in G_u$, and we want to make it a Horizontal transfer event. Let $L(S_x)$ denote the copy of $L(G_w)$ (the leaves of the subtree rooted in w) in the Species tree, thus the function σ maps each leaf of G_w to its copy in the leaves of S_x . In order to create a horizontal transfer in w , we need to find a vertex $y \in V(S)$ such that y and x are incomparable, and change the mapping of the leaves of G_w to the leaves of S_y . This creates a Horizontal Transfer in the DLT-reconciliation with high probability. Recall that in addition, we want to make those planted HT events red-to-red events, thus we search for “mostly red” vertices when choosing which vertex we want to make interesting and where the horizontal transfers will be mapped to.

S5.2 Noise

We tested our tool on the same random data with an additional noise factor on horizontal transfers and colors. Each noise level represents the number of random horizontal transfer edges and random colors of the species. 0% means no horizontal transfer edges were added except those of the planted pattern, and no change of the function $\text{color} : L(S) \rightarrow \{\text{red}, \text{black}\}$ was made, and 100% means that all of the edges were randomly changed into horizontal transfer and all of the species colors were randomly picked again. The horizontal transfers modifications were applied by changing the mapping between a Gene tree leave and a corresponding Species tree leave, i.e. σ . The colors noise was applied by changing the colors of the leaf of S randomly.

Fig. S6.A demonstrates the advantage of our approach across different noise levels. It is a demonstration on a random phylogenetic simulation, with a planted pattern. First, we constructed a random phylogenetic Species and Gene trees with 600 leaves and one planted



■ **Figure S6** (A) The scores of the vertices in difference noise level on the input. Purple vertex is a pre-planted vertex, obeys the sought pattern (B) Running time of the naive and efficient algorithms. Green triangles encodes measurement for the efficient version and red circles corresponds to the naive version.

pattern (marked in purple in Fig. S6.A). (see Appendix S5.1 for more details). For each noise level between 0% to 20% we constructed the hypergraph. For all experiments, we used $k = 100$, minimum size of subtree to be 0.1% of all edges and $c_{\Delta} = c_{\Theta} = 1$. Each noise level is an average of 50 random choices for the same amount of random horizontal transfers and color changes. The scores are as defined in Section 5.3.

We found that the score of the planted vertex is higher than that of any other vertex at lower noise levels, and it decreases as the noise level increases. Note that the additional noise increases the false positive founding. That is, when adding more noise, the vertices that are computed to be interesting are not necessarily those we seek. These findings support the claim that our method is able to find a pattern within a noisy data. The results indicate a high level of reliability when testing the engine on real biological data, which is often very noisy.

S5.3 Running Time

In orders to demonstrate the practicality of the theoretical improvements presented in Section 5.1, we compare the running time of the naive algorithm and the efficient version, by constructing hypergraphs for different inputs. We picked random binary trees with 100 to 1000 leaves. For each number of leaves, we randomly picked 10 trees, and constructed the corresponding hypergraphs in both methods, the naive and the efficient.

Fig. S6.B summarizes the running time test results. The green triangles are an average of the time measured for the efficient version of the algorithm, and the red circles are an average of the time measured for the naive version of the algorithm.

We found out that as we increase the number of leaves, the differences between the naive and the efficient algorithms becomes significant.

References