

## ***An efficient and accurate distance based algorithm to reconstruct tandem duplication trees***

*Olivier Elemento<sup>1,2</sup> and Olivier Gascuel<sup>1</sup>*

<sup>1</sup> *Département d'Informatique Fondamentale et Applications, LIRMM, 161 rue Ada, 34392, Montpellier,*

<sup>2</sup> *IMGT, the international ImMunoGeneTics database <http://imgt.cines.fr>, Laboratoire d'ImmunoGénétique Moléculaire (LIGM), Université Montpellier II, UPR CNRS 1142 , 141, rue de la Cardonille, 34396, Montpellier cedex 5, France*

Received on April 8, 2002; accepted on June 15, 2002.



GO BACK

CLOSE FILE

# Abstract

*The problem of reconstructing the duplication tree of a set of tandemly repeated sequences which are supposed to have arisen through unequal recombination, was first introduced by Fitch (1977, Genetics, 86, 93–104), and has recently received a lot of attention. In this paper, we describe DTSCORE, a fast distance based algorithm to reconstruct tandem duplication trees, which is statistically consistent. As a cousin of the ADDTREE algorithm (Sattath and Tversky, 1977, Psychometrika, 42, 319–345), the raw DTSCORE has a time complexity in  $O(n^5)$ , where  $n$  is the number of observed repeated sequences. Through a series of algorithmic refinements, we improve its complexity to  $O(n^4)$  in the worst case, but stress that the refined DTSCORE algorithm should perform faster with real data. We assess the topological accuracy of DTSCORE using simulated data sets, and compare it to existing reconstruction methods. The results clearly show that DTSCORE is more accurate than all the other methods we studied. Finally, we report the results of DTSCORE on a real dataset.*

**Supplementary information:** <http://www.lirmm.fr/w3ifa/MAAS/>

**Contact:** [gascuel@lirmm.fr](mailto:gascuel@lirmm.fr)

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

# Introduction

Tandemly repeated DNA sequences consist of two or more adjacent copies of a stretch of DNA, together forming an array of consecutive repeated sequences. They arise from tandem duplication, in which a sequence of DNA (which may itself contain several repeats) is transformed into two adjacent copies. Since copies are then free to evolve independently and are likely to undergo additional mutation events, they become approximate copies over time. Unequal recombination is widely viewed as the predominant biological mechanism responsible for the production of tandemly repeated sequences (Ohno, 1970; Smith, 1976; Fitch, 1977; Jeffreys and Harris, 1981; Elemento *et al.*, 2001, 2002).

Gene duplication (in tandem or not) is one of the most important evolutionary mechanisms for producing genes with novel functionalities (Ohno, 1970). Unravelling the pattern of duplications that has given rise to these duplicated genes, i.e. reconstructing their duplication history, would be very beneficial to the scientists studying their function and evolution.

The problem of reconstructing the duplication history of tandemly repeated sequences was first considered by Fitch (1977). It has not received much attention until recently, probably due to the lack of available repeated sequence data, and also because there has been no dedicated computer program available to reconstruct duplication histories from sequence data.

Indeed, the reconstruction strategy presented in (Fitch, 1977), and also in (Elemento *et al.*, 2001, 2002), consists in using traditional phylogenetic

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

reconstruction algorithms to reconstruct (near) optimal trees, without restriction to duplication trees, and to check whether these best trees are valid duplication trees. While this strategy is fast and simple, it is not guaranteed at all to find a duplication tree, as illustrated in (Fitch, 1977).

However, several specific algorithms which take into account the ordered nature of tandemly repeated sequences have been recently described in the literature. In (Benson and Dong, 1999; Tang *et al.*, 2001; Jaitly *et al.*, 2001), the authors provide reconstruction algorithms based on the parsimony principle, but these are limited either to the special case where only single copy duplications (i.e. when the duplicated fragment always contains a single basic copy) occurred, or to the analysis of short tandem repeats (minisatellites). In Elemento *et al.* (2001, 2002), we presented the DTEXPLORE algorithm, which performs an exhaustive exploration of the space of duplication trees, and selects the best ones according to the parsimony criterion. Although this procedure is guaranteed to find the optimal trees, it is relatively slow and limited to small data sets, i.e.  $n < 15$ , where  $n$  is the number of taxa.

In (Tang *et al.*, 2001), the authors proposed a distance based method, called the WINDOW method, that uses an agglomeration scheme similar to UPGMA (Sneath and Sokal, 1973) and NJ (Saitou and Nei, 1987). The WINDOW method has the advantage of being very simple and fast, but the cost function used to judge potential duplications supposes that the sequences followed a molecular clock mode of evolution. It is well known that some multigene families, such as the immunoglobulin genes (Ota and Nei, 1994) for example, do

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

not follow this mode of evolution: some duplicated genes become pseudogenes in the course of evolution and then evolve at a much faster rate than the other copies.

In this paper, we describe an efficient and accurate distance based algorithm, called DTSCORE, to deal with the problem of reconstructing tandem duplication trees. This algorithm belongs to the scoring method family (Barthélemy and Guénoche, 1991), whose most famous representative is the popular ADDTREE (Sattath and Tversky, 1977) algorithm. It is statistically consistent (Felsenstein, 1978; Atteson, 1999), i.e. the quality of the reconstruction improves as the sequences get longer, and can be used with sequences that do not follow the molecular clock mode of evolution. As a distance based method, our algorithm can use sophisticated sequence evolution models, such as those taking into account heterogeneous rates of evolution among sites (Golding, 1983), and obviates some fallbacks of the parsimony criterion: inconsistency, long branch attraction (Felsenstein, 1978). In its basic form, DTSCORE is an  $O(n^5)$  algorithm, but we provide here two algorithmic refinements to lower its time complexity to  $O(n^4)$  in the worst case, and show how the refined DTSCORE should perform even better with real data. The computational efficiency of this method makes it suitable for heavy statistical reliability analysis of the reconstructed histories, such as the bootstrap procedure (Felsenstein, 1985). Using simulations, we show that DTSCORE has better topological accuracy than every other tested reconstruction method, even when the molecular clock hypothesis is respected.

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

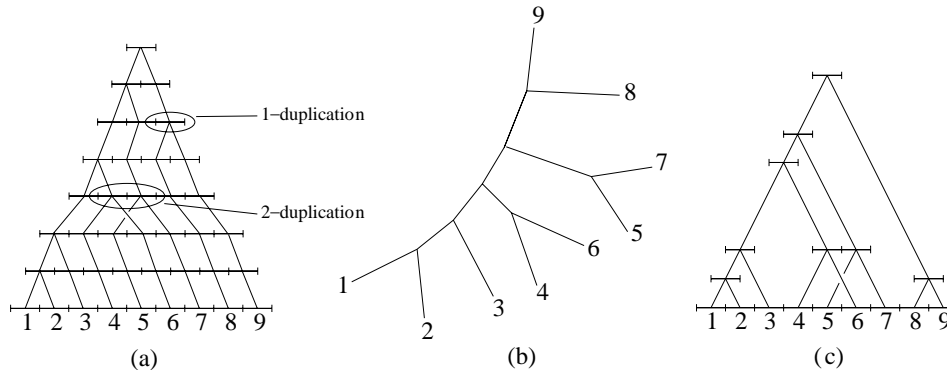
Acknowledgements

References



GO BACK

CLOSE FILE



**Fig. 1.** (a) duplication history, (b) duplication tree, and (c) partially ordered duplication history.

## Duplication model

The duplication model we assume in this paper, introduced by [Fitch \(1977\)](#) in the first place, is closely based on the unequal recombination process, which we suppose to be the only evolutionary mechanism (except point mutations) acting on the duplicated sequences.

Let  $\mathcal{O} = (1, 2, \dots, n)$  be the ordered set of sequences representing a locus, as it can be observed now. Initially containing a single copy, the locus has grown through a series of consecutive duplications. As shown in [Fig. 1a](#), a duplicated fragment may only contain a single repeat, in which case we say that

[Abstract](#)

[Introduction](#)

[Duplication model](#)

[An algorithm for ...](#)

[Refining the ...](#)

[Results](#)

[Conclusion](#)

[Acknowledgements](#)

[References](#)



GO BACK

CLOSE FILE

the duplication event is a 1-duplication. When the duplicated fragment contains 2, 3 or  $k$  repeats, we call the duplication event a 2-, 3- or  $k$ -duplication.

Under this duplication model, a duplication history is a rooted tree with  $n$  labelled and ordered leaves, in which internal nodes correspond to duplication events. In a real duplication history (Fig. 1a), the time intervals between consecutive duplications are completely known, and the internal nodes are ordered from top to bottom according to the moment they occurred in the course of evolution. However, in the absence of a molecular clock mode of evolution (which is most often the case), both the order between the duplication events of two different lineages and the root location are impossible to recover from the sequences. In this case, we are only able to infer a *duplication tree* (Fig. 1b), i.e. an unrooted phylogeny with ordered leaves, whose topology is compatible with at least one duplication history.

Recovering the position of the root can sometimes be achieved, through the use of rooting procedures (outgroups, midpoint, etc.), and creates a *partially ordered duplication history* (Fig. 1c), i.e. a duplication history in which the duplication events are partially ordered. In [Elemento et al. \(2001, 2002\)](#), we show that rooting a duplication tree is different from rooting a phylogeny: the root of a duplication tree necessarily lies on the tree path between the most distant repeats on the locus; moreover, it can be shown ([Gascuel et al., 2002](#)) that, assuming that the duplication trees have uniform distribution, the expected number of possible positions for the root is only equal to 2. For example, if a 2-duplication happens immediately after the initial 1-duplication

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

in a duplication history, the root must be located ‘above’ the 2-duplication, and there is only one possible root location.

A *cherry* is a pair of leaves  $\{g, d\}$  separated by a single internal node in a duplication tree  $T$ . The outcome of a terminal  $k$ -duplication in  $T$  defines what Tang *et al.* (2001) called a *window*. A window is a set  $(g_1, g_2, \dots, g_k, d_1, d_2, \dots, d_k)$  of  $2k$  adjacent copies in  $\mathcal{O}$ , such that every  $\{g_i, d_i\}$  with  $1 \leq i \leq k$  is a cherry in  $T$ . For example, the windows in Fig. 1 are (1,2), (4,5,6,7) and (8,9). In (Tang *et al.*, 2001; Elemento *et al.*, 2001, 2002), the authors described a very simple window-based algorithm for determining whether a given phylogeny  $T$  with ordered leaves is a duplication tree or not. This algorithm, which we called PDH (for PossibleDuplicationHistory, since it initially worked on rooted phylogenies), is a recursive procedure which progressively reduces  $T$  by deleting (agglomerating) the cherries that belong to recognized windows. The cherries (windows) are deleted until: (a)  $T$  has been reduced to a tree with 2 or 3 leaves, meaning that it constitutes a valid duplication tree, (b) it cannot go further, in which case  $T$  cannot be a duplication tree.

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

# An algorithm for reconstructing tandem duplication histories

We describe here the DTSCORE algorithm to reconstruct a duplication tree from the matrix of pairwise evolutionary distances between sequences. DTSCORE follows the same agglomerative process as PDH, i.e. it reconstructs a duplication tree by re-creating and agglomerating the cherries that belong to recognized windows. In this section, we present an initial version of DTSCORE, and describe its basic principles and properties. In the following section, we introduce two algorithmic improvements to decrease its computational time complexity.

## *The DTSCORE algorithm*

Let  $\mathcal{O} = (1, 2, 3, \dots, n)$  be the initial ordered set of copies, and  $D$  the distance matrix between the  $n$  copies in  $\mathcal{O}$ . The first step of the DTSCORE algorithm consists in computing the score for every pair of copies, and storing each score in an  $n \times n$  matrix  $S$ . As in the ADDTREE algorithm, computing the score of each pair relies on the four-point condition (Zarestkii, 1965; Buneman, 1974) and can be summarized as follows: if we consider a quartet of different copies  $\{i, j, k, l\}$  and  $D$  as a tree distance among copies, the smallest sum among  $(D(i, j) + D(k, l))$ ,  $(D(i, k) + D(j, l))$ , and  $(D(i, l) + D(j, k))$  defines the two external pairs. For example, if  $(D(i, j) + D(k, l))$  is the smallest sum, then the external pairs are  $\{i, j\}$  and  $\{k, l\}$ . However, in practice,  $D$  is only close to a

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

tree distance. If  $(D(i, j) + D(k, l))$  is the smallest sum, then  $\{i, j\}$  and  $\{k, l\}$  are good candidates as external pairs in the quartet  $\{i, j, k, l\}$ . The score of a pair  $\{i, j\}$ , denoted  $S(i, j)$ , is then simply the number of times the pair  $\{i, j\}$  is seen as a good candidate.

As in PDH, DTSCORE does not operate on single pairs, but on windows. At each step of DTSCORE, the window  $W = (g_1, \dots, g_k, d_1, \dots, d_k)$  whose fitness is optimal is selected to be agglomerated. The fitness of a window of  $2k$  adjacent copies may be defined as the average score over the  $k$  pairs forming the window. In this case, we have the following formula:

$$AVG(W) = \frac{1}{k} \sum_{i=1}^k S(g_i, d_i)$$

The problem with this window fitness function is that the low score of poorly supported pairs can be offset by several other well supported pairs within the same window. To overcome this problem, a simple solution is to take the minimum score over every pair covering the window. In this case, the window fitness function becomes:

$$MIN(W) = \min_{i=1}^k S(g_i, d_i)$$

We will see how this window fitness function is used as the basis for an efficient refinement to the DTSCORE algorithm.

- Abstract
- Introduction
- Duplication model
- An algorithm for ...
- Refining the ...
- Results
- Conclusion
- Acknowledgements
- References



⏪	⏩
◀	▶
GO BACK	
CLOSE FILE	

Finally, it is also possible to use both the *MIN* and *AVG* fitness functions together to form what we call the *MINAVG* fitness function. In this fitness function, the *MIN* function is used first, and the *AVG* function is only used to decide between  $W$  and  $W'$ , when  $MIN(W) = MIN(W')$ .

Not all entries of the scoring matrix  $S$  need to be calculated, since we only need to consider pairs that can be part of a complete window. For example, the score  $S(1, r)$ , where  $r$  is the number of copies in the running matrix, is always useless. More generally, only the scores  $S(i, i + k)$  with  $i \geq 1$ ,  $i + k \leq r$ , and  $k \leq r/2$  need to be calculated.

After selection of the optimal window, an ordered set of  $k$  nodes  $C = (c_1, \dots, c_k)$  is created, and every  $g_i$  and  $d_i$  are linked to  $c_i$  in  $T$ .  $(g_1, \dots, g_k, d_1, \dots, d_k)$  is then replaced by  $(c_1, \dots, c_k)$  in  $\mathcal{O}$ . The distance from  $c_i$  to every other copy  $p$  in  $\mathcal{O}$  is calculated in the following way:  $D(c_i, p) = [D(g_i, p) + D(d_i, p)]/2$ . The distance from  $c_i$  to  $c_j$  is given by  $D(c_i, c_j) = [D(g_i, d_j) + D(g_j, d_i) + D(d_i, d_j) + D(g_i, g_j)]/4$ .

Depending on the size of the last window that has been agglomerated, DTSCORE terminates when  $\mathcal{O}$  contains 2 or 3 copies. The DTSCORE algorithm is described in [Fig. 2](#).

Note that the branch lengths of the resulting tree are not estimated with DTSCORE, but can be obtained by least-squares methods, such as ([Gascuel, 1997](#)).

- Abstract
- Introduction
- Duplication model
- An algorithm for ...
- Refining the ...
- Results
- Conclusion
- Acknowledgements
- References



GO BACK

CLOSE FILE

## BASIC DTSCORE ALGORITHM

```
input an  $n \times n$  distance matrix  $D$ ;  
let  $S$  be an  $n \times n$  matrix;  
let  $\mathcal{O} = (1, 2, 3, \dots, n)$ ,  $r = |\mathcal{O}|$ ;  
while  $r$  is greater than 3 do  
    compute  $S(i, i + k)$  for every pair  $\{i, i + k\}$  with  $0 < k \leq r/2$ ,  $i \geq 1$ ,  
     $i + k \leq r$ ;  
    find the window  $W = (g_1, \dots, g_k, d_1, \dots, d_k)$  from  $\mathcal{O}$  with maximal  
    fitness;  
    define  $k$  new nodes  $C = (c_1, \dots, c_k)$  and link  $g_i$  and  $d_i$  to  $c_i$  ( $1 \leq i \leq k$ );  
    compute distances from  $c_i$  to every other copy  $p$  ( $p \notin C$ ) with  $D(c_i, p) =$   
     $[D(g_i, p) + D(d_i, p)]/2$   
        and between  $c_i$  and  $c_j$  with  $D(c_i, c_j) = [D(g_i, d_j) + D(g_j, d_i) +$   
         $D(g_i, g_j) + D(d_i, d_j)]/4$ ;  
    replace  $W$  by  $C$  in  $\mathcal{O}$  and  $D$ ;  
     $r \leftarrow r - k$ ;  
end while  
link the 2 or 3 remaining copies together and output  $T$ ;
```

**Fig. 2.** Basic DTSCORE algorithm.

### *Properties*

Some of the interesting properties of DTSCORE are inherited from ADDTREE. The most important one is certainly that DTSCORE is consistent, i.e. it always

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE



method (Tang *et al.*, 2001), when dealing with sequences that do not follow a molecular clock mode of evolution.

At each step, there are  $\sum_{k=1}^{\lfloor r/2 \rfloor} (r - k)$  different scores to compute. Although this number is smaller than the number of scores ADDTREE calculates at each step, it is still in  $O(r^2)$ . Computing  $S(i, j)$  is done by considering every other pair of copies  $\{y, z\}$ . Since we have  $1 \leq y < z \leq r$ , there are  $r(r - 1)/2$  pairs contributing to  $S(i, j)$ . Computing the contribution of  $\{y, z\}$  to  $S(i, j)$  is done in  $O(1)$  time, thus calculating  $S(i, j)$  takes  $O(r^2)$  time, and computing the score for every needed  $S(i, j)$  requires  $O(r^4)$  time. Supposing that we agglomerate one cherry at a time, the basic DTSCORE algorithm requires  $O(n^5)$  time and  $O(n^2)$  space (the size of  $S$  and  $D$ ).

**Abstract**

**Introduction**

**Duplication model**

**An algorithm for ...**

**Refining the ...**

**Results**

**Conclusion**

**Acknowledgements**

**References**



**GO BACK**

**CLOSE FILE**

# Refining the DTSCORE algorithm

## *First algorithmic refinement*

If we take  $MIN$  as the window fitness function, it is often not necessary to compute every score  $S(i, i + k)$  for a given  $k > 1$ . Let  $F^*$  be the fitness of the optimal window found so far. Now consider the window starting at  $i$  and containing  $2k$  adjacent copies. We first compute the score  $S(i, i + k)$ . If  $S(i, i + k) \leq F^*$ , then it is clearly neither useful to compute the scores of the other pairs in the same window, nor to consider the fitness of the other windows that include the pair  $\{i, i + k\}$ . Therefore we can ‘jump’ to the pair  $\{i + k, i + 2k\}$ . If  $S(i, i + k) > F^*$ , we compute the score of the neighbor pairs of  $\{i, i + k\}$  and seek a complete  $k$ -window whose fitness is greater than  $F^*$ . If successful, we update  $F^*$ , otherwise we jump to the next pair as described above. Note that this refinement can also be used with the  $MINAVG$  fitness function, but we will jump to the pair  $\{i + k, i + 2k\}$  only when  $S(i, i + k) < MIN^*$ , where  $MIN^*$  is the optimal  $MIN$  fitness found so far.

This refinement modifies the total number of scores  $S(i, j)$  to be computed, but it does not improve the worst case complexity of the DTSCORE algorithm. However, in practice, it considerably reduces the number of scores  $S(i, j)$  to be computed (Table 1). Let us consider the special case where the duplication history to be reconstructed contains mostly single duplications, which often seems to be the case with real data (Fitch, 1977; Tang *et al.*, 2001; Elemento *et al.*, 2001, 2002). Suppose that DTSCORE always finds one of the  $S(i, i + 1)$

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

scores to be optimal (which is likely to be the case if the correct duplication history only contains 1-duplications). In this case, the number of scores to be calculated at each step is the sum of the following terms:  $(r - 1)$  scores  $S(i, i + 1)$ , approximately one half of  $(r - 2)$  scores  $S(i, i + 2)$ , one third of the  $(r - 3)$  scores  $S(i, i + 3)$ , and so on. This sum can also be expressed as  $\sum_{k=1}^{\lfloor r/2 \rfloor} \frac{r-k}{k}$ , and the total number of scores to be calculated in the best case is in  $O(r \log(r))$  at each step, instead of  $O(r^2)$  in the basic DTSCORE algorithm.

## *Second algorithmic refinement*

In the basic DTSCORE algorithm, computing the score  $S(i, j)$  is done from scratch and therefore always requires considering every other pair  $\{y, z\}$ . The second refinement is based on the fact that some of the scores in  $S$  do not need to be calculated from scratch. At step  $t$ , let  $(g_1, \dots, g_k, d_1, \dots, d_k)$  be the optimal window, and let  $(c_1, \dots, c_k)$  be the newly created copies. We agglomerate one cherry at a time; so let  $\{g, d\}$  be the cherry with root  $c$  currently being agglomerated. Due to this agglomeration, some of the previously computed  $S(i, j)$  scores can be updated, while some others must be computed from scratch:

- (a) When  $(i \neq g, d)$  and  $(j \neq g, d)$ ,  $S(i, j)$  can be updated by considering the contribution of  $\{g, d\}$ ,  $\{g, z\}$ ,  $\{d, z\}$  and  $\{c, z\}$ , where  $z$  is any copy  $\neq i, j, g, d, c$ . The removal of  $g$  and  $d$  induces that the contribution of  $\{g, z\}$ ,  $\{d, z\}$  and  $\{g, d\}$  may decrease  $S(i, j)$  by 1, while the addition of

- Abstract
- Introduction
- Duplication model
- An algorithm for ...
- Refining the ...**
- Results
- Conclusion
- Acknowledgements
- References



GO BACK

CLOSE FILE

$\{c, z\}$  may or may not increase  $S(i, j)$  by 1.

(b) Every  $S(c, p)$  score requires to be computed from scratch.

To analyze the improvement induced by this second refinement, we assume that the first refinement is not used. At the first step, we have to compute  $O(n^2)$  scores, and each score is computed in  $O(n^2)$  time. So, the first step has  $O(n^4)$  time complexity. At the subsequent steps, it is easily seen that each time a pair is agglomerated, we must (a) update  $O(r^2)$  scores in  $O(r)$  time, and (b) compute from scratch  $O(r)$  scores in  $O(r^2)$  time. So each non-initial step requires  $O(r^3)$  time, and the total time complexity is  $O(n^4)$ , instead of  $O(n^5)$  in the basic algorithm.

Note that this algorithmic refinement is not due to any of the duplication tree constraints. Therefore it can also be applied to the original ADDTREE algorithm.

### *Using both refinements together*

In the first refinement, we simply reduce the number of scores to be calculated. In the second one, we modify the way some of the scores are computed: if  $S(i, j)$  has been calculated at the previous step, it is updated in linear time, instead of being re-computed in quadratic time. Therefore, both refinements are complementary.

In [Table 1](#), we show the average number of scores that are calculated during a run of both versions (basic and refined) of DTSCORE, on 50

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

**Table 1.** Average (out of 50 runs) number of scores calculated by the basic and refined versions of the DTSCORE algorithm

	10	15	20	25	30	35	40	45	50
basic DTSCORE, # scores	103	337	793	1550	2637	4241	6296	8757	12467
refined DTSCORE, # scores	67	181	363	614	934	1363	1860	2379	3158
refined DTSCORE, # scores in $O(n^2)$	45	99	192	310	456	636	859	1088	1387

simulated data sets (using the method described in the next section) and for several values of  $n$ . For the refined version of DTSCORE, we show both the total number of scores that are computed and the number of scores calculated in quadratic time. These numbers clearly show that the combined refinements to the DTSCORE algorithm provide large improvements over the basic version. Moreover, assuming that 1-duplications are generally favoured over  $k$ -duplications, it is very likely that the performance increase of the refined DTSCORE algorithm will be even considerably larger with real data. On the speed performance side, the refined version of DTSCORE reconstructs a duplication tree from a 50-copies distance matrix in approximately 0.3 seconds on a 500 MHz Intel PIII machine. On the same data, the basic and the  $O(n^4)$  (only the second refinement) versions of DTSCORE reconstruct trees in 2.5 and 0.7 s, respectively. When combining both refinements, DTSCORE compares quite favourably with the FITCH  $O(n^4)$  program (Felsenstein, 1989), from the PHYLIP package, which reconstructs a tree from the same distance matrix in 52 seconds, but as expected, it is far behind NJ (also from PHYLIP), which reconstruct a tree from the same distance matrix in only about 0.01 seconds.

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

# Results

## *Simulation protocol*

We compare the topological accuracy of the 5 following distance methods : WINDOW (Tang *et al.*, 2001), NJ (Saitou and Nei, 1987), and DTSCORE using the different window fitness functions, for  $8 \leq n \leq 26$ . We do not compare DTSCORE to the the other reconstruction methods presented in (Benson and Dong, 1999; Tang *et al.*, 2001; Jaitly *et al.*, 2001), since they are restricted either to 1-duplications, or to short repeated sequences. Since there was no available WINDOW method implementation at the time we were writing this paper, we use our own implementation. For each  $n$ , we generate 1000 duplication trees and their associated data set, and count the number of times each method reconstructs the full topology of the trees. We study both the cases in which the generated data sets follow, and do not follow the molecular clock mode of evolution.

Simulated data sets are generated using the following procedure. First a duplication tree  $T$  with no branch lengths is randomly uniformly generated using the method described in (Gascuel *et al.*, 2002). We randomly value the branches using the same method as in (Kuhner and Felsenstein, 1994) and obtain a totally ordered duplication history that satisfies the molecular clock assumption (as in Fig. 1(a)). The branch length expectation in this history is about 0.035 mutations per site. To obtain non-molecular clock trees, we independently multiply every branch by  $1 + 0.8 X$ , where  $X$  is drawn from

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

an exponential distribution with parameter value 1.0. To obtain molecular clock trees, we simply multiply each branch by 1.8. The maximum pairwise divergence within the trees produced in this way is in the range [0.1079; 0.2809], and seems in accordance with the real data we studied in (Elemento *et al.*, 2001, 2002).

The SEQ-GEN (Rambault and Grassly, 1997) program is then used to produce a 1000bp-long nucleotide multiple alignment from the generated tree, using a F84 model of substitution (Felsenstein and Churchill, 1996). A distance matrix is computed from this multiple alignment using the same model of substitution and, finally, each algorithm is ran against this distance matrix.

### *Performance comparison*

The results are displayed in Table 2 for the simulations with molecular clock (MC), and in Table 3 for the simulations without molecular clock (NO-MC). They clearly indicate that the DTSCORE algorithm performs much better than both NJ and the WINDOW method, in both simulations. In both the MC and NO-MC simulations, the 3 window fitness functions perform similarly in terms of recovering the correct tree, for every  $n$  considered, but *MINAVG* provides slightly better results overall. Note that the other benefit of using *MINAVG* is that it makes it possible to use the first refinement described above, whereas using *AVG* does not allow it.

As expected, the WINDOW method performs better in the MC case than in the NO-MC one, but it is just slightly better than NJ in the MC case. The

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

**Table 2.** Molecular clock (MC) duplication trees. Number of duplication trees (out of 1000) correctly reconstructed by the various tested methods

	8	10	12	14	16	18	20	22	24	26
WINDOW method	819	736	627	453	275	188	129	114	99	57
Neighbor-Joining	815	746	625	399	229	159	97	64	50	44
DTSCORE <i>MINAVG</i>	859	804	727	540	374	299	215	196	170	137

performances of NJ and WINDOW become very poor as the number of copies increases, especially in the NO-MC case (for  $n = 26$ , the WINDOW method is only able to recover 2 duplication trees out of 1000 in the NO-MC experiment). The poor results of the NJ algorithm are easily explained by the fact that it explores the space of phylogenies, without restriction to duplication trees. When  $n$  increases, its chances of finding a duplication tree rapidly decrease, since the proportion of duplication trees among phylogenies becomes very small (Elemento *et al.*, 2002). Due to its window fitness function, the WINDOW method is likely to suffer from the same weaknesses as UPGMA, which was shown to perform worse than NJ, even with sequences that follow the molecular clock mode of evolution (Saitou and Nei, 1987).

### *Application to the TRGV genes*

We also apply DTSCORE to the 9 tandemly repeated genes of the TRGV locus (Lefranc *et al.*, 1986), whose duplication tree has been reconstructed using

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

**Table 3.** Non molecular clock (NO-MC) duplication trees. Number of duplication trees (out of 1000) correctly reconstructed by the various tested methods

	8	10	12	14	16	18	20	22	24	26
WINDOW method	740	484	389	294	126	54	20	6	6	2
Neighbor-Joining	903	724	597	365	235	137	90	54	36	34
DTSCORE <i>MINAVG</i>	922	824	713	491	397	273	224	159	135	111

DTEXPLORE (Elemento *et al.*, 2001, 2002). Using the same data, DTSCORE finds the same duplication tree as DTEXPLORE. In (Elemento *et al.*, 2001, 2002), we showed that this reconstructed duplication tree has strong biological support, for two reasons: first it successfully predicts a polymorphism that occurs in the human population; second, we obtain the same tree when using traditional phylogenetic reconstruction programs on the same data, but without restriction to duplication trees. We show in the same paper that this is not likely due to chance, since only 3.5% of phylogenies are also duplication trees for 9 copies.

As in (Elemento *et al.*, 2001, 2002), we use the bootstrap procedure (Felsenstein, 1985) to assess the reliability of this duplication tree. We generate 1000 pseudosamples, apply DTSCORE to each of these pseudosamples, and then compute the bootstrap proportion of every branch in the initial duplication tree. The bootstrap proportions are similar as those previously calculated. However DTSCORE ‘crunches’ the 1000 pseudosamples in less than 3 seconds on a 500 MHz PIII machine, while it takes DTEXPLORE more than 13 hours

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

on a 5-nodes cluster (of nearly identical machines) to process the same amount of data.

*Abstract*

*Introduction*

*Duplication model*

*An algorithm for ...*

*Refining the ...*

**Results**

*Conclusion*

*Acknowledgements*

*References*



**GO BACK**

**CLOSE FILE**

# Conclusion

The DTSCORE algorithm for reconstructing duplication trees we present in this paper performs much better at retrieving the correct duplication tree than any other method we studied. We introduce two refinements to reduce its time complexity, making it suitable for computationally intensive tasks, such as bootstrap analysis, or analysis of large data sets. A DTSCORE implementation in the C language is available on our web page. The DTDRAW program, available at the same address can be used to draw the (rooted) duplication trees obtained from the DTSCORE algorithm. Although both DTSCORE and DTEXPLORE reconstruct the same duplication tree on the TRGV data set, a direction for further research could be to compare the topological accuracy of both algorithms, as well as the effectiveness of both parsimony and distances approaches for duplication trees.

*Abstract*

*Introduction*

*Duplication model*

*An algorithm for ...*

*Refining the ...*

*Results*

*Conclusion*

*Acknowledgements*

*References*



GO BACK

CLOSE FILE

# Acknowledgements

We thank Andy McKenzie and Marie-Paule Lefranc for their helpful comments on the preliminary versions of the manuscript.

*Abstract*

*Introduction*

*Duplication model*

*An algorithm for ...*

*Refining the ...*

*Results*

*Conclusion*

*Acknowledgements*

*References*



GO BACK

CLOSE FILE

## References

- Atteson,K. (1999) The Performance of Neighbor-Joining Methods of Phylogenetic Reconstruction. *Algorithmica*, **25**, 251–278.
- Barthélemy,J. and Guénoche,A. (1991) *Trees and proximity representations*. Wiley.
- Benson,G. and Dong,L. (1999) Reconstructing the duplication history of a tandem repeat. In Lengauer,T., Schneider,R., Bork,P., Brutlag,D., Glasgow,J., Mewes,H.-W. and Zimmer,R. (eds), *Proceedings of the Intelligent Systems in Molecular Biology ISMB'99*. pp. 44–53.
- Buneman,P. (1974) A note on metric properties of trees. *J. Combin. Theor.*, **17**, 48–50.
- Elemento,O., Gascuel,O. and Lefranc,M. (2001) Reconstruction de l'histoire de duplication de gènes répétés en tandem. *Actes des Journées Ouvertes Biologie Informatique Mathématiques*. pp. 9–11.
- Elemento,O., Gascuel,O. and Lefranc,M. (2002) Reconstructing the duplication history of tandemly repeated genes. *Mol. Biol. Evol.*, **19**, 278–288.  
[MEDLINE Abstract](#)
- Felsenstein,J. (1978) Cases in which parsimony or compatibility methods will be positively misleading. *Syst. Zool.*, **27**, 401–410.
- Felsenstein,J. (1985) Confidence limits on phylogenies: an approach using the bootstrap. *Evolution*, **39**, 783–791.
- Felsenstein,J. (1989) PHYLIP—PHYLogeny Inference Package. *Cladistics*, **5**, 164–166.

Abstract

Introduction

Duplication model

An algorithm for ...

Refining the ...

Results

Conclusion

Acknowledgements

References



GO BACK

CLOSE FILE

- Felsenstein,J. and Churchill,G. (1996) A hidden Markov model approach to variation among sites in rate of evolution. *Mol. Biol. Evol.*, **13**, 93–104. [MEDLINE Abstract](#)
- Fitch,W. (1977) Phylogenies constrained by cross-over process as illustrated by human hemoglobins in a thirteen-cycle, eleven amino-acid repeat in human apolipoprotein A-I. *Genetics*, **86**, 623–644. [MEDLINE Abstract](#)
- Gascuel,O. (1997) Concerning the NJ algorithm and its unweighted version, UNJ. In Mirkin,B., McMorris,F., Roberts,F. and Rzhetsky,A. (eds), *Mathematical Hierarchies and Biology, DIMACS Series in Discrete Mathematics and Theoretical Computer Science*. American Mathematical Society, Providence, pp. 149–170.
- Gascuel,O., Hendy,M., Jean-Marie,A. and McLachlan,S. (2002) The combinatorics of tandem duplication trees. In preparation.
- Golding,G. (1983) Estimates of DNA and protein sequence divergence: an examination of some assumptions. *Mol. Biol. Evol.*, **1**, 125–142. [MEDLINE Abstract](#)
- Jaitly,D., Kearney,P., Lin,G. and Ma,B. (2001) Methods for reconstructing the history of tandem repeats and their application to the human genome. *J. Comput. Syst. Sci.*, In press.
- Jeffreys,A. and Harris,S. (1981) Processes of gene duplication. *Nature*, **296**, 9–10.
- Jukes,T. and Cantor,C. (1969) *Mammalian Protein Metabolism, Chapter Evolution of protein molecules*. Academic Press, pp. 21–132.

[Abstract](#)

[Introduction](#)

[Duplication model](#)

[An algorithm for ...](#)

[Refining the ...](#)

[Results](#)

[Conclusion](#)

[Acknowledgements](#)

[References](#)



GO BACK

CLOSE FILE

- Kimura,M. (1980) A simple model for estimating evolutionary rates of base substitutions through comparative studies of nucleotide sequences. *J. Mol. Evol.*, **16**, 111–120. [MEDLINE Abstract](#)
- Kuhner,M. and Felsenstein,J. (1994) A simulation comparison of phylogeny algorithms under equal and unequal evolutionary rates. *Mol. Biol. Evol.*, **11**, 459–468. [MEDLINE Abstract](#)
- Lefranc,M., Forster,A., Baer,R., Stinson,M. and Rabbitts,T. (1986) Diversity and rearrangement of the human T-cell rearranging genes: nine germ-line variable genes belonging to two subgroups. *Cell*, **45**, 237–246. [MEDLINE Abstract](#)
- Lefranc,M., Forster,A. and Rabbitts,T. (1986) Rearrangement of two distinct T-cell gamma-chain-variable-region genes in human DNA. *Nature*, **319**, 420–422. [MEDLINE Abstract](#)
- Ohno,S. (1970) *Evolution by Gene Duplication*. Springer, New York.
- Ota,T. and Nei,M. (1994) Divergent evolution and evolution by the Birth-and-Death process in the immunoglobulin VH gene family. *Mol. Biol. Evol.*, **11**, 469–482. [MEDLINE Abstract](#)
- Rambault,A. and Grassly,N. (1997) Seq-Gen: an application for the Monte Carlo simulation of DNA sequence evolution. *Comput. Appl. Biosci.*, **13**, 235–238. [MEDLINE Abstract](#)
- Saitou,N. and Nei,M. (1987) The neighbor-joining method: a new method for reconstructing phylogenetic trees. *Mol. Biol. Evol.*, **4**, 406–425. [MEDLINE Abstract](#)

[Abstract](#)

[Introduction](#)

[Duplication model](#)

[An algorithm for ...](#)

[Refining the ...](#)

[Results](#)

[Conclusion](#)

[Acknowledgements](#)

[References](#)



GO BACK

CLOSE FILE

- Sattath,S. and Tversky,A. (1977) Additive similarity trees. *Psychometrika*, **42**, 319–345.
- Smith,G. (1976) Evolution of repeated DNA sequences by unequal crossover. *Science*, **191**, 528–535. [MEDLINE Abstract](#)
- Sneath,P. and Sokal,R. (1973) *Numerical Taxonomy*. W.H. Freeman and Company, pp. 230–234.
- Tang,M., Waterman,M. and Yooseph,S. (2001) Zinc finger gene clusters and tandem gene duplication. In El-Mabrouk,N., Lengauer,T. and Sankoff,D. (eds), *Proceedings of RECOMB 2001*. pp. 297–304.
- Zaretskii,K. (1965) Constructing a tree based on a set of distances among its leaves. *Upekki Math. Nauk.*, **20**, 90–92. In Russian.

[Abstract](#)

[Introduction](#)

[Duplication model](#)

[An algorithm for ...](#)

[Refining the ...](#)

[Results](#)

[Conclusion](#)

[Acknowledgements](#)

[References](#)



GO BACK

CLOSE FILE