

Tree signature of gene families

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Abstract

Genome-scale data sets routinely comprise thousands of genes from hundreds of species, which tell us complementary aspects of their evolution — the evolution of the species is a mosaic of the evolutionary history of its composing genes. Several methods have been developed to visualise the similarity between histories told by each gene, under certain circumstances. This visualisation and comparison is essential to detect outliers, clusters of similar genes, and possibly description of the reason for disagreement between them. However the circumstances under which we can quantify this disagreement relies on being able to map the leaves of one gene tree to another — in practice this is equivalent to removing the effects of paralogy, and working only with single copy genes or inferred orthologous groups. Here we present a way of comparing whole gene families, even when they have vastly different sizes (due to duplications, losses) and few overlapping species. The idea is to describe gene family trees within a coordinate system imposed by a set of possible species trees, what we call their tree signature. Gene families can not be compared directly, but we use the fact that those with a similar history (of duplications, losses, coalescences) should have resembling signatures.

A fundamental unit in phylogenomic analysis is the gene (or genomic locus), and the most detailed evolutionary history of a gene includes the duplication and loss events by which an ancestral locus gave rise to all observed diversity of loci and genes — the so-called gene family, of which a single copy gene is a particular case. Each gene family will then be described by all the loci within a species connected through an common ancestor (i.e. inferred to be

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homologous to each other). And their histories are expected to differ from one another due to the coalescent, duplications, losses, and other biological events. Therefore, even for the simplest case of single copy genes, we might still observe distinct patterns of their presence and absence amongst species, and conflicting inferred phylogenies due to the coalescent, lateral transfers, and the very inference process. The accumulation of large-scale phylogenomic data sets leads to new challenges of comparison and visualisation of distinct gene families, as well as of detecting the influence of each genomic region into the overall phylogenomic signals. Many state-of-the-art phylogenetic methods take gene trees as input, and model the incongruence among them in various ways, based on parametric and non-parametric assumptions (Mirarab and Warnow, 2015; Vachaspati and Warnow, 2015). Many of these methods require the input gene trees to have at most one representative from each species (e.g. by requiring the user to first run an orthology inference pipeline). This limitation is hard to circumvent since almost all tree distance measures (required to measure incongruence between two trees) assume that the same leaves are present on both trees.

There has been several attempts at describing phylogenetic trees as vectors of features, suitable for statistical comparison, such as Leigh et al. (2008, 2011); Susko et al. (2006); Narechania et al. (2016); Nye (2011); Yoshida et al. (2015); Lewitus and Morlon (2015); Kendall and Colijn (2016); Colijn and Plazzotta (2018). There are also a few methods that rely on pairwise tree distance matrices, which could then be projected into a new coordinate system.

Unsupervised learning algorithms accept one of two forms of input: a design (also called feature) matrix X of size $n \times p$ (n samples with p dimensions each), or a dissimilarity matrix D of size $n \times n$ describing the distances between each pair of samples. Given D , one can project the samples into a feature space for further analysis (using multidimensional scaling, for instance). However, this projection needs to be recalculated if new samples arise. Our method, on the other hand, allows for disentangling the acquisition of sample gene trees and their projection, since their feature space can be described without resorting to the whole set of existing sample trees. This can become particularly relevant when the number of sample gene trees exceeds largely the number of reference species trees.

Visualisation and comparison of gene trees has been increasingly recognised as a way to objectively partition phylogenetic signal and to detect potential sources of heterogeneity (Gori et al., 2016; Jombart et al., 2017; Huang et al., 2016). So far all these methods rely on pairwise tree distance matrices, which implies that only uniquely labelled trees can be compared (with the potential exception of Kendall et al. (2018)). However in many cases we cannot or prefer not

to decide beforehand the orthologous groups. In these cases we must work with the so-called multi-labelled trees (or mul-trees, for short), which are trees with potentially more than one leaf with same label (labelled by the same species, in our case). At the same time, dissimilarity matrices are not the only input for classification algorithms, and describing samples through a coordinate system can have advantages.

There are many new algorithms thanks to big data, and our data sets are also increasing, therefore we can make use of their novelties if we write our problem as a big data one. **to fill in something** This analysis can also help in ‘gene shopping’, i.e. when only genomic regions with desired properties are selected (Smith et al., 2018). On the other hand, we might be concerned if a certain selection of genes can be responsible for a bias in the results.

Each gene family tree is represented by a set of features, and may contain paralogs or missing species. Each gene family can be represented by several trees, all sharing same pattern of missing/duplicate species, as in Bayesian posterior distributions. (However for testing purposes we might prune individual trees from a gene family.)

A “gene family” and a “cluster” will usually be used interchangeably, although we know that several gene families with their sets of trees may cluster together etc. The term “cluster” will be preferred for the resulting statistic or observation in general, and not to the underlying process it tries to capture. “gene family” will be used to a set of trees that should always be clustered together (never be split between clusters).

The features are distance measures to a set of common, full reference trees. The reference trees are species trees, and are full (or complete) in the sense that must have all species under analysis (even if missing from some gene family).

The selection of ‘reference’ species trees follow the same rationale behind centroidQR (Jeon, Park, and Rosen 2001; Park, Jeon, and Ben Rosen 2003), pivot-based indexing, or landmark-based manifolds in machine learning: instead of comparing all gene family trees with each other using a predefined tree distance, we first compare them to a potentially smaller number of ‘landmark’ (species) trees. However there is an important difference: in our case there may be very few, if any, dissimilarities that can be calculated between arbitrary gene family trees with several leaves with same species label (e.g. paralogs), or with no species in common. On the other hand there are several tree distances available that can cope with gene-species tree pairs – and the species trees should have all species present.

If we are only interested in a few alternative hypothesis, let’s say a particular branch/node,

then most distances fail since they give equal weight to all distances (since we compare gene trees directly). OTOH by using anchoring sptrees we can "weight" these hypotheses by their representativity in the reference sptrees (minimal case is to use just two sptrees, as "only" dimensions in the eigenbasis).

At the same time, choosing just "a few" sptrees allows our matrix to be lower dimensional than a full pairwise distance. This becomes more evident when 1) gene families are much larger than sptrees (more leaves), and 2) many samples from many genefams are analysed (e.g. 1M trees per family).

The idea is that although we may lose a lot of resolution when comparing two gene family trees directly (assuming such comparison can be accomplished), we may have higher resolution [signal] by comparing each gene family to a species tree. The difference lies in the number of species in common: when comparing two gene families G_1 and G_2 representing respectively n_1 and n_2 species (over possibly N species), they will have in the worst case only $\max(0, n_1 + n_2 - N) \leq \min(n_1, n_2)$ — where $\min(n_1, n_2)$ is the worst case comparison between G_1 or G_2 and the species tree.

1 Methods

The gene family trees represent orthogroups or root HOGs [ref], that is, a tree describing all sequences assumed to share a common ancestral sequence (including paralogs, or several individuals from the same population). These trees are the input to the algorithm and may have been estimated by any phylogenetic method — the algorithm is agnostic to the source of disagreement (and therefore to the reason for the multiple leaves with same species label) or to the inference procedure. The reference trees represent possible species trees, and must be on the same set of all species (i.e. all species must be present in all reference trees). The set of reference trees should capture the variability between gene trees with respect to the set of distances used to describe them. Therefore a good choice would be a set of optimal species trees for the most dissimilar sets of gene families, although here we usually limit ourselves to a few species trees inferred from a single set of gene families, with further randomisation in a few cases. It is important to notice that the reference species trees are not restricted to the optimal ones (under some notion of optimality) and do not need to include all optimal species trees. However having good candidates for the species trees will help interpreting the gene trees

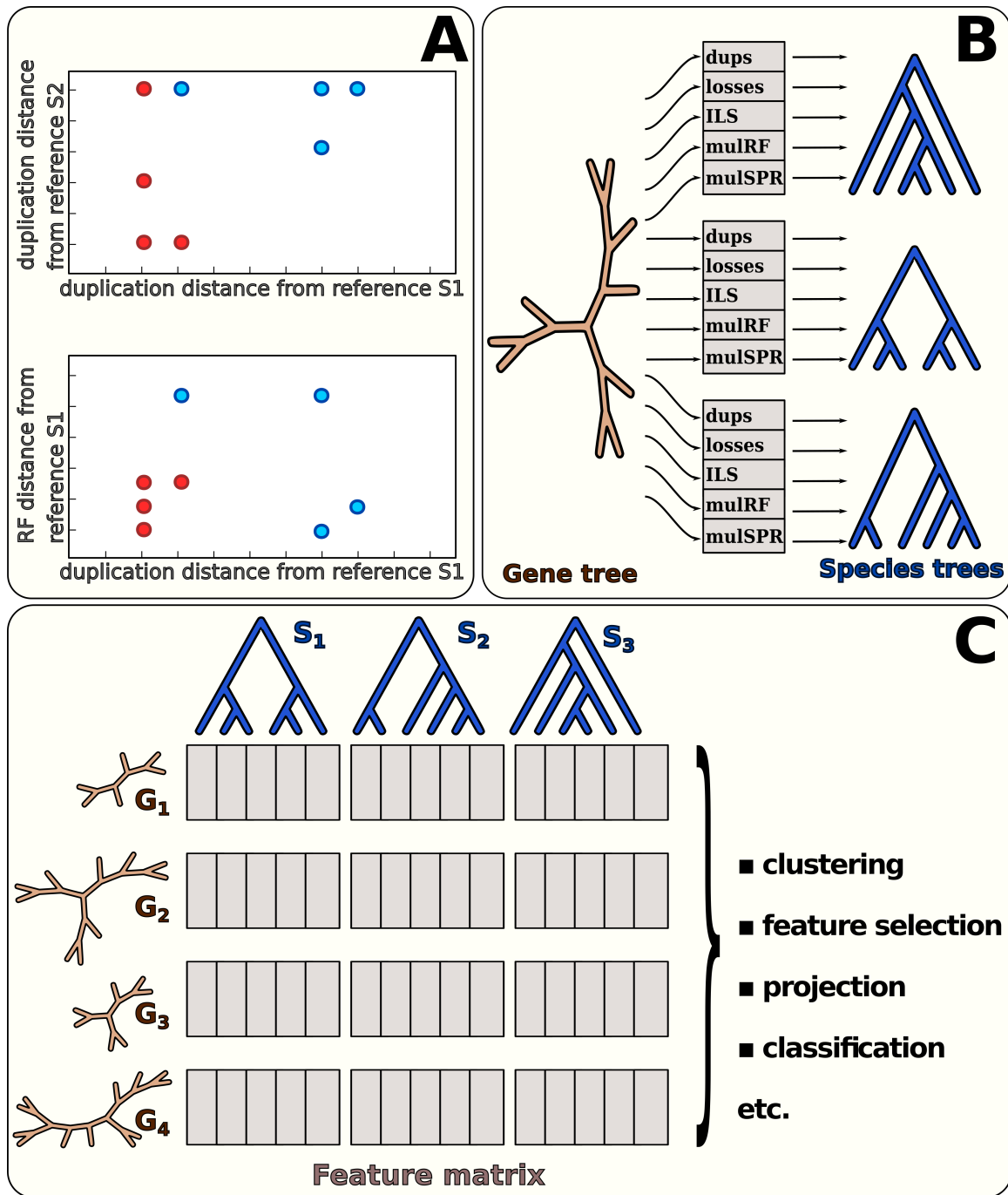


Figure 1: Schematic representation of the tree signal calculation. In panel A we show two simple cases for a sample of 8 gene family trees: at the top we compare each gene tree to two distinct reference (species) trees using the minimum number of duplications (duplication distance), and at the bottom we compare all sample gene trees to a single reference tree, but using two distinct metrics — the Robinson-Foulds (RF) distance and the duplication distance. Both comparisons provide little information in isolation, but when combined allow for distinguishing the two groups of gene families (represented by distinct colours). Panel B shows how the tree signal of a single gene family tree can be calculated, given a set of species trees and a set of distances. Notice that currently we work with unrooted gene trees and rooted species trees. In panel C we show that once we have the tree signal from each gene family, then we can create a feature matrix (‘design matrix’) which can be used in downstream analyses.

in terms of them. The gene trees are assumed to be unrooted since the basic phylogenetic inference models can't infer the root location, but our method can be easily adapted for rooted gene family trees. The reference species trees are rooted, although some distances disregard this information. The reference species trees are fixed beforehand, but once they are set they can be used to create the “tree signal” of any gene family online, as long as all species present in the gene family are represented in the reference species trees.

describe the vector

$$v(t_j, T) = \{d_i(t_j, T) \forall T \in T, i = (dups, loss, ils, RF, SPR)\} \forall j = 1 \dots k \quad (1)$$

i.e. the spectral signature of gene tree t_j is the set of combinations of distances i and reference trees T in a specific order. In the simplest case, a single distance and a single tree could be used, as e.g. their RF distance to a point estimate of their species tree. This would lead to a one-dimensional spectral signature, which may not be able to discriminate well different gene trees. A natural extension is then to use more reference trees, in such a way that gene trees now can be closer to one reference or another, or to use more distances, that will describe distinct ways in which the gene trees relate to the reference.

1.1 Distances

We implemented several gene-species tree distances, in particular the reconciliation-based ones available in `iguenomu`, the multi-labelled tree version of the Robinson-Foulds distance called `mulRF` [citation], and two new distances based on the the same ‘extended’ species tree from the `mulRF` distance, namely `mulSPR` and `mulHdist`. All distances utilise the topological information only, neglecting branch lengths. Although we refer to them as ‘distances’ they are in fact dissimilarity measures, and not true distance metrics since they do not satisfy the symmetry condition. The three reconciliation-based distances implemented are the minimum number of duplications, minimum number of losses, and minimum number of deep coalescences (also called ancestral polymorphisms or incomplete lineage sortings), and are based on the LCA mapping between gene tree and species tree nodes. Since they originally work on rooted gene trees, we try all possible gene rootings and store the minimal distance among all possibilities — the species tree is rooted, however.

The other three distances are based on the concept of an ‘extended’ species tree, which

replaces each leaf from the species tree by a multifurcation with all leaves from the gene family tree mapping to this species (leaf) [\[citation\]](#). The resulting extended species tree and the gene family tree will have thus a one-to-one mapping between leaves. The mulRF distance is then just the (unrooted) Robinson-Foulds distance between these trees. The mulSPR and the mulHdist, equivalently, are just the SPR and Hdist distances between the gene family tree and the extended species tree: the SPR distance is the approximation described in [\[citation\]](#), and the Hdist is the total cost of matching each edge from the gene tree to its optimal counterpart on the species tree (it has its name since we use the Hungarian method for solving this assignment problem). This matching is also used by the SPR algorithm to find the smallest disagreement split [\[citation\]](#). The Hdist represents therefore the minimum number of leaves in disagreement per edge, summed over all edges. If the gene tree is not multi-labelled (i.e. all leaves map to distinct leaves on the species tree) then the mulSPR and the mulHdist correspond to the SPR and Hdist distances implemented in [\[citation\]](#). These distances neglect the species tree root location, treating it as unrooted.

1.2 Normalisation

Since we are comparing gene family trees with different numbers of leaves, species, and leaves per species, we must rescale the distances to a common range. For all implemented distances, lower and upper bounds can be found, but in practice they are too permissive and therefore we resort to randomisation to find tight bounds for the distances. This is achieved by, for each gene family t and set of reference species trees T , after calculating the distances $d_i(t, T)$ for all distances i and species trees T , generate a new set of random species trees τ and calculate the distances to these trees. We implemented two independent normalisations, that are concatenated into the vector of tree signals: the p-value distance and the MinMax rescaled distance. The ‘p-value’ distance $p_i(t, T)$ counts the fraction of species trees in total (i.e. amongst both randomised τ and reference T) presented a distance as small as the observed:

$$p_i(t, T) = \frac{\sum_{k \in \{\tau, T\}} I(d_i(t, k) \leq d_i(t, T))}{|\tau| + |T|} \quad (2)$$

where $I(x)$ is the indicator function of event x . The MinMax distance $m_i(t, T)$ is the original

distance rescaled to the zero-one interval:

$$m_i(t, T) = \frac{d_i(t, T) - \text{Min}_i}{\text{Max}_i - \text{Min}_i} \quad (3)$$

where Min_i and Max_i are, respectively, the minimum and maximum distances observed among both $d_i(t, T)$ and $d_i(t, \tau)$ for distance i .

The vector is thus

$$v(t_j, T) = \{\{p_i(t_j, T), m_i(t_j, T)\} \forall T \in T, i = (\text{dups}, \text{loss}, \text{ils}, \text{RF}, \text{SPR})\} \text{ for all } j = 1 \dots k \quad (4)$$

1.3 Choice of reference trees

Once the distances (dissimilarity measures in fact) and the reference trees are defined, we can calculate the signature of each gene tree independently. The more distances are used the more we may discriminate between the gene trees, and therefore we can implement and use as many measures as possible — remembering that there are just a few that can be used in general for a gene tree/species tree pair. However the choice of the reference trees may affect our ability to distinguish between gene trees, since our rationale is that gene trees can be compared in terms of the species trees they support according to each biological phenomenon. Given N species, the number of possible rooted reference trees is $r(N)=(2N-3)!!$ which already exceeds 10^7 even for $N=10$. However, in practice we don't need that many reference trees since many of them will not be supported by any gene tree in the sample. Ideally our set of reference trees is then all species trees that can be supported by at least one gene tree in the sample. That is, if there is a distance measure i and gene tree t s.t. $d_i(t, T') < \epsilon(i, t)$ then T' should be added to the list of reference trees (where $\epsilon(i, t)$ is a small, arbitrary value in the distribution of distances d_i over all possible species trees given t). Since finding such trees T' can be challenging as well, a good strategy seems to be to find trees that summarise the information from subsets of genes from the sample. One example is to use methods that incorporate uncertainty and therefore output sets of species trees instead of finding a single point estimate (De Oliveira Martins, Mallo, and Posada 2016). Notice that even random trees might be at distinct distances from two given gene trees, but this distinction depends also on the discriminatory power of the distance measure. Also, we expect that by using collections of gene trees in the reference tree search instead of each gene tree we reduce the number of possible species trees, since small, incomplete gene trees are not informative in the sense that

they favour equally a large number of species trees (not necessarily close to other gene trees).

Notice that this relies on knowing the set of gene trees in advance, which somehow weakens our argument for continuous update, but in practice we hope that a broad choice of reference trees (by using not only the ‘optimal’ ones) can alleviate this problem. *[needs rephrasing]*

2 Results

We tested this model using two simulation scenarios and one real data set. The simulations include both uniquely-labelled trees, to allow for comparison with traditional pairwise distance-based methods, as well as genome-level simulation scenarios, leading to mul-trees.

For the first simulation scenario, starting from a random tree T_0 on n leaves, we applied a series of consecutive SPR branch swapping, storing all resulting trees $T_i (0 \leq i \leq N)$. As a result we know that T_i and T_{i-1} disagree by only one SPR, T_i and T_{i-2} by two SPRs, etc., neglecting cases where the branch swappings cancel each other out. Therefore we can use their relative location in this series (the ‘SPR chain’) as an indicator of their dissimilarity. We collected them into 4 sets of 10 consecutive trees each to serve as our sample gene trees, separated by y trees – some of which were used as reference trees. To test the effect of missing data we randomly removed leaves from each sample tree, such that trees belonging to the same ‘group’ (i.e. consecutives in our chain of trees) have the same leaves removed. Only the sample trees have missing leaves, but not the reference trees (by design of our model). [Both the sample trees (representing gene trees) and the reference trees (representing species trees) belong to the chain, but only the sample trees have missing leaves.]

The results are shown in figure 2, where we compare the effect of using reference trees belonging to the SPR chain (i.e. similar to the sample trees in an SPR sense) or using randomly selected reference trees on the metric multidimensional scaling (MDS) projection of the trees. We can conclude that choosing carefully the reference trees (i.e. that are close to the samples) can help separating the sample gene family trees, even when these sample trees have missing data. On the other hand using random trees did not seem to compromise the overall separation between groups. In this simulation scenario all gene tree pairs can be directly compared since we do not have mul-trees (each species is uniquely represented in the gene family tree), and therefore can be compared using distance matrix-based models (Gori et al. 2016). We therefore used our library to emulate the behaviour of treeCL (Gori et al. 2016)

but using the approximate SPR distance in addition to the RF distance, normalised to account for the unequal number of leaf comparisons. Pairwise distance matrices created using both measures provided MDS coordinates comparable to our tree signal using good reference trees (results not shown).

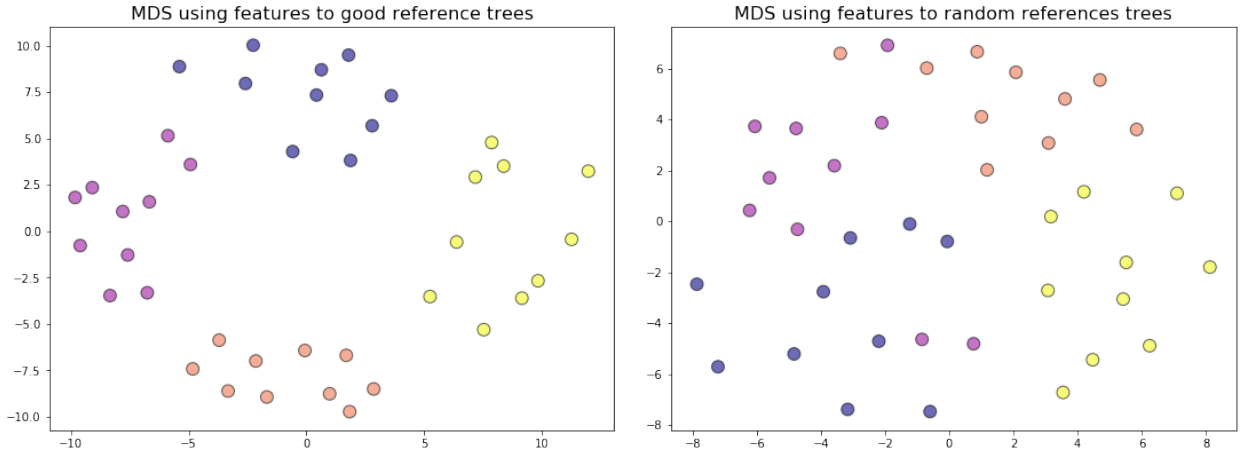


Figure 2: SPR chain simulation with missing data. On the left panel we see the MDS projections of the samples when their signal is calculated from similar reference trees, and on the right we have the projections when random species trees are used. The colors represent the four groupings (consecutive trees in the SPR chain, separated from each other by more SPR branch swappings) defined in the simulation.

The second simulation scenario was based on a genome-level simulation, where the gene trees are simulated, using the software Simphy (Mallo, de Oliveira Martins, and Posada 2015), according to the multispecies coalescent within a locus tree, which is generated under a duplication-loss model from a species tree. We generated 4 species trees with 20 species and from each species tree we simulated 50 gene families, assuming randomly between one or two genomes from each species (simulating the sampling process of populations under the coalescent). Finally we removed up to half the leaves from each gene family, and we used 116 trees similar to the true species trees as reference trees — generated by random branch swapping on the original ones.

There are many parameters controlling Simphy (from the multispecies coalescent to the birth-death process), and for most of them we let the software sample from distributions, in order to allow for heterogeneity between gene families. We tried several such combinations and show here a typical case, based on the observed distribution of leaves and species per gene family tree, and where a bit less than half the species are common to gene family pairs. The parameters chosen led to an expectation of one duplication and one loss per branch of the species tree, with 0.2 expected horizontal gene transfers per branch, and moderate levels of incomplete lineage sorting. Parameter values more extreme led to large gene families with

less than half the species represented, and with very few (less than four) species in common per pair.

The result for a typical simulation is shown in figure 3, where we see that gene families from distinct species trees can be discriminated.

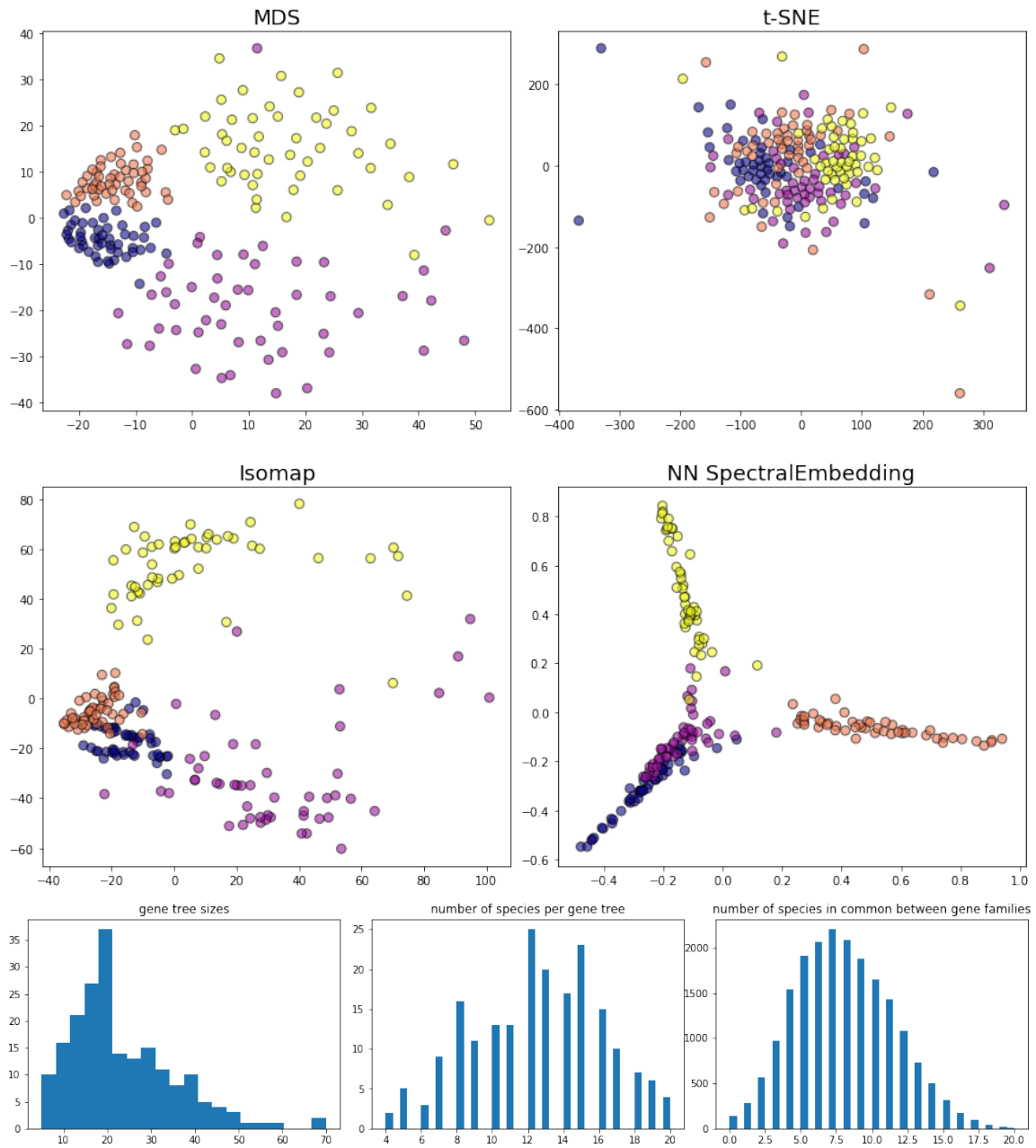


Figure 3: Typical case (simply simulation). Colors represent underlying species trees.

3 Discussion

Euclid’s first theorem states that “things which are equal to the same thing are equal to each other”. We make use of this principle to compare gene family trees, which cannot be compared

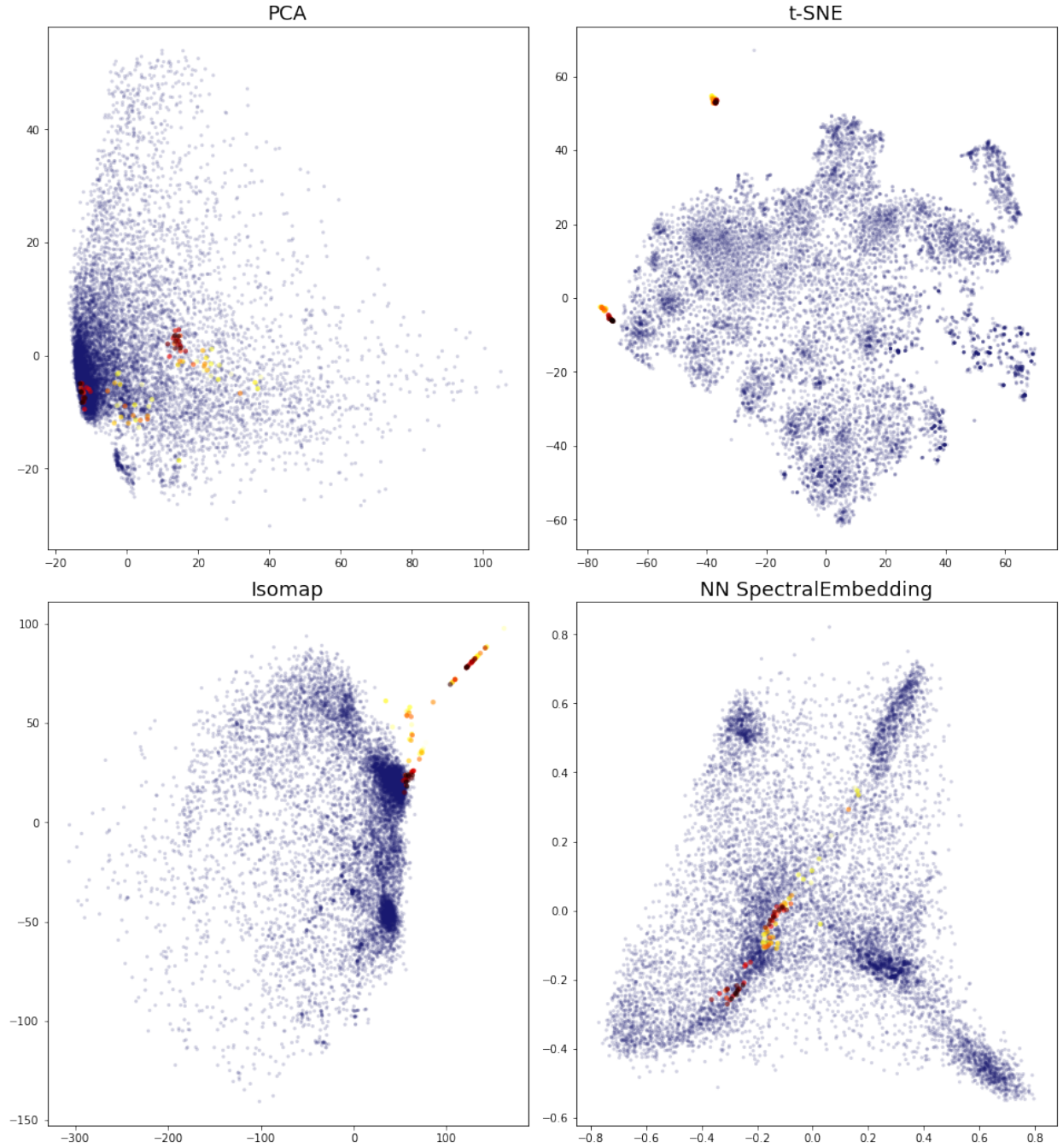


Figure 4: Fungal data set

to each other but that can be compared to the same thing – species trees. They will be equal, however, only in terms of the biologically-inspired dissimilarity measures that we can compute, and therefore we should use as many measures as possible.

We propose a method that allows for the partition/visualisation of gene families integrated with the species tree estimation.

As has been noted before (Gori et al. 2016), the SPR distance is a strong candidate for describing differences between trees in the context of gene partitioning, and here we show that indeed it can be successfully used to visualise and cluster gene families.

Our proposed algorithm is a combination of concatenation of multiple views (Zhao et al. 2017; Xu, Tao, and Xu 2013) (where each gene-species tree pair dissimilarity is a view) and centroidQR or landmark-based representation (Chen and Cai 2011; Rafailidis, Constantinou, and Manolopoulos 2017; Vin De Silva 2003), where the landmarks are sensible species trees. As such, it can be improved through recent developments on both multi-view learning and landmark-based manifolds. In special we expect more improvement over the choice of reference trees, and its relation to species tree inference. In particular we are working on an iterative version of our algorithm where the gene tree space informs species tree inference algorithms, which in turn may allow for more detailed tree spaces.

All results here employed unsupervised learning, but it is now straightforward to extend the analysis to supervised cases, where the samples may belong to e.g. posterior distributions of gene trees and each class is a gene family. Another idea is to split the gene family trees into well-supported and weakly-supported classes, to see if there is a reasonable separation between them. Since the features are associated to species trees, feature selection techniques can be interpreted in terms of the underlying species tree signals.

It is important to notice that we are not interested in the (unconditional, theoretical problem of) comparison between trees, but in the specific problem of gene tree comparison conditional on possible scenarios of species trees. This means that choosing the set of relevant species trees will influence the resulting space, and that it should be like this. `feature`, not a `bug`.

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