

Topological surveillance of potentially adaptive mutations in the evolution of the coronavirus SARS-CoV-2

CoVtRec report as of 22 September 2023

Michael Bleher^{2*}, Lukas Hahn^{2*}, Maximilian Neumann^{*}, Samuel Braun³, Holger Obermaier³, Mehmet Soysal³, René Caspart³, Andreas Ott^{1,2*}

¹Mathematics Department, Karlsruhe Institute of Technology, Karlsruhe, Germany

²Institute for Mathematics, Heidelberg University, Heidelberg, Germany

³Steinbuch Centre for Computing, Karlsruhe Institute of Technology, Karlsruhe, Germany

*Correspondence: mbleher@mathi.uni-heidelberg.de (M.B.)
lhahn@mathi.uni-heidelberg.de (L.H.)
neumann.mn@icloud.com (M.N.)
andreas.ott@kit.edu (A.O.)

Abstract

The appearance of new variants in the evolution of the coronavirus SARS-CoV-2 underlines the importance of being able to quickly identify mutations that could confer some adaptive advantage to the virus, such as immune evasion or higher infectivity. Here we apply CoVtRec, a fast and scalable surveillance system based on Topological Data Analysis, for the identification of emerging potentially adaptive mutations in the ongoing evolution of SARS-CoV-2. CoVtRec is based on a new topological approach to the study of recurrent mutations in large genomic datasets developed in [1].

Results

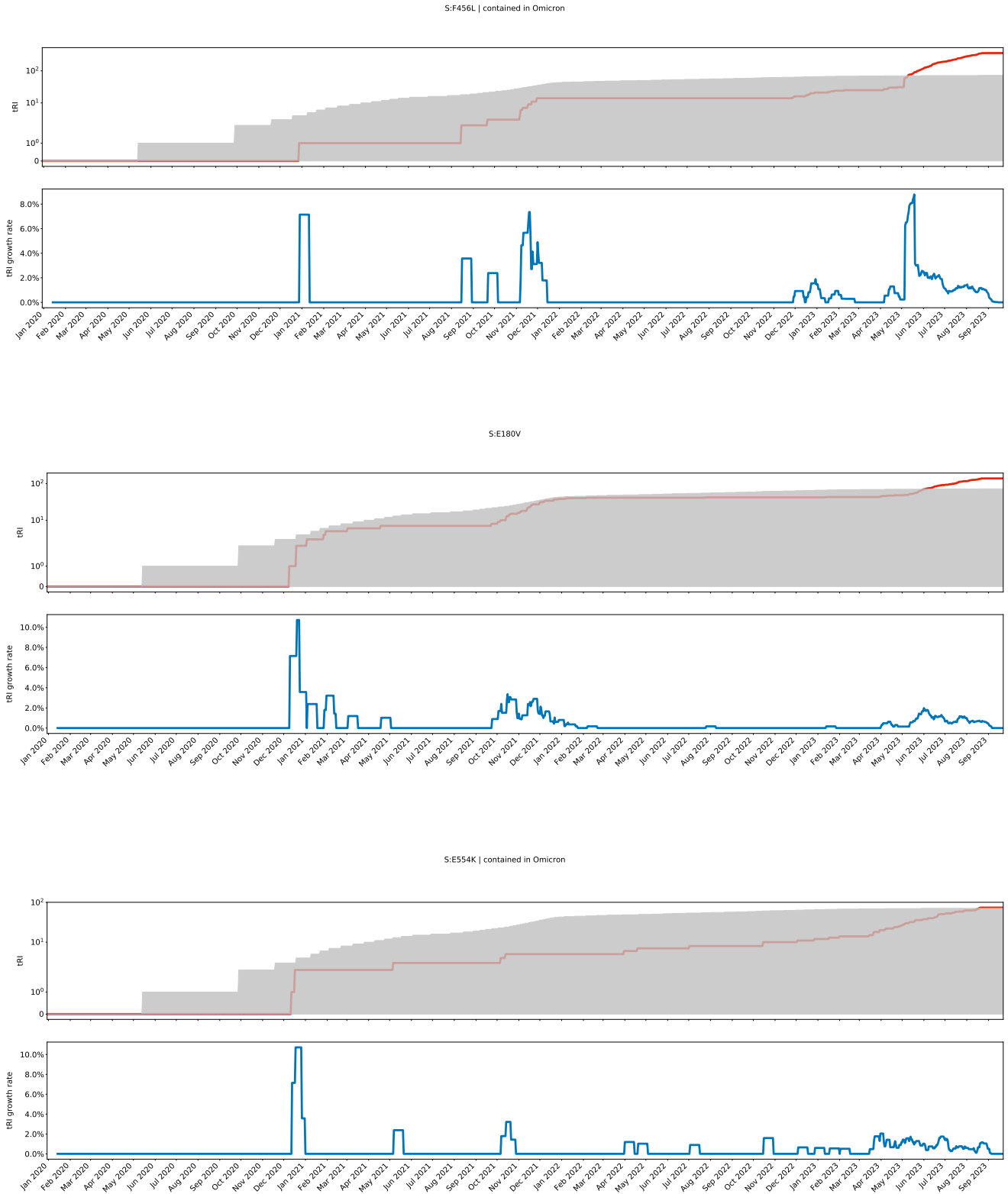
We analyzed topological signals for the ongoing convergent evolution of the coronavirus SARS-CoV-2 on the Spike gene from 15 January 2019 until 22 September 2023. To that end, we performed a topological recurrence analysis for a curated alignment of 14,439,513 high-quality SARS-CoV-2 Spike gene sequences shared via GISAID, the global data science initiative [2, 3]. For each Spike mutation we computed its topological recurrence index (tRI) and the corresponding time series analysis chart. The topological recurrence index is a topological measure for the potential adaptiveness of a given mutation (see [1, 4] for details).

We present a list featuring the top ten amino acid changes on the Spike gene with currently highest tRI growth rate in August 2023 (see [Table 1](#)). Here signals with $tRI \geq 72$ are statistically significant ($p < 0.05$). It was demonstrated in [1] that these mutations are potentially adaptive and might therefore appear in future variants. We also present time series analysis charts (see [Figure 1](#)) showing (i) the development of the topological signal as well as its significance over time, (ii) major lineages containing the mutation, and (iii) the date from which on the topological signal became significant.

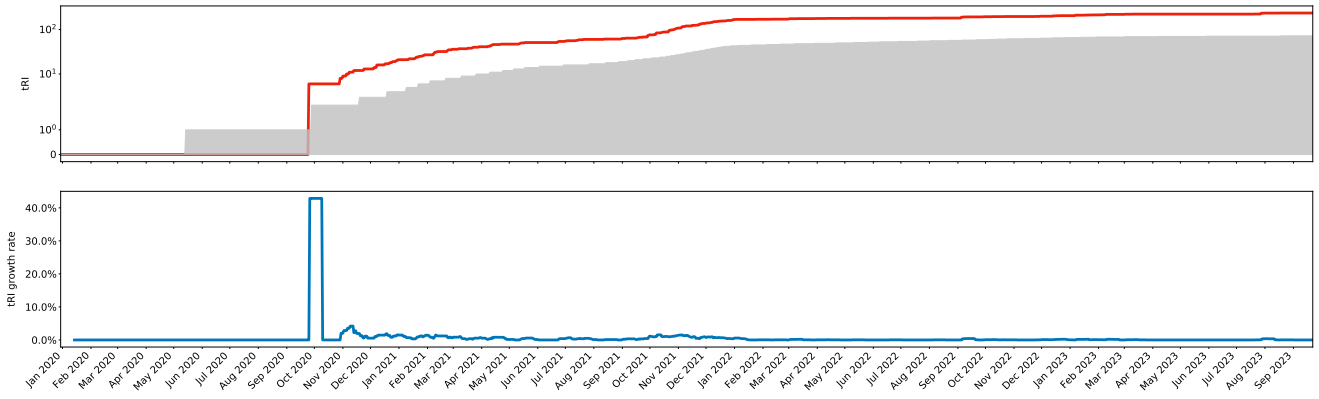
SAAV	tRI	notable variants
F456L	358	Omicron
E180V	138	
E554K	74	Omicron
V1122L	235	
Q52H	98	Omicron
T547I	576	
Y200C	78	
F186S	76	
F490S	152	Omicron, Lambda
G184V	95	

Table 1. The top ten amino acid changes on the Spike gene with currently highest tRI growth rate in August 2023. For a given mutation, the table displays its topological recurrence index (tRI) and notable variants containing the mutation.

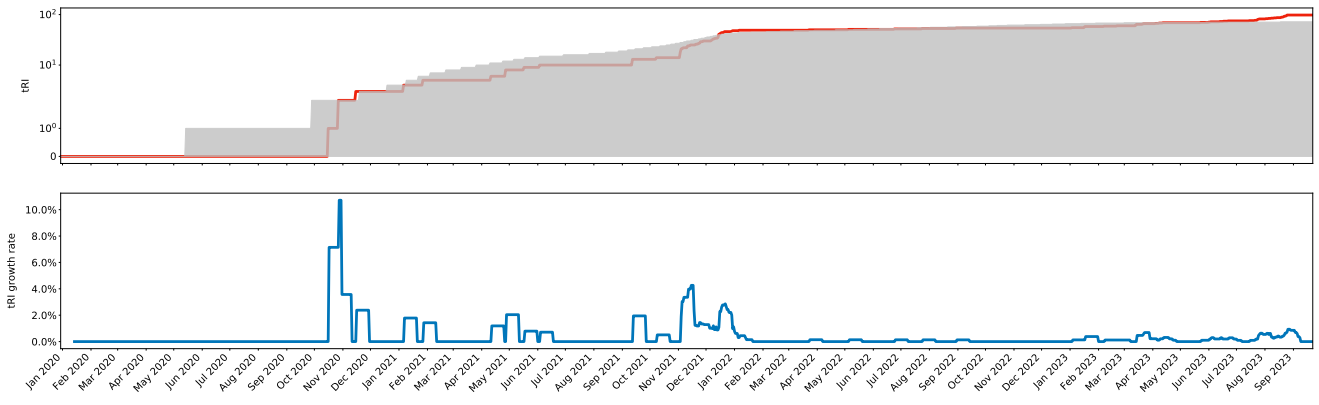
Figure 1. Time series analysis charts for the mutations listed in [Table 1](#). Each chart shows the topological recurrence index (tRI, in red) and the tRI growth rate (in blue) from 15 January 2019 until 22 September 2023. In the upper diagram the shaded region marks the level of significance.



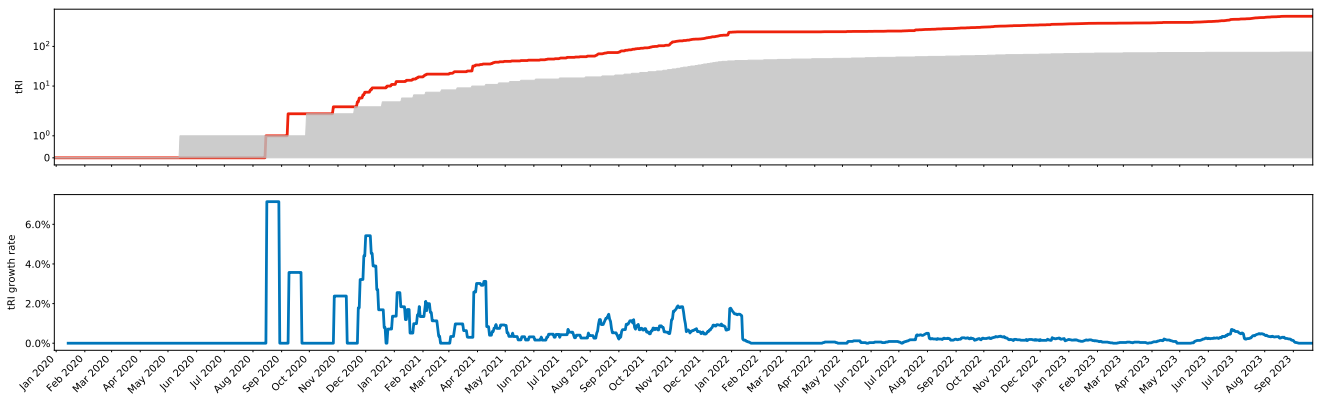
S.V1122L



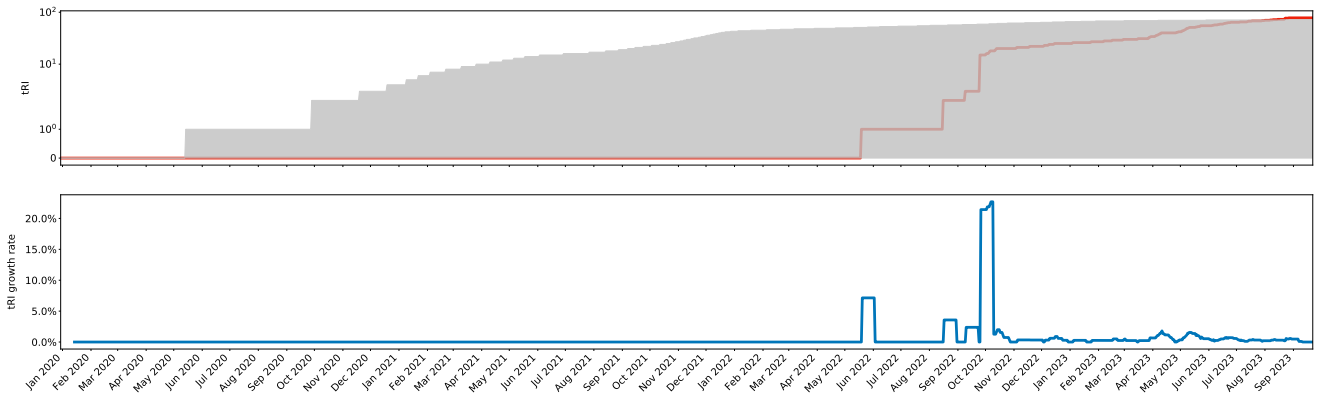
S.Q52H | contained in Omicron



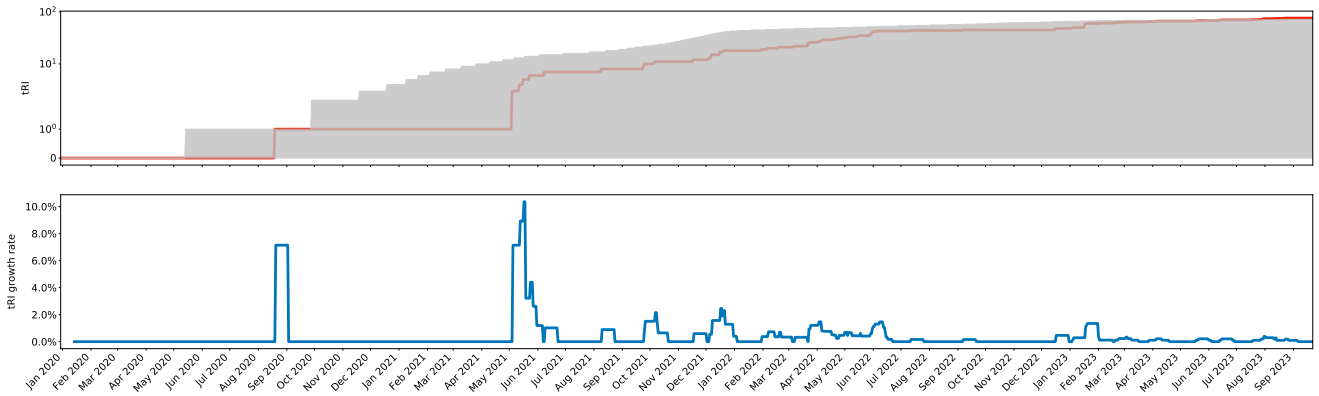
S.T547I



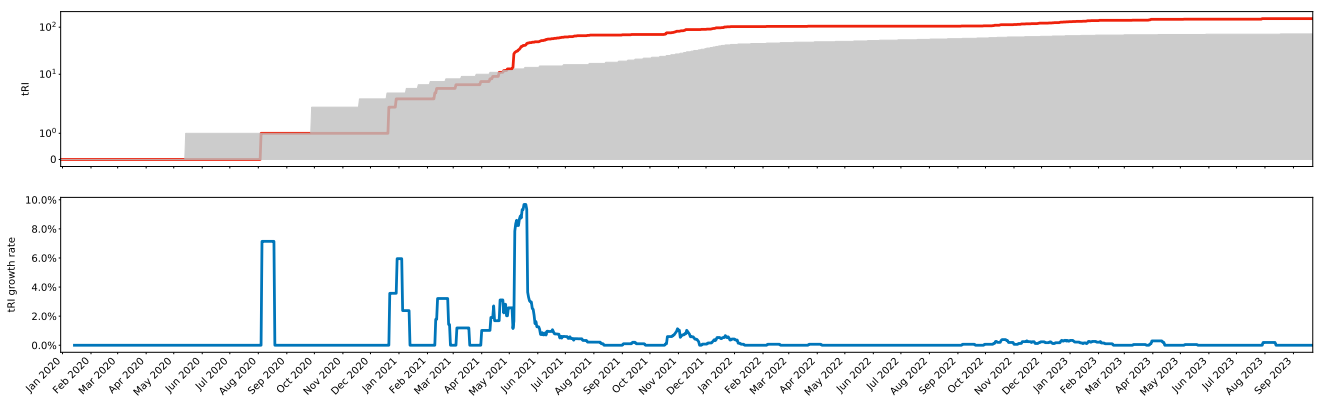
S:Y200C

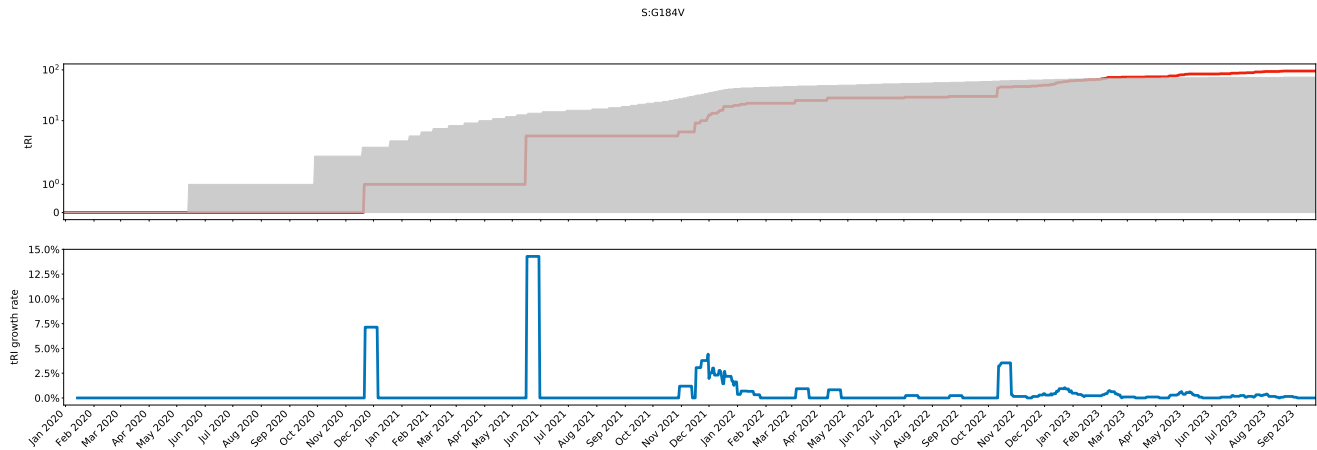


S:F186S



S:F490S | contained in Omicron, Lambda





Methods

Data acquisition and data preparation

Our analysis is based on the alignment `msa_0922.fasta` downloaded from the GISAID EpiCoV Database [2, 3] on 24 September 2023. This alignment comprises 14,439,513 SARS-CoV-2 whole genome sequences that have been aligned to the reference sequence Wuhan/WIV04 with GISAID accession number EPI_ISL_402124 using MAFFT [5]. Sequences in this alignment were truncated to the Spike gene (reference site positions 21,563 to 25,384). Subsequently the following sequences were removed: (i) sequences containing any characters other than A, C, T, G or -, and (ii) sequences that occur only once in the alignment. This resulted in an alignment comprising 9,349,486 complete SARS-CoV-2 Spike genes of length 8,075nt.

Topological recurrence analysis

The Spike gene alignment contains a subalignment comprising 236,193 genetically distinct sequences. A list of accession numbers of all sequences in this subalignment, along with an acknowledgement of the contributions of both the submitting and the originating laboratories, is accessible at <https://doi.org/10.55876/gis8.231002cu>. We used `Hammingdist` (Version 0.19.0) [6] to compute the genetic distance matrix of this subalignment. Subsequently we used `Ripser` [7] to compute the representative cycles for the persistent homology of the Vietoris–Rips filtration associated to the genetic distance matrix. The computation of persistence barcodes was restricted to small genetic distance scales (`Ripser` scale parameter threshold set to 2). Next a complete list of SNV cycles (topological cycles all of whose edges correspond to single nucleotide variations) in the given alignment was generated from the corresponding `Ripser` output. Then we used custom code implemented in Python to compute the *topological recurrence index* (*tRI*) for each such SNV. Summing over all SNVs determining an SAAV (single amino acid variation), we computed the *tRI* for each SAAV. Lastly, from the distribution of the *tRI* measurements over the whole Spike gene we inferred the level of significance for the *tRI* per SAAV. Using Vietoris–Rips transformations in multipersistent homology, we computed *tRI* time series analysis charts at daily resolution from the natural stratification by time of genomic data. We also computed the *tRI* growth rate (14 days moving average). For a more detailed description of the topological recurrence analysis see [1, 4].

Data availability

All SARS-CoV-2 genome data used in this work are available from the GISAID EpiCov Database [2, 3] at <https://www.gisaid.org> and are accessible at <https://doi.org/10.55876/gis8.231002cu>.

Code availability

Code used for the analyses is available at <https://github.com/ssciwr/hammingdist> and <https://github.com/Ripser/ripser/tree/tight-representative-cycles>. All other code is available from the corresponding authors upon request.

Acknowledgements

The authors gratefully acknowledge all data contributors, i.e. the Authors and their Originating laboratories responsible for obtaining the specimens, and their Submitting laboratories for generating the genetic sequence and metadata and sharing via the GISAID Initiative [2, 3], on which this research is based. An acknowledgement table is accessible at <https://doi.org/10.55876/gis8.231002cu>. The authors acknowledge the use of de.NBI Cloud and the support by the High Performance and Cloud Computing Group at the Zentrum für Datenverarbeitung of the University of Tübingen and the German Federal Ministry of Education and Research (BMBF) through grant no 031 A535A. They thank M. Hanussek for IT support and early access to VALET [8]. The authors further acknowledge support from the Interdisciplinary Center for Scientific Computing at Heidelberg University and the development work of the Scientific Software Center of Heidelberg University carried out by L. Keegan and D. Kempf [6]. This research was funded by the Federal Ministry of Education and Research (BMBF) and the Baden-Württemberg Ministry of Science as part of the Excellence Strategy of the German Federal and State Governments (KIT Centers, “Topological Genomics”), and by the Vector Foundation (“Topological Genomics”). M.B. and L.H. were supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany’s Excellence Strategy EXC 2181/1 - 390900948 (the Heidelberg STRUCTURES Excellence Cluster). L.H. thanks the Evangelisches Studienwerk Villigst for their support.

Author contributions

M.B., L.H., M.N., A.O. designed the study; A.O. curated data; A.O. performed computational analyses; M.B., L.H., M.N., A.O., S.B., H.O., M.S., R.C. developed and implemented software; M.B., L.H., A.O. acquired computing resources; M.B., L.H., A.O., M.N. drafted the manuscript; all authors contributed to the final version of the report.

Competing interests

The authors declare no competing interests.

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