Taxonium: a web-based tool for exploring large phylogenetic trees

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The COVID-19 pandemic has resulted in a step change in the scale of sequencing data, with more genomes of SARS-CoV-2 having been sequenced than any other organism on earth. These sequences reveal key insights when represented as a phylogenetic tree, which captures the evolutionary history of the virus, and allows the identification of transmission events and the emergence of new variants. However, existing web-based tools for analysing and exploring phylogenies do not scale to the size of datasets now available for SARS-CoV-2. We have developed Taxonium, a new tool that uses WebGL to allow the exploration of trees with tens of millions of nodes in the browser for the first time. Taxonium links each node to associated metadata and supports mutation-annotated trees, which are able to capture all known genetic variation in a dataset. We describe insights that analysing a tree of five million sequences can provide into SARS-CoV-2 evolution, and provide an application at cov2tree.org for exploring a public tree of more than five million SARS-CoV-2 sequences. Taxonium can be applied to any tree, and is available at taxonium.org, with source code at github.com/theosanderson/taxonium.

Introduction

Genomic researchers responded to the emergence of SARS-CoV-2 with rapid collaboration at unprecedented scale. Open protocols were quickly generated for amplicon sequencing (Tyson et al., 2020), and allowed researchers across the globe to produce ever-growing genomic datasets stored both in the INSDC databases (Cochrane et al., 2016), and in GISAID (Shu and McCauley, 2017), with the latter recently surpassing 11 million sequences. Importantly, new tools were also developed to understand the functional diversity of these samples, by assigning them into lineages proposed by the community (Rambaut et al., 2020; O’Toole et al., 2021), and allowing interactive exploration of trends in these data over time (Hodcroft, 2021; Chen et al., 2022; Tsueng et al., 2022).

The fundamental representation of an epidemic for genomic epidemiology is a phylogenetic tree, which for RNA viruses closely approximates the transmission tree of the viral epidemic and allows the direction of migration of viral lineages to be understood (Wohl et al., 2016). When trees are annotated with the mutations that have occurred at each internal node, they capture information about parallel and convergent evolution, which can identify recurrent mutations of concern.

The unparalleled size of SARS-CoV-2 datasets has posed challenges for the array of tools that researchers have previously relied upon to manipulate, analyse, and visualise genomic data. In particular, the construction of phylogenetic trees, and the visualisation of these trees, have been major bottlenecks preventing full-scale analyses. There are two broad responses possible to this issue. One is to downsample the sequences analysed in order to create a smaller dataset with which existing tools are able to work efficiently. This has been an important approach, and has allowed NextStrain (Hadfield et al., 2018) to provide one of the most widely-used and important tools for exploring SARS-CoV-2 genetic diversity. Briefly, the NextStrain pipeline downsamples sequences in a rational way, and then uses iqtree (Minh et al., 2020) to assemble them into a tree, assigns chronology and ancestral states to this tree using TreeTime (Sagulenko et al., 2018), and displays the results in a user-friendly interactive interface using Auspice (Hadfield et al., 2018). All three of these post-downsampling stages are bottlenecks which prevent the
use of full datasets, and so NextStrain analyses are typically limited to ~4,000 nodes—sampled in a structured way to ensure they either provide an overview of the pandemic or hone in on particular sequences of interest.

The new scale of data available provides an impetus to develop new tools that are able to operate on these large datasets directly without downsampling. Recently the development of UShER (Turakhia et al., 2021) has permitted larger trees to be built than ever previously. UShER takes a starting tree, built with iqtree or a similar approach, and incrementally adds sequences by maximum parsimony. For densely sampled sequencing efforts, as in the SARS-CoV-2 pandemic, such an approach still yields tree topologies of very high quality (Thornlow et al., 2022). To turn this distance tree into a time tree, by estimating a time associated with each node in the tree, we recently developed Chronumental (Sanderson, 2021) which uses stochastic gradient descent to efficiently construct chronologies from very large trees, which was not possible with previous approaches. A final necessary component is a tool for exploring these large trees, ideally in a browser.

Here we describe Taxonium, a web-based tool for analysing and exploring large trees. Taxonium scales to trees with millions of nodes, and allows for rapid panning and zooming using WebGL. In addition to reading Newick format trees, Taxonium can also display UShER mutation-annotated trees which capture genotype information in mutations at internal nodes. It permits searching for nodes by metadata or genotype, and a range of annotation options. Taxonium is available in a server-backed mode, which in a matter of seconds loads to allow exploration of all publicly available SARS-CoV-2 sequences, and also a fully client-side mode suitable for exploring custom datasets, including those with sensitive data.

Results

The Taxonium web client allows exploration of million-node phylogenies in the browser

To address the need for analysis of very large phylogenies, we built the Taxonium web client, a React application available at taxonium.org. One major bottleneck for previous approaches was the use of web technologies involving SVG or Canvas to visualize the tree, which have performance limitations. We instead use WebGL, as implemented via DeckGL (Uber, 2016), for efficient visualisation of the tree. Even so, rendering every node in the tree would still be too slow, and would involve hundreds of nodes overplotted on each pixel when a tree was zoomed out. We address this by rendering a sparsified version of the tree, with the sparsification dependent on the zoom level such that only nodes that would be hidden by other nodes are excluded. This approach allows for fast and responsive tree exploration.

The input to Taxonium is a tree (e.g. in Newick format) and, optionally, metadata. Metadata is associated with each node of the tree, and the tree can be coloured by any chosen metadata item. Colours are by default selected using an algorithm that hashes the metadata’s string value into a unique colour, ensuring consistency over time without the need for comprehensive look-up tables. In addition, the tree can be searched based on the metadata, with identified nodes circled. Complex hierarchical boolean combination queries using AND, OR, or NOT are supported.

The user interface of the Taxonium web client is shown in Figure 1. The tree, at the left hand side of the screen, can be panned, and can be zoomed in the vertical and horizontal axes independently. The latter is a crucial feature for large trees, which are invariably much larger in their y-axis. A toggleable minimap is provided for orientation. The right hand panel allows users to search for nodes of interest, to select how the tree is coloured, and to select between a chronological and a distance tree. It also displays information about the selected node; similar information is available upon hovering over a node of interest.

In addition to accepting traditional trees, Taxonium also supports mutation annotated trees (MATs, McBroome et al. (2021)), generated by UShER, where internal
nodes are annotated with mutations inferred to have occurred at that point in the phylogeny (Figure 2). Since an MAT essentially captures the full sequence of each sample in the tree, its use as an input permits the user to colour the tree by genotype at any desired site (Figure 3), or alternatively to search for particular mutations in internal nodes (Figure 4), and to filter by how many leaf nodes these mutations gave rise to.

Taxonium can allow visualisation of trees entirely in the client (Figure 2, l.h.s.), which is especially important for trees which may contain sensitive patient-level data. Trees are loaded either from a Newick file and TSV metadata file, or from a custom preprocessed Taxonium JSONL format combining the two. The Taxonium JSONL format contains a pre-computed layout for the tree, reducing the amount of computation required for its display, but Newick files can also be laid out in the client, which is achieved using an approach heavily based on JStree (Li). More expensive computational operations, such as the sparsification of the tree for display, are performed in a web worker in order to maintain a responsive interface.

An optional server-based implementation empowers rapid analysis

The client-side only version of Taxonium is highly responsive, and permits loading trees with millions of nodes on typical consumer computers. However, the process of deserialising tree data from disk into Javascript objects in memory is a bottleneck, requiring one minute and 20 seconds for a tree of 5.4 million sequences. Large trees also demand increasing amounts of RAM and download bandwidth which might rule out the use of lower spec devices. To allow near instantaneous access to trees with millions of nodes on almost any internet-connected device, we built a server-backed mode for Taxonium, in which a server reads trees from disk in advance and then serves required parts of them to each client on demand (Figure 2, r.h.s.). The server-backed mode is more efficient, as it does not require all data to be sent to the client, and the computationally expensive operations can be performed on a more powerful machine. Using this mode, a 5.4 million sequence tree can initially load in seconds. We continue to offer the client-side mode, which has the advantage that it can be used with custom data, and especially for data that may be sensitive and not suitable for uploading.

The Taxonium backend is implemented in NodeJS using Express. It runs from the same codebase that runs in the web worker in the browser. We made substantial efforts to make this backend code as efficient as possible. Nodes are stored sorted by their y coordinates, meaning that two binary searches can be used to identify the slice of nodes that lie within a supplied window.

User-friendly tooling for tree generation

We provide a simple Python application, taxoniumtools, which allows straightforward generation of a Taxonium JSONL file from an UShER MAT. The Taxonium JSONL format combines tree topology, node metadata, and mutations, in a row-wise format.
The tree's structure is encoded only in the `parent_id` property of each node. Taxoniumtools uses TreeSwift (Moshiri, 2020) for rapid loading of the Newick string located within the UShER MAT file. Optionally it can run Chronumental (Sanderson, 2021) as part of the building process and integrate the resulting time tree into the final JSONL file. Full documentation for Taxonium and Taxoniumtools is available at docs.taxonium.org.

**A resource for the phylogenetic analysis of all public SARS-CoV-2 genomes**

We used Taxonium to build the Cov2Tree web application (cov2tree.org), which allows users to explore the full global diversity of public SARS-CoV-2 sequences (Figure 3).

Cov2Tree is based on the daily-updated USHER tree built by McBroome et al. (2021), which currently contains 5.6 million sequences. We provide a time tree inferred by Chronumental, and also provide a daily-updated file containing the date placements inferred by Chronumental which can allow the identification of sequences with metadata errors (Sanderson, 2021). We run a backend server that supports the Cov2Tree application, meaning that the user needs only to load the data for the region of the tree on which they have zoomed in. This helps to enable analysis in lower bandwidth settings. Users can colour the tree by PANGO lineage, by sample country, or by genotype, and use searches to conduct complex queries.

The application of Taxonium to global SARS-CoV-2 datasets provides important insights into the evolution of the virus. Taxonium is the only tool that readily displays the number of independent times a given mutation has occurred during viral evolution, and the lineages in which these mutations evolved. This can be a key analytical approach to understand evolutionary processes such as epistasis. For example, Taxonium reveals a very heavy enrichment for occurrences of S:452M/S:452Q are within the BA.2 lineage (Figure 3), providing evidence of epistatic interactions between this position and BA.2 defining mutations. Similar effects are seen at S:212.

Taxonium has also been used to probe regional introduction events and transmission clusters during the SARS-CoV-2 pandemic (McBroome et al., 2022), to identify a convergent origin for two sets of mutations which each create a new ORF (Mears et al., 2022), and to examine new tools for pandemic-scale tree reconstruction (De Maio et al., 2022).

### Taxonium has applications beyond SARS-CoV-2.

We have used Taxonium to create a tool that allows exploration of the NCBI Taxonomy database (Federhen, 2012). The resulting visualisation, which can be found at taxonomy.taxonium.org, allows interactive viewing of the taxonomic relationships between 2.2 million species, as well as searches.

We have also collaborated with the Serratus project (Edgar et al., 2022) to allow visualisation of trees of virus sequences identified in a search of petabases of sequence from the Sequence Read Archive. Each viral order and family at serratus.io/trees now provides an option to open a custom Taxonium tree.

With the arrival of the 2022 monkeypox outbreak in Europe, we launched mpx.taxonium.org to allow exploration of an open genomic dataset from LAPIS (Chen, 2022).

### Taxonium scales to larger trees than any existing tool

We argue that Taxonium is currently the tool that best scales to the largest trees. To examine this we here compare a number of tools for their ability to load a very large tree. We stress that many of these tools were likely not specifically designed to be able to load trees of this size, unlike Taxonium.

We used the example of a Newick tree derived from a recent USHER public tree (McBroome et al., 2021) fea-
turing 5,326,538 sequences \(^3\). On a Macbook Pro (2018 version, 2.3 GHz quad-core i5), Taxonium loaded this tree from the Newick file in 31 seconds. Archaeopteryx (Han and Zmasek, 2009) took >5 minutes to load this tree with stack size set to 5 GB, and then was essentially unresponsive. Empress 1.20 (Cantrell et al., 2021) did not load this tree in the browser in any reasonable length of time. We were unable to upload this file to iTOL (Letunic and Bork, 2021) or the ETE Tree Explorer (Huerta-Cepas et al., 2010). We attempted to load the same file on Microreact.org (Argimón et al., 2016) (which now uses Phylocanvas.GL), but the screen locked up and had not loaded within a reasonable time. A Phylocanvas.GL demo \(^4\) does show that the library (Abudahab et al., 2021) is able to load a SARS-CoV-2 tree with >1M leaves, panning relatively slowly on our hardware.

We found it difficult to evaluate the performance of Dendroscope: we were able to open this file – for which we increased its allotted RAM to 5 GB. The tree loaded in 1 minute and 23 seconds. However it rendered as a single black rectangle which only began to resolve upon zooming in substantially, making it difficult to extract insights about the tree. Dendroscope used all available RAM whereas Taxonium used 1.7 GB. In general, Taxonium felt substantially more responsive.

It must be noted that all these tools have different feature sets. Many of the tools above allow for features absent from Taxonium, such as re-rooting, displaying trees radially, collapsing subtrees, and more. Support for these features to an extent trades-off against scale. Conversely, Taxonium is unique among these tools in the ability to output vector graphics. In contrast, Taxonium is intended primarily for exploring a tree dynamically – in the case of very large trees, this often the only way to extract useful information.

One challenge in this new era of vast datasets is the variable quality of sequences, and therefore resultant phylogenies. Artifacts in sequences (e.g. Heguy et al. (2022); Sanderson and Barrett (2021); Sanderson et al. (2021)) are often systematic, and in such cases can create entire clades brought together by shared errors. Existing efforts to tackle these issues have been important, for example pooling knowledge of known sites of common spurious mutations (De Maio et al., 2020). The development of new pipelines and assemblers that minimize artifacts will be important in the future, and the development of tree-building algorithms that are able to consider the possibility of variation due to artifacts, or pre-tree masking steps that mask different sites in each sequence, may be valuable. Widespread deposition of raw reads would allow systematic assembly by pipelines designed to minimise systematic errors. In Taxonium we provide a search option that highlights “revertant” mutations in which a branch apparently mutates back towards the reference genome. In large SARS-CoV-2 phylogenies, many of these mutations appear to in fact represent sequencing artifacts, or reversion from them, and so this approach may help identify areas of a tree that may have technical issues.

Taxonium is an ongoing open source project to create and maintain a tree viewer able to scale to the latest phylogenies. We welcome contributions from the community and hope that the features described here will be useful to those working on epidemiological surveillance and outbreak response.

\(^3\)The tree can be downloaded \(\text{here}\)
\(^4\)https://www.phylocanvas.gl/examples/very-large-tree.html
Materials and methods

Data sources

In order to be able to share trees through a web application, we present data at Cov2Tree and in this paper derived from SARS-CoV-2 sequences made available openly in the INSDC databases. We are fortunate to be able to use a pre-computed UShER tree also made available openly on a daily basis (McBroome et al., 2021).

The Taxonium web client

The Taxonium web client is implemented in React. All source code is available at https://github.com/theosanderson/taxonium/tree/master/taxonium_web_client. The core of the visualisation runs in DeckGL, which is heavily modified to allow independent zooming in X and Y. The data consumed by DeckGL is generated either in a web worker (local mode) or in from an external API running the Taxonium backend (remote mode).

In either case, the key endpoint provides a sparsified tree, computed by cutting the tree to a region just larger than the bounding box of the user’s current page, then filtering out nodes that overlie another, and then adding all ancestral nodes of those selected to ensure that the tree returned is a pruned version of the full tree. Outputting a full pruned tree means that the genotypes of all terminal nodes can be computed by traversing the mutations associated with each node. The returned dataset includes all metadata for each included node, meaning that users can select any item to colour nodes by, or alternatively can colour nodes by genotype.

Alternatively the Search endpoint allows users to search across the whole dataset, with nodes matching the search circle in the interface. The same filtering strategy is applied to the results of search, meaning that even searches that return millions of results can be interacted with fluidly. Taxonium is capable of storing two different distance metrics in the same tree, allowing users to switch between the genetic distance and the temporal phylogeny.

Taxonium backend

The Taxonium backend is implemented in NodeJS in an Express-based framework. Full source code is available at https://github.com/theosanderson/taxonium/tree/master/taxonium_backend. The core code for filtering and searching that runs in the web-worker for the front-end is reused through a shared package, taxonium_data_handling.

The backend keeps the full tree in memory, then serves filtered slices of it to users on demand. In the case of the SARS-CoV-2 dataset, the server backend requires around 5 GB of RAM per server instance. We run Cov2Tree on an autoscaling Kubernetes cluster.

Taxonimtools and tree processing

The taxonomitools package is written in Python and distributed with PyPI. Tree manipulation is performed with TreeSwift (Moshiri, 2020). The package includes the ability to number internal nodes, with a numbering scheme that matches UShER newick exports. An optional feature, used for display on Cov2Tree, “shears” off outlier nodes with very few descendants, which often represent sequencing errors or occasionally recombinants. This pruning can help to make large trees more interpretable.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

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