

# Topological Surveillance of Recurrent Mutations in SARS-CoV-2

CoVtRec report as of 28 June 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 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

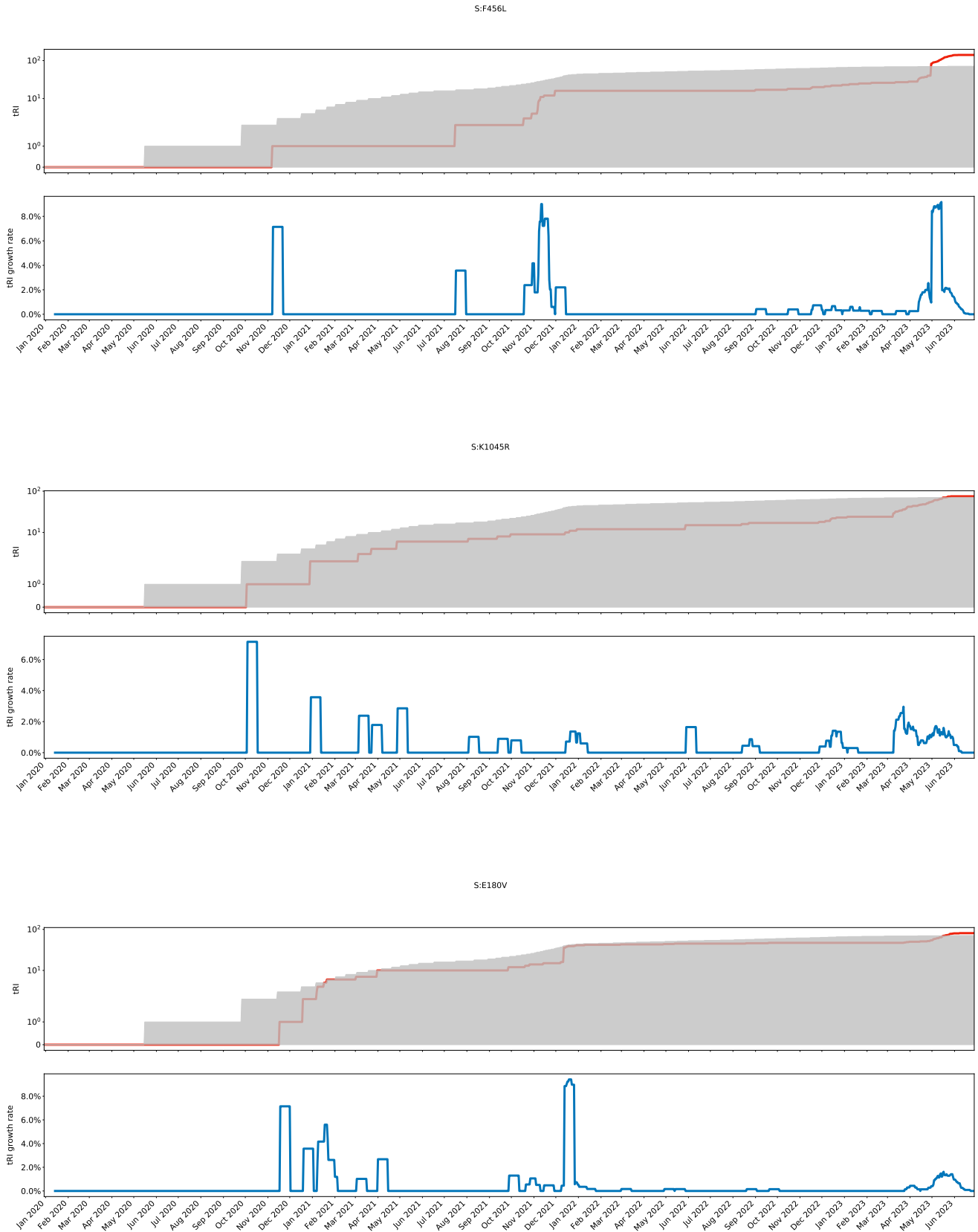
We analyzed topological signals for the ongoing convergent evolution of the coronavirus SARS-CoV-2 on the Spike gene from 15 January 2019 until 28 June 2023. To that end, we performed a topological recurrence analysis for a curated alignment of 14,192,791 high-quality SARS-CoV-2 Spike gene sequences 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 June 2023 (see Table 1). Here signals with  $tRI \geq 71$  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.

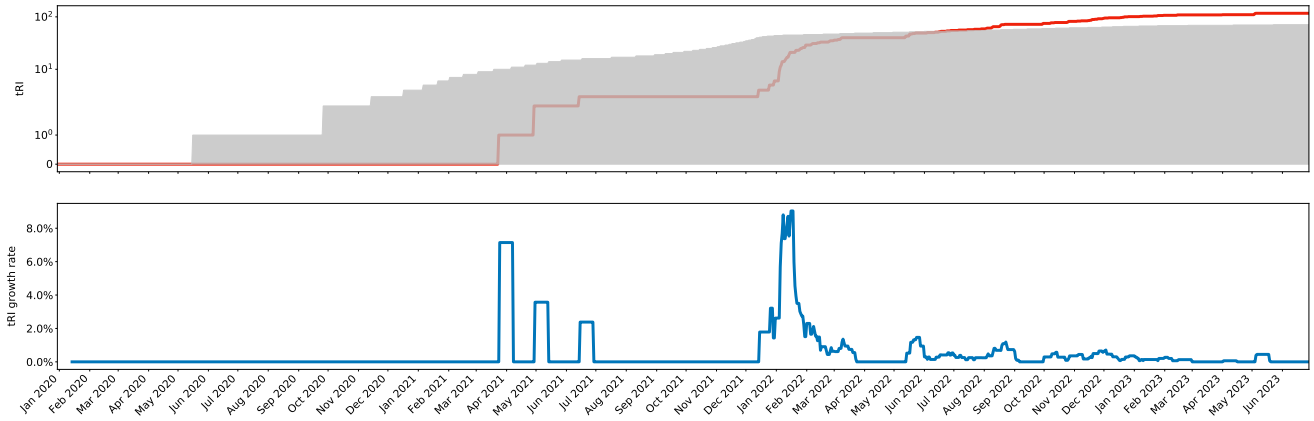
SAAV	tRI	notable variants
F456L	141	
K1045R	75	
E180V	81	
Y505H	117	Omicron
G252V	135	
Q52H	75	
N148T	127	
P621S	132	
T883I	333	
T51I	140	

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

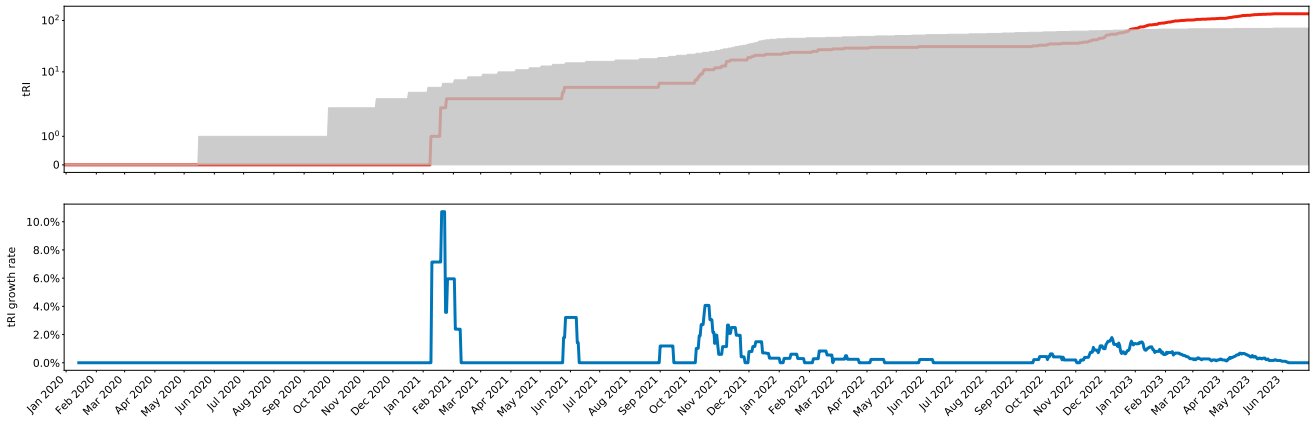
**Figure 1.** Time series analysis charts for the mutations listed in **Table 1**. Each chart shows the topological recurrence index (tRI, in red) and the tRI growth rate (in blue) from 15 January 2019 until 28 June 2023. In the upper diagram the shaded region marks the level of significance.



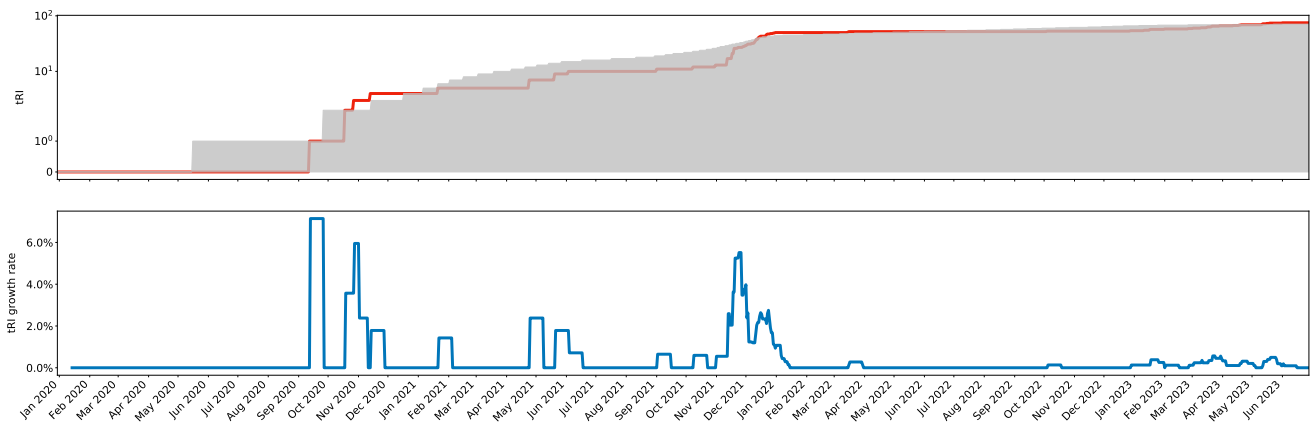
S:Y505H | contained in Omicron



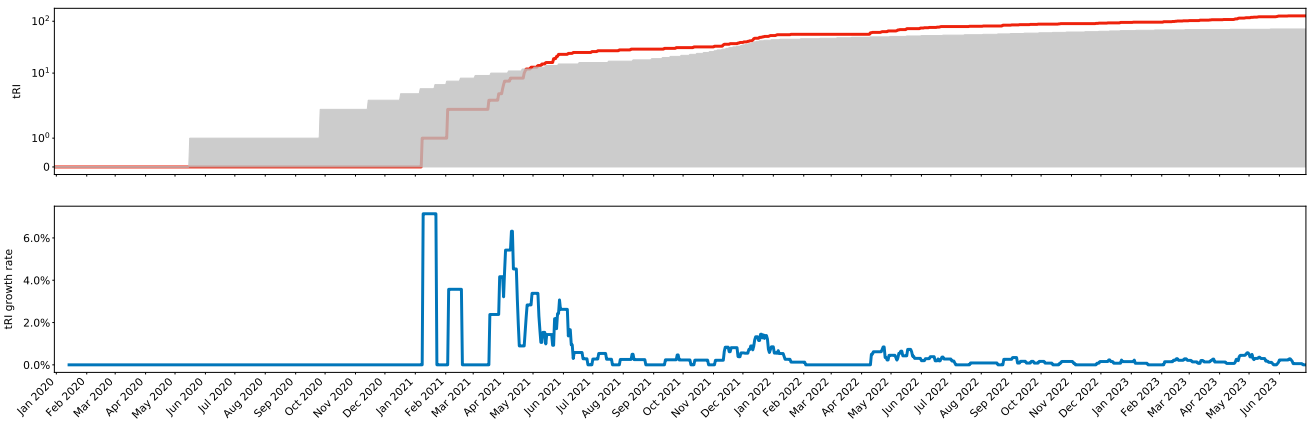
S:G252V



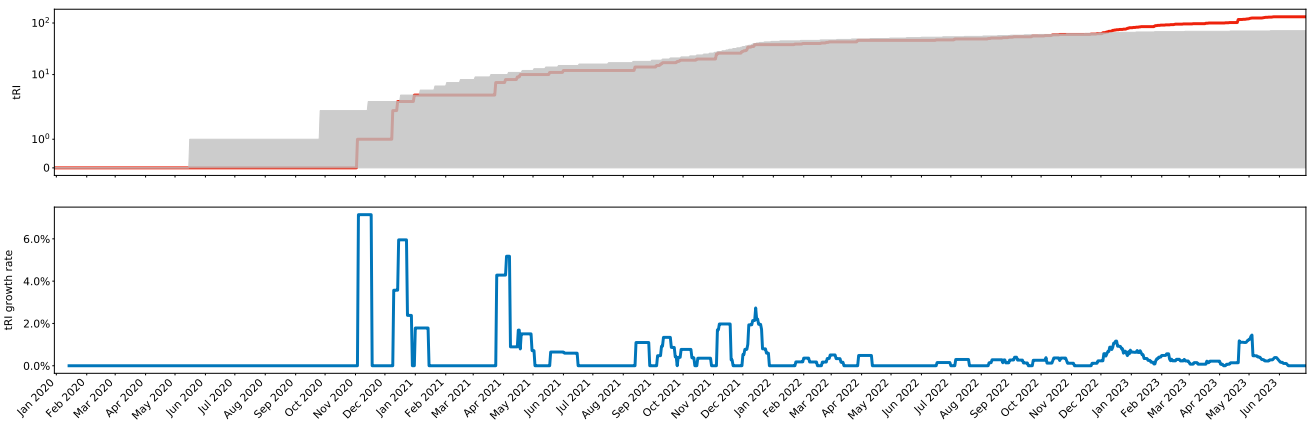
S:Q52H



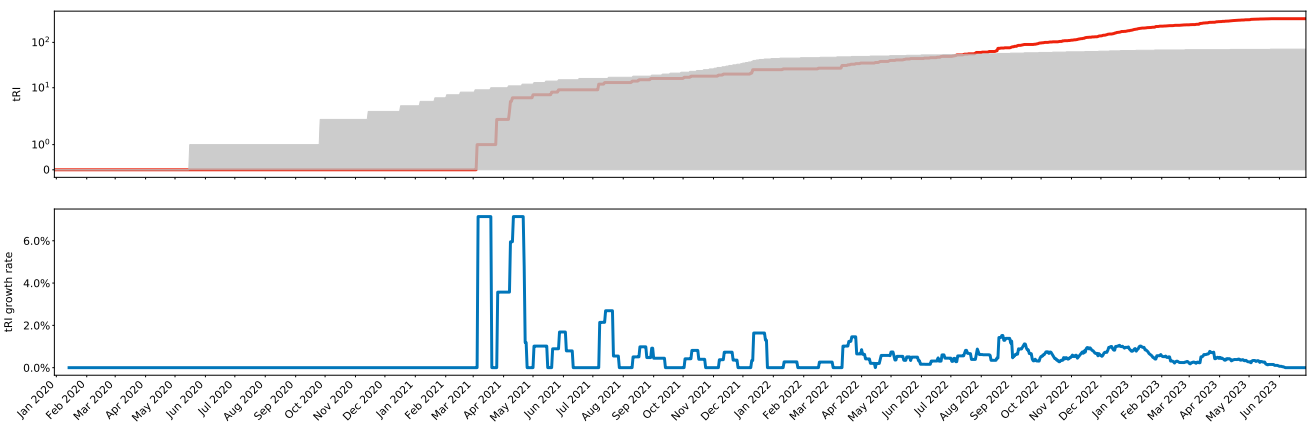
S:N148T



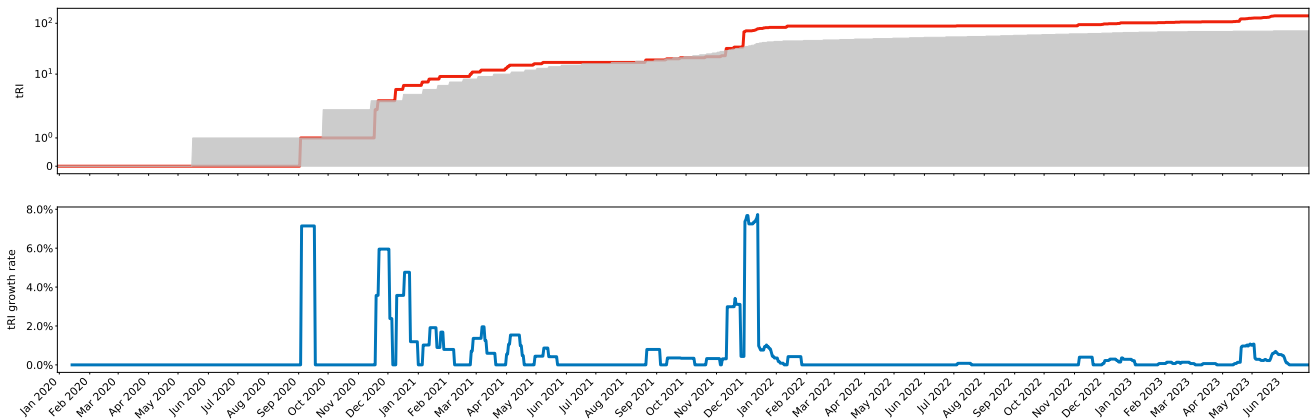
S:P621S



S:T883I



S:T511



## Methods

### Data acquisition and data preparation

Our analysis is based on the alignment `msa_0628.fasta` downloaded from the GISAID EpiCoV Database [2, 3] on 1 July 2023. This alignment comprises 14,192,791 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 9,191,612 complete SARS-CoV-2 Spike genes of length 8,052nt.

### Topological recurrence analysis

The Spike gene alignment contains a subalignment comprising 228,668 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/gis8.230703ms>. 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/gis8.230703ms>.

## 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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## 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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