

# DAMBE7: New and Improved Tools for Data Analysis in Molecular Biology and Evolution

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## Abstract

DAMBE is a comprehensive software package for genomic and phylogenetic data analysis on Windows, Linux, and Macintosh computers. New functions include imputing missing distances and phylogeny simultaneously (paving the way to build large phage and transposon trees), new bootstrapping/jackknifing methods for PhyPA (phylogenetics from pairwise alignments), and an improved function for fast and accurate estimation of the shape parameter of the gamma distribution for fitting rate heterogeneity over sites. Previous method corrects multiple hits for each site independently. DAMBE's new method uses all sites simultaneously for correction. DAMBE, featuring a user-friendly graphic interface, is freely available from <http://dambe.bio.uottawa.ca> (last accessed, April 17, 2018).

**Key words:** phylogenetics, bioinformatics, missing distance imputation, rate heterogeneity over sites.

DAMBE is for descriptive and comparative sequence analysis (Xia 2013, 2017) featuring a graphic, user-friendly, and intuitive interface, and available free for Windows, Linux, and Macintosh computers at [dambe.bio.uottawa.ca](http://dambe.bio.uottawa.ca). DAMBE7 represents a major upgrade with many new functions including new sets of significance tests for position weight matrix and Gibbs sampler for de novo characterization of sequence motifs. I outline three functions most relevant to molecular evolution and phylogenetics. A supplemental file (Using\_New\_Functions.docx) is included in [Supplementary Material](#) online.

## Imputing Missing Distance and Phylogeny Simultaneously

This function is implemented for building large trees of phages which often 1) are too diverged to build a multiple sequence alignment (MSA), and 2) do not share homologous genes/sites (e.g., S3 and S4 in [fig. 1a](#)). This is also true for many transposons from which one cannot get a meaningful MSA, and researchers are limited to align the sequences against the consensus (Gallus et al. 2015). One can do pairwise alignment among most of the sequences and compute their distances, but some sequence pairs do not share homologous sites and need to have their distances imputed from those computable distances. This allows one to build trees and likely will revolutionize phage taxonomy which is not based on phylogeny.

This distance-imputation function is currently missing. MEGA (Kumar et al. 2016) does not impute missing distances, neither does PHYLIP's DNADIST (Felsenstein 2014). Fitch and Kitsch programs can estimate missing distances if a user tree is provided.

For a distance matrix with  $N$  missing distances (parameters), DAMBE searches the tree space and parameter space to find a tree with the  $N$  parameters that minimizes

$$RSS = \sum \frac{[D_{ij} - E(D_{ij})]^2}{D_{ij}^m} \quad (1)$$

where  $D_{ij}$  and  $E(D_{ij})$  are the observed and patristic distance, and  $m$  is typically 0, 1, or 2. [Figure 1c](#) is the phylogenetic tree reconstructed from the distance matrix in [figure 1b](#) with two shaded distances missing.

For sequences such as that in [figure 1a](#), DAMBE will compute all computable distances and impute the missing distances. When bootstrapping/jackknifing is used, distance imputation and phylogeny inference are done for each resampled data. One may also have unaligned sequence data and use PhyPA (Xia 2016) to build phylogenetic trees and obtain bootstrap/jackknife support.

There are cases where a unique solution cannot be obtained. For example, when a missing distance is for two sister taxa (e.g., bonobo and chimpanzee in [fig. 1b and c](#)), we can find minimum RSS but the solution for missing  $D_{ij}$  is not unique, with different values for missing  $D_{ij}$  resulting in the same minimum RSS. The patristic distances  $D_{p,bonobo,i}$  and  $D_{p,chimpanzee,i}$  where  $i$  stands for other species, do not change when  $x_1$  changes to  $x_2$  ([fig. 1d](#)), so  $D_{p,bonobo,i}$  and  $D_{p,chimpanzee,i}$  will remain the same, and so does RSS in [equation \(1\)](#). DAMBE use the midpoint distance in such cases.

## Bootstrap/Jackknife Support for PhyPA

For each pair of sequences, we can obtain a vector  $\mathbf{S}$  of 10  $N_{ij}$  values (number of pairs with nucleotide  $i$  in one sequence and  $j$

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estimated number of substitution for a site. Applying equations (3) and (4) to data from the three sites (fig. 1g) independently will generate one inapplicable case for site 2 (under  $D_{IE}$  in fig. 1g with IE for independent estimation). We can estimate all  $D_i$  and  $\kappa$  simultaneously by maximizing the following log-likelihood:

$$\ln L = \sum_{i=1}^N \{N_{s,i} \ln[E(P_i)] + N_{v,i} \ln[E(Q_i)] + N_{l,i} \ln[1 - E(P_i) - E(Q_i)]\} \quad (5)$$

where  $N$  is the number of sites,  $N_{s,i}$  and  $N_{v,i}$  and  $N_{l,i}$  are recorded number of transitional, transversional difference and no difference from pairwise comparisons along the tree between nodes on each side of each branch at site  $i$ . SE generates no inapplicable cases ( $D_{SE}$  in fig. 1g) and leads to the second improvement in using more realistic models such as F84 or TN93 instead of the K80 correction in GZ-gamma (Gu and Zhang 1997). SE distance is used in MEGA (Tamura et al. 2004) and DAMBE (Xia 2009) which includes MLCompositeF84 and MLCompositeTN93 for F84 and TN93 models, respectively, but has never been used in estimating the shape parameter.

## Supplementary Material

Supplementary data are available at *Molecular Biology and Evolution* online.

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