Application of Networking Approaches to Assess the Chemical Diversity, Biogeography, and Pharmaceutical Potential of Verongiida Natural Products

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**Supporting Information:**

**S1. Genus Reference List**

**S2. Network Considerations**

**S3. Molecular Fingerprints, Similarity and Scaffolding**

**S4. Network Optimisation and Visualisation**

**S5. Bipartite Network Compounds vs Species (Full Size)**

**S6. Physicochemical Properties of Compounds and PCA Analysis**

**S7. References**

**S1. Genus Reference List**

**Table S1:** Reference Table arranged by Genus.

|  |  |  |
| --- | --- | --- |
| **Genus** | **Total NPs** | **References** |
| *Aiolochroia* Wiedenmayer, 1977 | 15 | [[1-4](#_ENREF_1)] |
| *Anomoianthella* Bergquist, 1980 | 1 | [[5](#_ENREF_5)] |
| *Aplysina* Nardo, 1834 | 140 | [[1](#_ENREF_1), [6-65](#_ENREF_6)] |
| *Aplysinella* Bergquist, 1980 | 63 | [[66-77](#_ENREF_66)] |
| *Hexadella* Topsent, 1896 | 12 | [[78-82](#_ENREF_78)] |
| *Ianthella* Gray, 1869 | 95 | [[83-116](#_ENREF_83)] |
| *Pseudoceratina* Carter, 1885 | 232 | [[25](#_ENREF_25), [117-184](#_ENREF_117)] |
| *Suberea* Bergquist, 1995 | 115 | [[174](#_ENREF_174), [185-208](#_ENREF_185)] |
| *Verongula* Verrill, 1907 | 51 | [[1](#_ENREF_1), [6](#_ENREF_6), [22](#_ENREF_22), [38](#_ENREF_38), [209-215](#_ENREF_209)] |

**S2. Network Considerations**

The term “degree” is usually used in reference to a single node or can be considered as a mean value for the entire network. It is a count of the number of edges that are attached to a particular node. Degree usually has a strong positive correlation with the network density function (Equation 1) which can be defined as the number of edges observed in a network divided by the total number of possible edges in a network (V(V-1)/2).

|  |  |
| --- | --- |
|  | (Equation 1) |

In most cases it is observed that when the average node degree decreases in a network, so does the network density value, as there are ultimately less edges present. This is the case when threshold values (Tc) are applied to CSNs. As Tt is increased there is always a downward trend of [[216](#_ENREF_216)].

Assortativity is a measure of whether a graph contains nodes that primarily connect only to other nodes with a similar degree. Graphs can have a high density and high average degree, but this is no indication as to whether nodes with high degree are grouping together or if high degree nodes only connect to low degree nodes. A network is said to be assortative when, on average, high degree nodes are connected to other high degree nodes. This concept is intrinsically linked to the homophily principle (the concept that nodes will cluster based on having similar properties to each other) as it is an attempt at measuring the distribution of nodes within a network that are clustered due to characteristics beyond the similarity score. The value of the Degree Assortativity (Assortativity coefficient) is defined by ‘ *r* ‘ inEquation 2 and lies within the range -1 ≤ *r* ≤ 1 [[217](#_ENREF_217)].

|  |  |
| --- | --- |
|  | (Equation 2) |

Where *ki*and *kj* are the node degree values for the nodes *i* and *j* respectively, and *m* is the total number of edges in the network in question. The figure e*ij* represents edge relationships or weighting between the nodes *i* and *j*. The value δ*ij* is known as the Kronecker delta and is a function of the variables *i* and *j* as in Equation 3 [[217](#_ENREF_217)].

|  |  |
| --- | --- |
|  | (Equation 3) |

Another useful metric that is often used in network analysis and optimisation is the network modularity (*Q*), defined by Equation 4. Modularity is a description of how strongly a given network is divided into groups of highly connected nodes that are themselves not strongly connected to other modules within the network. This idea is linked to assortativity and homophily as it is often used as the tool to measure groupings within networks, particularly in the process of clustering.

|  |  |
| --- | --- |
|  | (Equation 4) |

Modularity optimised clustering is assigned in this study using the default Gephi cluster method, otherwise referred to as the Louvain algorithm [[218](#_ENREF_218)]. It is measured as a function of the classes that each node is placed into using this method. These classes are represented by *ci* and *cj* in Equation 4, where each class is defined as an integer ranging from 1 to *nc* and are held to account by the Kronecker delta of Equation 3 [[217](#_ENREF_217)].

The average clustering coefficient (ACc) is a global network metric that is related to the idea of modularity and graph density. The ACc is a probability measure regarding the number of triangular groups that are created within a network. Thus, if a node N1 is connected to two nodes N2 and N3, the ACc value indicates the probability that there will also be a connection between the nodes N2 and N3 creating a triangular group, and thus contributing towards a more densely interconnected network. Clustering coefficients are first considered on a local scale where the local clustering coefficient of a single node (Cc) is defined by Equation 5 [[217](#_ENREF_217)].

|  |  |
| --- | --- |
|  | (Equation 5) |

As in Equation 2, *ki* refers to the degree of the node *i*, but the value *Ni* is also used, which is the number of edges that exist between the direct neighbours of the node *i*, thereby forming a triangular structure with the node *i* and two directly adjoining neighbours. This same concept can be applied to consider the average clustering coefficient of the network as a whole, where ACc is the mean of the clustering coefficients of each node in the network.

**S3. Molecular Fingerprints, Similarity and Scaffolding**

Organic molecules, such as the natural products addressed in this current study, are often displayed as topographical networks of atoms, where the 3D nature of the compounds is implied. From a computational perspective however, compounds can be modelled or represented as either 2D or 3D entities. In the latter, there is a much larger amount of data quantified for theoretical molecules than in 2D illustrations. Clearly, as compound libraries get larger, the method chosen to represent compound features begins to play a larger role in the efficiency of interrogating these libraries. For this reason, all compound representations in this work are 2D global representations due to the relative simplicity and lower computational requirements of 2D models. The encoding of all the molecular structures considered in this work has been performed using SMILES codes, which is a commonly used system that allows for the representation of organic molecules in line notation and is highly compatible with many cheminformatic software packages and is often used as the basis for molecular representation [[219](#_ENREF_219), [220](#_ENREF_220)].

Cheminformatics studies involving molecular similarity as a concept are usually heavily reliant on the methodology used to describe molecular features. To assess similarity of organic compounds it is necessary to accurately describe the features of each compound and represent this information as a structure key in the form of a binary bit string or bit vector. The resultant structure key is often referred to as the molecule’s fingerprint. Fingerprints are then compared using the Tanimoto coefficient. The current work utilised the Morgan fingerprints (r=2, 2048), similar to the frequently used ECFP4 fingerprint.

**S4. Network Optimisation and Visualisation**

As CSN networks are created using a similarity metric (Tanimoto), the creation process requires a similarity threshold (Tt) to be applied to the network to observe useful clustering. There is, unfortunately, no ideal universal threshold value that can be applied to achieve an optimal network. This value will always be situational and specific to each data set. As a highly diverse data set may result in a higher frequency of lower Tanimoto scores requiring a very different threshold to achieve informative data compared to a data set with high frequency of larger Tanimioto score. Hence, applying the same threshold to a highly diverse data set and a nominally diverse data set will yield two networks with very different topology. The literature describes methods that have been explored using the network density property to help guide in selecting a threshold value that will appropriately represent data without compromising modularity or average clustering coefficient [[216](#_ENREF_216), [221](#_ENREF_221)]. These methods have been developed using both diverse and non-diverse compound data sets that have been applied to small organic compounds. These studies observed that a good approximation of the appropriate network density value, leading to desirable network characteristics can be made between 2.5-5.0 % [[216](#_ENREF_216), [221](#_ENREF_221)]. The methodology adopted for threshold selection involved optimisation of key network statistics (network degree assortativity, clustering coefficient, transitivity and network density, **Figure 1**, to achieve an appropriate threshold and density value **Figure 2**. Observation of key network statistics showed that the threshold value of 0.5 results in a local maximum of network transitivity as well as degree assortativity two statistics that display the promotion of homophily within the networks as well as significant local clustering at this threshold. This threshold also results in a minimum number of isolates (6.9% of nodes) as well as maintaining a network density close to the literature suggested value of 5.0% (6.2%).

Chart, histogram

Description automatically generated

**Figure S1**: Network statistics for CSN (Morgan2, 2048).

Diagram

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**Figure S2**: Networks displayed at differing Tanimoto threshold values (Tt) using Morgan2 fingerprints.

**S5.** Bipartite Network Compounds vs Species (Full Size).

Diagram

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**Figure S3**: Simple Bipartite Network used to create monopartite projection of compound sharing with species arranged via genus.

**S6. Physicochemical Properties of Compounds and PCA Analysis**

All physicochemical properties (**Figures 4-7**) for compounds were calculated using the OSIRIS property explorer followed by PCA analysis using Minitab version 19.2.

Chart, bar chart

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**Figure S4:** Physicochemical properties (cLogP, nHBAcc and nHBDon) for NPs from *Aiolochroia*, *Aplysina*, *Aplysinella* and *Hexadella*.

Chart, bar chart

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**Figure S5:** Physicochemical properties (cLogP, nHBAcc and nHBDon) for NPs from *Ianthella*, *Pseudoceratina*, *Suberea* and *Verongula*.

Chart, waterfall chart

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**Figure S6:** Physicochemical properties (nRotB, TPSA and MW) for NPs from *Aiolochroia*, *Aplysina*, *Aplysinella* and *Hexadella*.

Chart, waterfall chart

Description automatically generated

**Figure S7:** Physicochemical properties (nRotB, TPSA and MW) for NPs from *Ianthella*, *Pseudoceratina*, *Suberea* and *Verongula*

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