Topological Surveillance of Recurrent Mutations in SARS-CoV-2

CoVtRec report as of 26 April 2023

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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 early warning system based on Topological Data Analysis, for the identification and surveillance 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

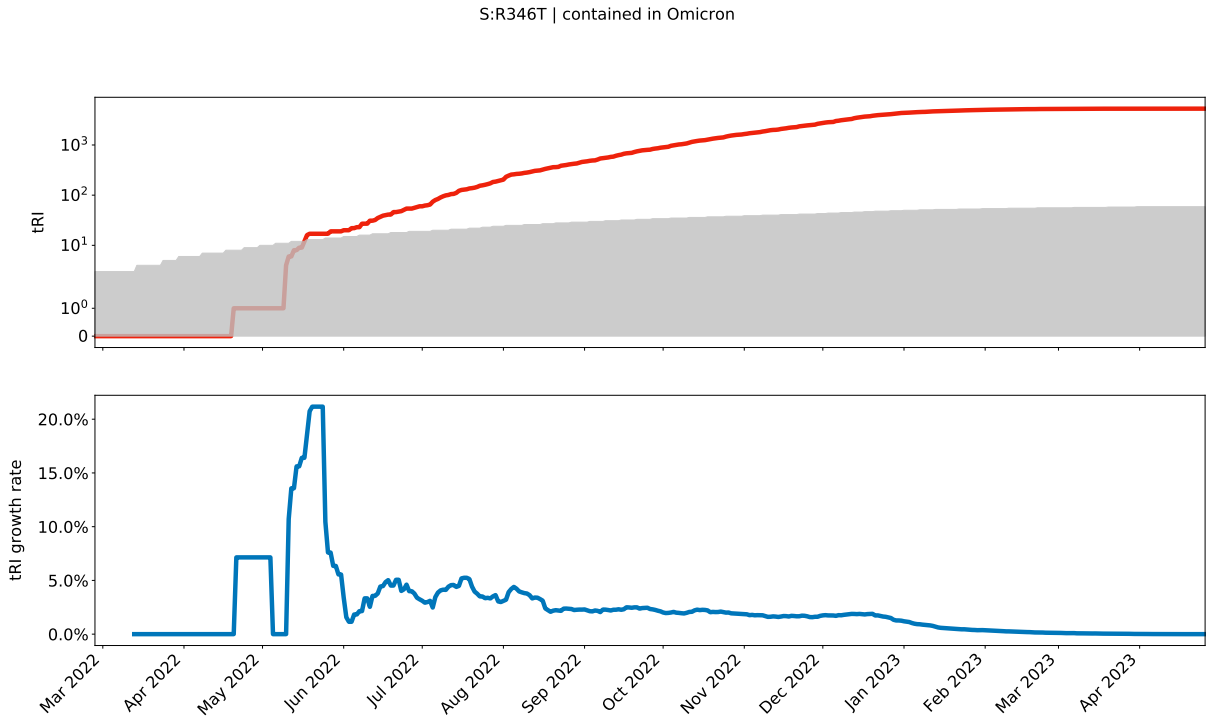
We analyzed topological signals for the ongoing convergent evolution of the coronavirus SARS-CoV-2 on the Spike gene from 26 January 2022 until 26 April 2023. To that end, we performed a topological recurrence analysis for a curated alignment of 13,954,275 high-quality SARS-CoV-2 Spike gene sequences 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).

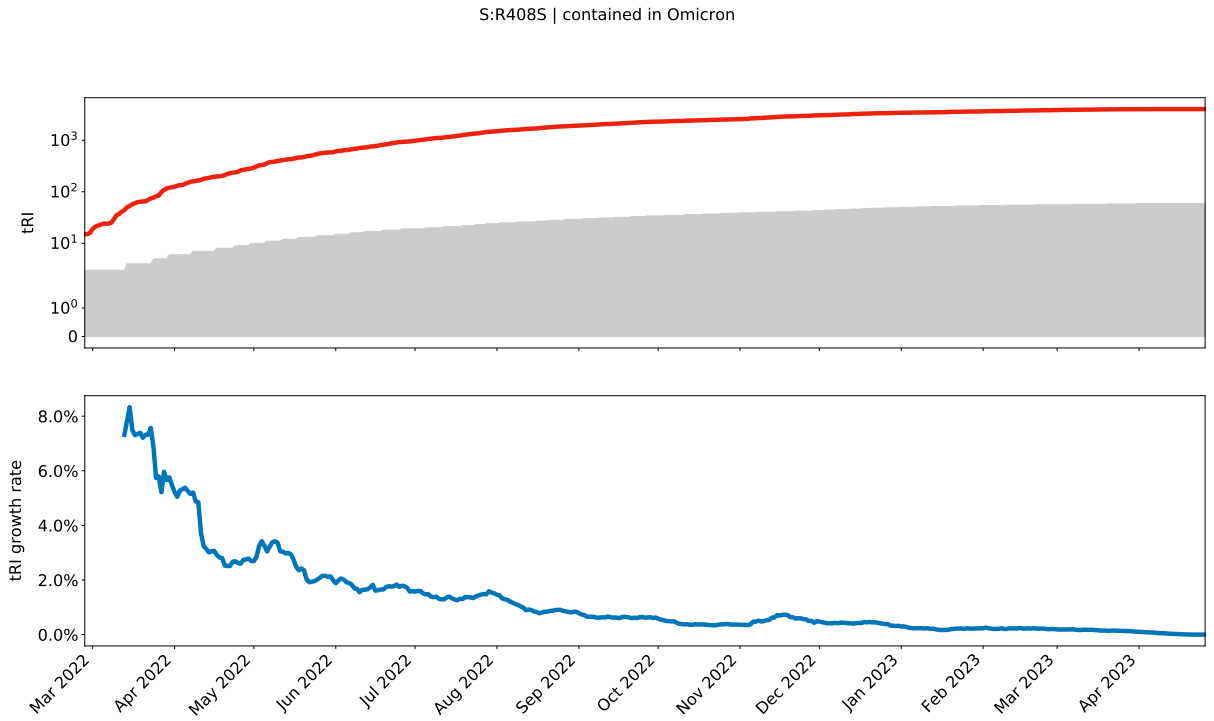
We present a list featuring the top ten amino acid variations on the Spike gene that show strongest topological recurrence index as of 26 April 2023 (see Table 1). Here signals with tRI ≥ 59 are statistically significant ($p < 0.05$). It was demonstrated in [1] that these mutations are potentially adaptive 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
R346T	5298	Omicron
R408S	4017	Omicron
N440K	3979	Omicron
L5F	2933	Iota
K417N	2098	Beta, Omicron, Mu
A1020S	1894	
N658S	1824	
T76I	1667	Lambda
V3G	1561	
G142D	1329	Delta, Omicron, Kappa

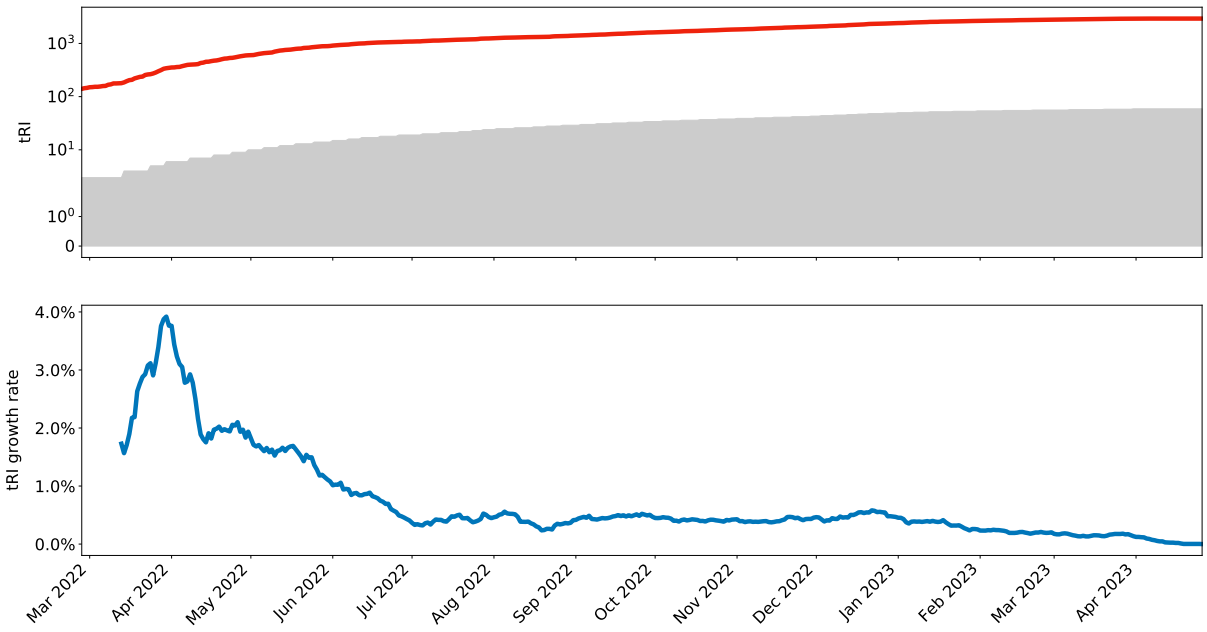
Table 1. The top ten amino acid changes on the Spike gene showing strongest topological recurrence index as of 26 April 2023. For a given mutation, the table displays its topological recurrence index (tRI) and notable variants containing the mutation.

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 26 January 2022 until 26 April 2023. In each chart, in the upper diagram the shaded region marks the level of significance.

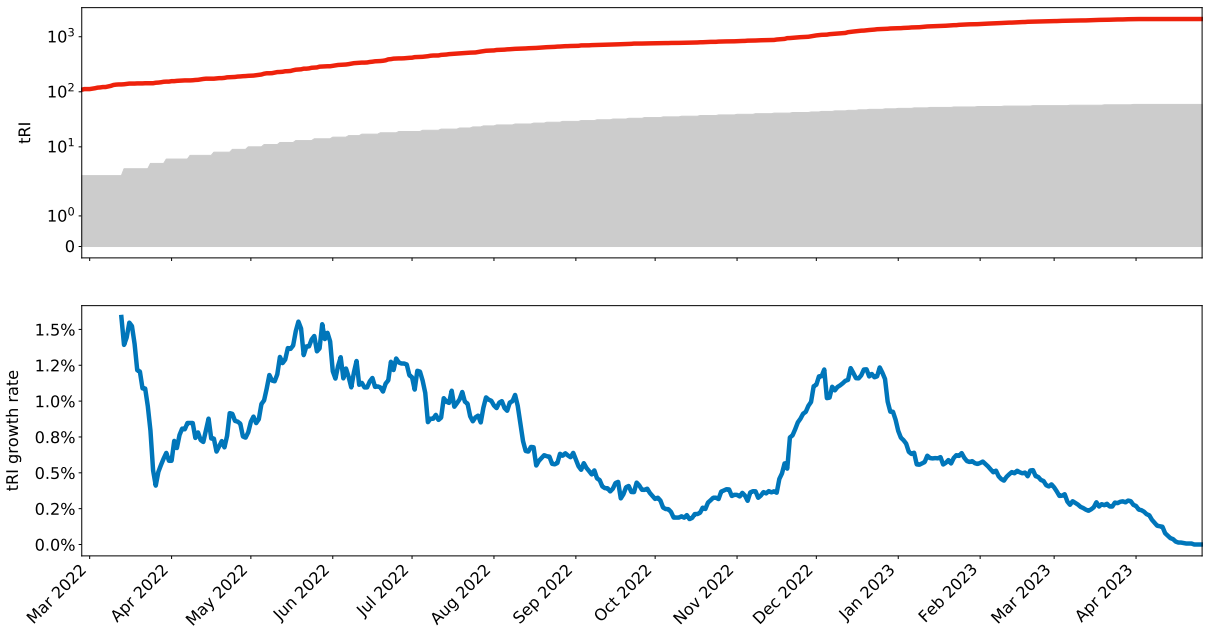




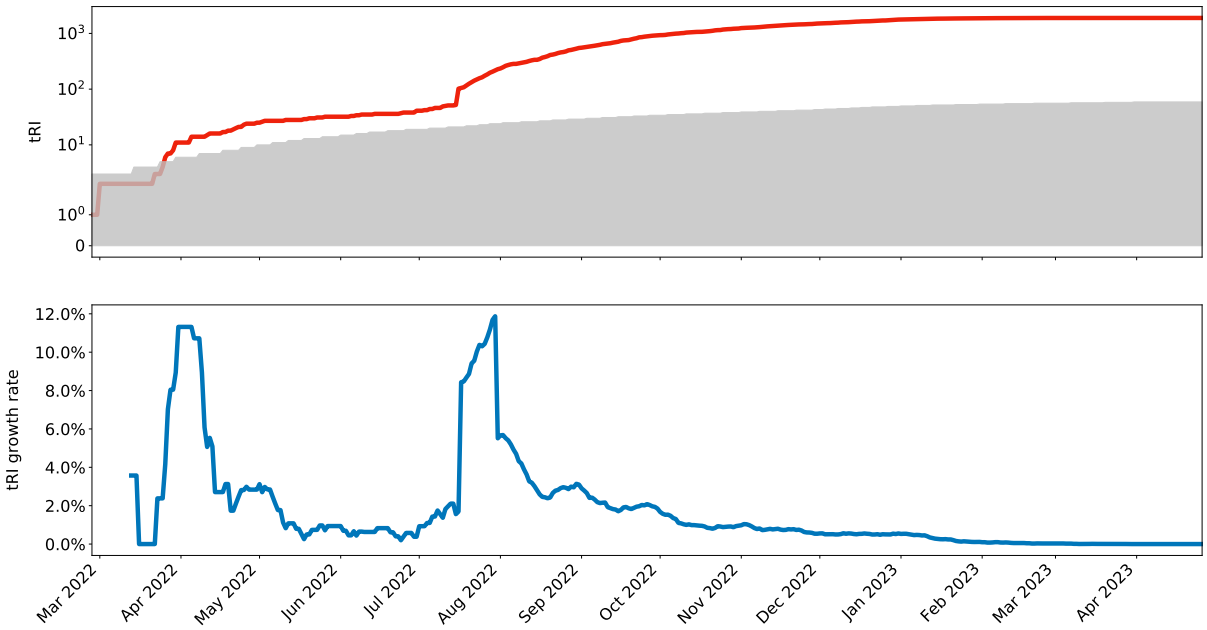
S:L5F | contained in Iota



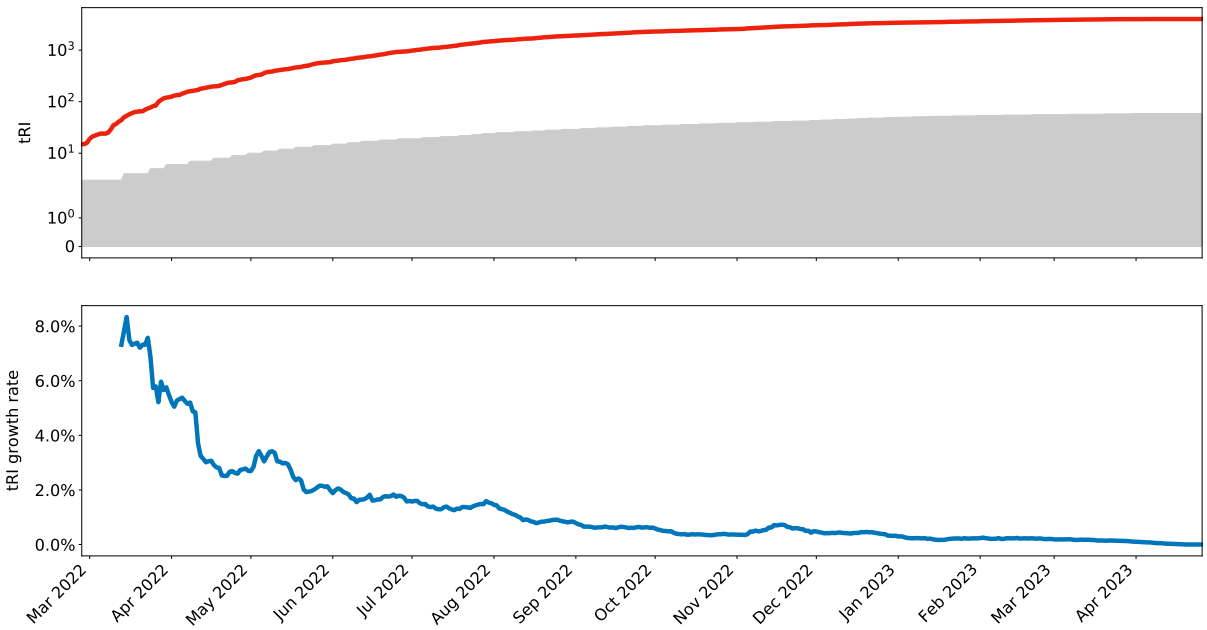
S:K417N | contained in Beta, Omicron, Mu



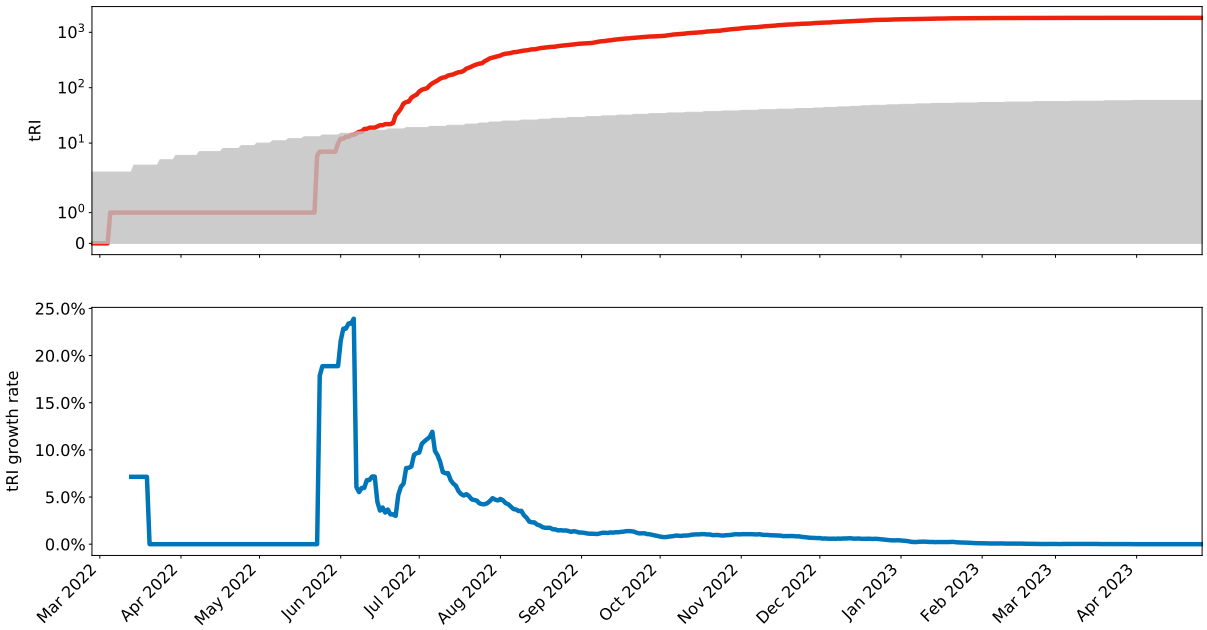
S:A1020S



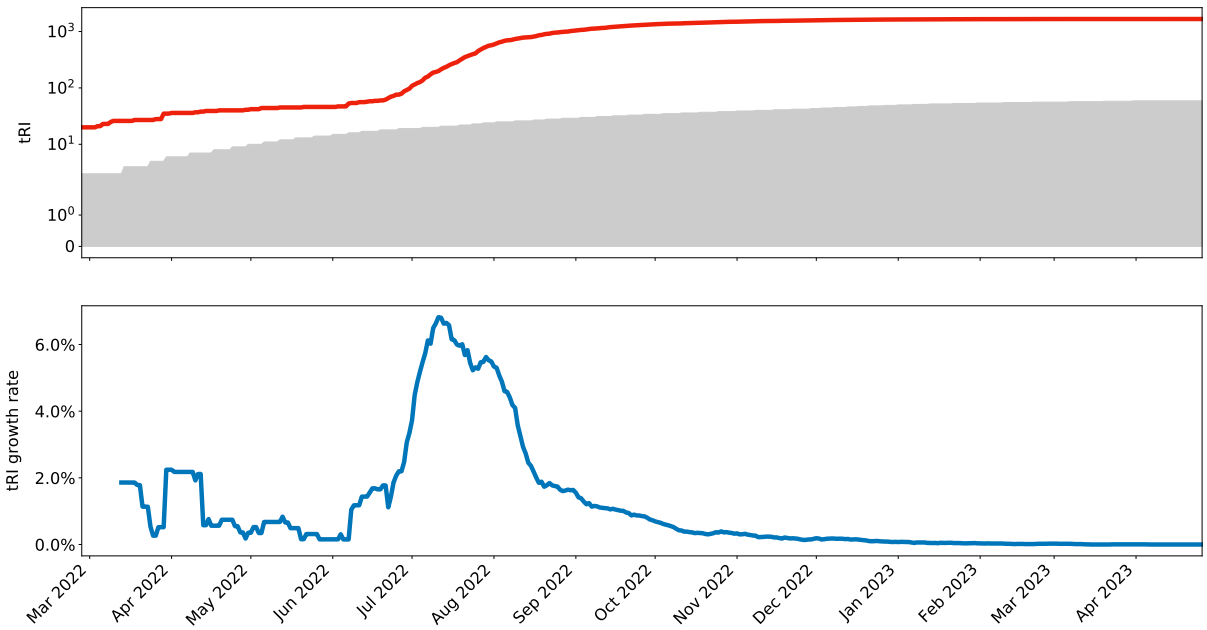
S:R408S | contained in Omicron



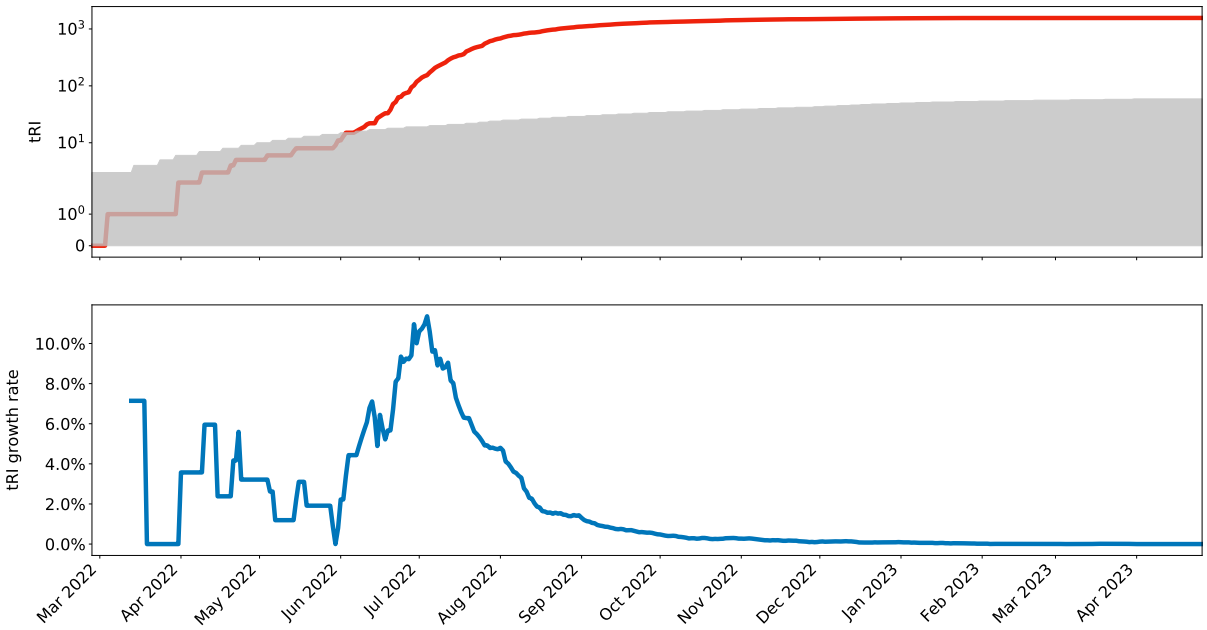
S:N658S



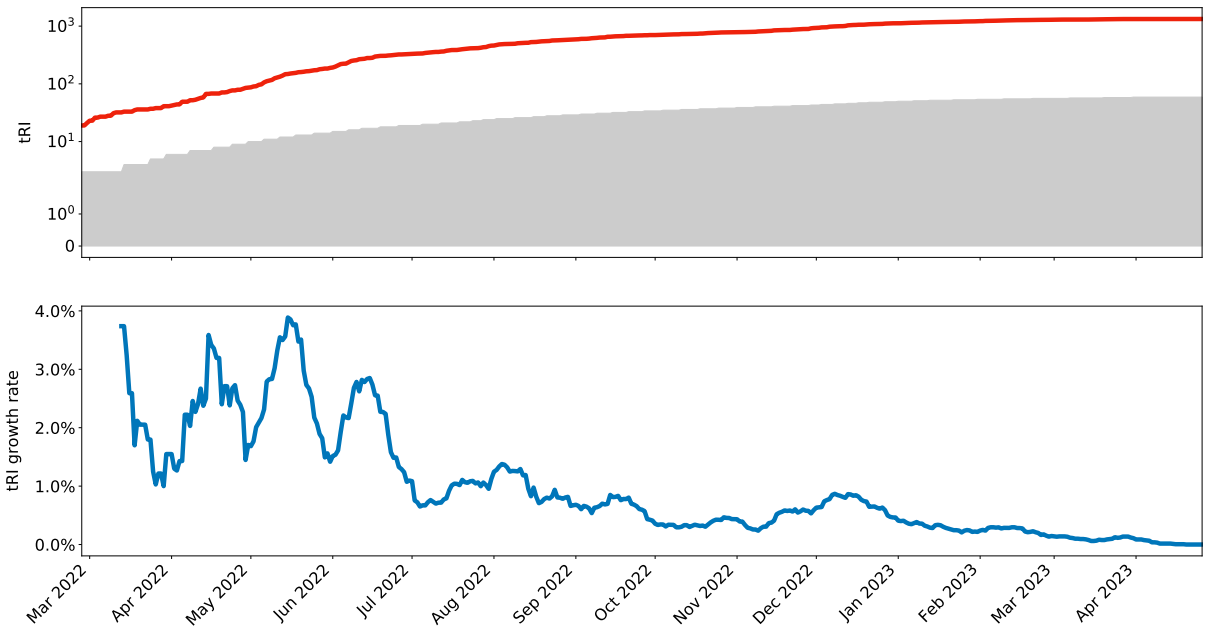
S:T76I | contained in Lambda



S:V3G



S:G142D | contained in Delta, Omicron, Kappa



Methods

Data acquisition and data preparation

Our analysis is based on the alignment `msa_0426.fasta` downloaded from the GISAID EpiCoV Database [2, 3] on 28 April 2023. This alignment comprises 13,954,275 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), and subsequently sequences containing any characters other than A, C, T, G or - were removed. This resulted in an alignment comprising 3,879,441 complete SARS-CoV-2 Spike genes of length 7,950nt. A list of accession numbers of all sequences in this alignment, along with an acknowledgement of the contributions of both the submitting and the originating laboratories, is accessible at https://doi.org/10.55876/gis8.230430nf.

Topological recurrence analysis

The Spike gene alignment contains 223,590 genetically distinct sequences. We used `Hammingdist (Version 0.19.0)` [6] to compute the genetic distance matrix of this alignment. 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/gis8.230430nf.

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.

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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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