Real-time phylogenetics with UShER

COVID-19 Genomic Epidemiology Toolkit: Module 3.3

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cdc.gov/coronavirus
## Toolkit map

### Part 1: Introduction
- 1.1 What is genomic epidemiology?
- 1.2 The SARS-CoV-2 genome
- 1.3 How to read phylogenetic trees
- 1.4 Emerging variants of SARS-CoV-2

### Part 2: Case Studies
- 2.1 SARS-CoV-2 sequencing in Arizona
- 2.2 Healthcare cluster transmission
- 2.3 Community transmission

### Part 3: Implementation
- 3.1 Getting started with Nextstrain
- 3.2 Getting started with MicrobeTrace
- **3.3 Linking epidemiologic data**
Tracking viral evolution

Images from nextstrain.org
UShER: Real-time phylogenetic placement

- Ultrafast Sample placement on Existing Trees

- Designed to take user sequences and
  1. Accurately place them onto global phylogeny
  2. Construct new subtrees
  3. Enable easy visualization

- Runs quickly (<1 second) to facilitate genomic epidemiology
Constant flow and huge datasets overwhelm typical phylogenetics approaches

- Typical phylogenetic workflow:
  1. Gather data
  2. Calculate tree
Constant flow and huge datasets overwhelm typical phylogenetics approaches

- Typical phylogenetic workflow:
  1. Gather data
  2. Calculate tree
  3. More data!
  4. Recalculate tree?
Constant flow and huge datasets overwhelm typical phylogenetics approaches

- Typical phylogenetic workflow:
  1. Gather data
  2. Calculate tree
  3. More data
  4. Recalculate tree
  5. More data!
  6. Recalculate tree?

Repeat... forever
The UShER approach for phylogenetics

UShER takes as input:
1. phylogenetic tree
2. list of mutations in each sample

Sample A: A U C U U G A G U C
Sample B: A U C U U A U G U C
Sample C: A U C G U A A G C C
Sample D: A C C G U A A G U U

A. 2U, 4U, 6G
B. 2U, 4U, 7U
C. 2U, 9C
D. 10U
The UShER approach for phylogenetics

Using parsimony, UShER maps mutations onto the existing tree.
The UShER approach for phylogenetics

UShER stores this **mutation annotated tree**.
The UShER approach for phylogenetics

**New samples** are added using maximum parsimony by checking every possible placement.

Sample E: 10U, 14G
UShER placements are highly accurate

UShER finds the correct placement in 97% of the cases.

When incorrect, placements are still usually very close to the true site.
UShER output

UShER outputs a subtree of 50 most closely related samples to a user’s sample.

User’s sample in red

This subtree can be visualized and explored using the Nextstrain platform.
UShER’s quality control metrics

<table>
<thead>
<tr>
<th>Fasta Sequence</th>
<th>Size</th>
<th>#Ns</th>
<th>#Mixed</th>
<th>Bases aligned</th>
<th>Insertions</th>
<th>Deletions</th>
<th>#SNVs used for placement</th>
<th>Neighboring sample in tree</th>
<th>Lineage of neighbor</th>
<th>Imputed values for mixed bases</th>
<th>#Maximally parsimonious placements</th>
<th>Parsimony score</th>
<th>Subtree number</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypothetical_uploaded_sequence_1</td>
<td>29903</td>
<td>0</td>
<td>0</td>
<td>29903</td>
<td>0</td>
<td>0</td>
<td>37</td>
<td>2</td>
<td>England/CAMC-AEAA07/2020</td>
<td>0</td>
<td>2</td>
<td>32</td>
<td>127</td>
</tr>
</tbody>
</table>

The parsimony score - Number of mutations unique to a user’s sample branch.

- 1. 6G
- 2. 4U
- 3. 7U
- 4. 2U
- 5. 9C
- 6. 10U
UShER’s quality control metrics

The number of equally parsimonious placements for an added sample.

1. 6G
2. 4U
3. 7U
4. 2U
5. 9C
6. 10U

Sample E: 2N, 4N, 6N, 7N, 9N, 10N...
Uploading data

https://genome.ucsc.edu/cgi-bin/hgPhyloPlace

sequences.fasta

>genome_01
AUGAUGCAUGCUGCAUGAUG
CGUCAUGACACUGAUCG
>genome_02
AUGAUGCAUGCUGCAUGAUG
CGUCAUGACACUGAUCG
...

Summary

- UShER places samples onto a global phylogeny of SARS-CoV-2 genomes.
  - Learning about relationships among user samples, e.g., the number of unique introductions in an area.
  - Rapid sequence quality control.

- UShER resources:
  - Hands-on example data: https://github.com/russcd/USHER_DEMO
  - The UShER source code: https://github.com/yatisht/usher
  - Manuscript: https://www.biorxiv.org/content/10.1101/2020.09.26.314971v1
  - UShER’s web resource: https://genome.ucsc.edu/cgi-bin/hgPhyloPlace
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Learn More

- Other modules
  - Getting started with Nextstrain – Module 3.1
  - Getting started with MicrobeTrace – Module 3.2

- COVID-19 Genomic Epidemiology Toolkit
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