INSTITUTE FOR MATHEMATICS

STRUCTURES
CLUSTER OF
EXCELLENCE

UNIVERSITÄT
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4TH WORKSHOP ON COMPUTATIONAL PERSISTENCE, GRAZ 2024

FAST COMPUTATION OF PATHWISE PERSISTENCE

IN PANDEMIC-SCALE SARS-COV-2 GENOME DATA

based on

arXiv:2106.07292

arXiv:2207.03394

& ongoing work

Joint w/

Andreas Ott, Maximilian Neumann (Karlsruhe)

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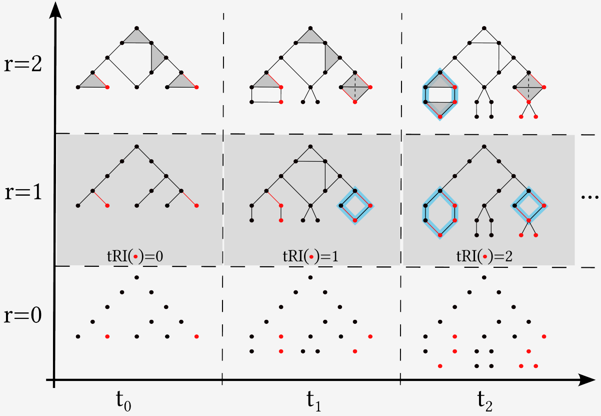
Juan Patiño-Galindo (Mount Sinai)

Mathieu Carrière (Inria Sophia-Antopolis)

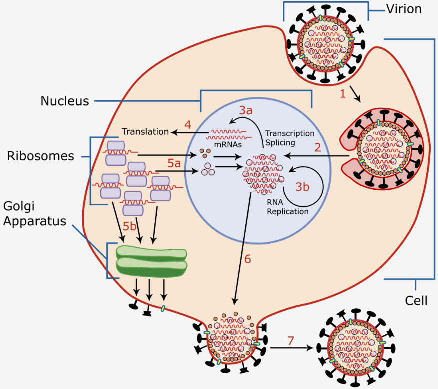
Raul Rabadan (Columbia)

Ulrich Bauer (Munich)

Samuel Braun, Holger Obermaier, Mehmet Soysal, René Caspart (Karlsruhe)



A Brief Introduction to Genomics and Epidemiology



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Viral Genome

Encodes instructions for host cell.

Sequence of nucleotides A, C, T, G.

```
>seq-id|date|location
ATGAAGAGCTTAGTCCTAG
```

Viral Life Cycle

1. Virus binds to host cell
2. Viral genome enters cell & nucleus
3. Replication and Transcription of viral RNA
4. Translation *(production of viral proteins)*

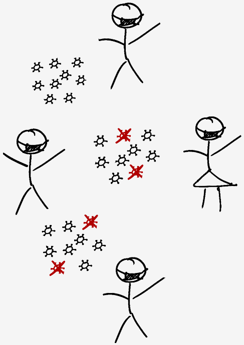
5. & 6. Assembly

7. Release

A Brief Introduction to Genomics and Epidemiology

Transmission modulates frequencies

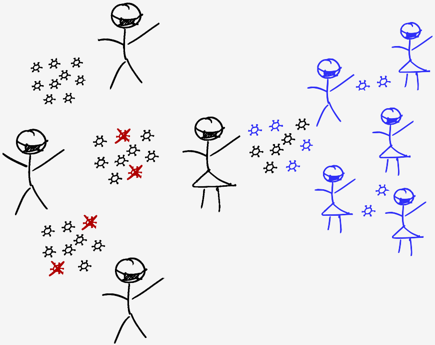
- not every mutation is beneficial



A Brief Introduction to Genomics and Epidemiology

Transmission modulates frequencies

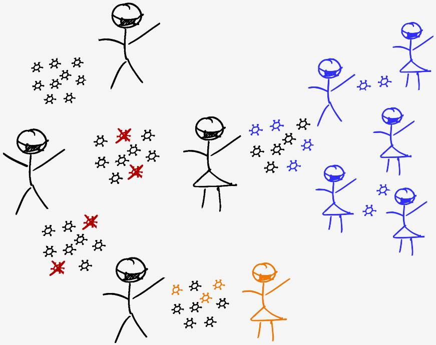
- not every mutation is beneficial
- mutations that spread widely are not necessarily beneficial (founder effects)



A Brief Introduction to Genomics and Epidemiology

Transmission modulates frequencies

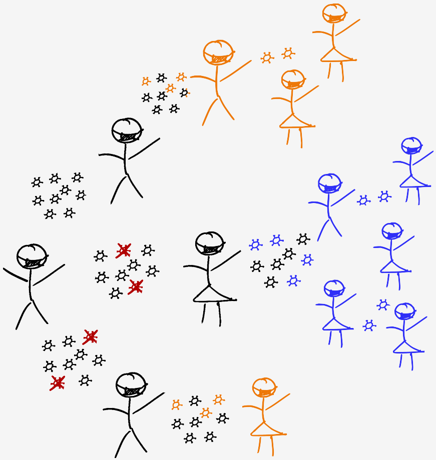
- not every mutation is beneficial
- mutations that spread widely are not necessarily beneficial (founder effects)
- not every beneficial mutation catches on



A Brief Introduction to Genomics and Epidemiology

Transmission modulates frequencies

- not every mutation is beneficial
- mutations that spread widely are not necessarily beneficial (founder effects)
- not every beneficial mutation catches on
- BUT: beneficial mutations tend to *appear repeatedly* (and may then spread more widely)



Recurrence is a hallmark of increased fitness.

Example: evolution of wings (birds, bats, insects)

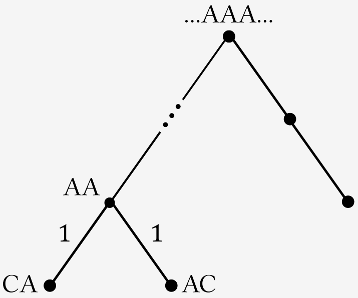
Geometry of Viral Evolution

Monitor evolution of virus and determine influence of (single or groups of) mutations on its fitness.

Construct **phylogenetic tree** from sequences.

Hamming distance = Tree distance

Minimum spanning tree reconstructs ancestral relations



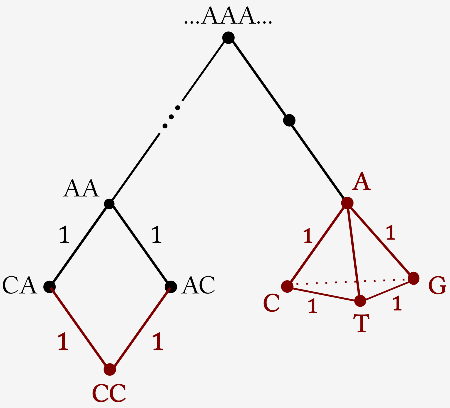
Geometry of Viral Evolution

Monitor evolution of virus and determine influence of (single or groups of) mutations on its fitness.

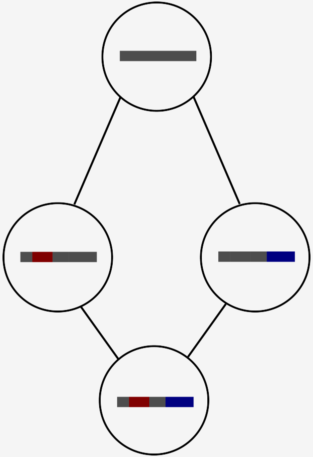
Construct **phylogenetic network** from sequences.

Hamming distance $\neq$ Tree distance

Minimum spanning tree reconstructs ancestral relations, but is not unique.



Topology of Viral Evolution



Reassortment

Some viruses have disconnected genome, e.g. Flu (HxNy).
Co-infection can lead to ”reassortment” during assembly.

Recombination

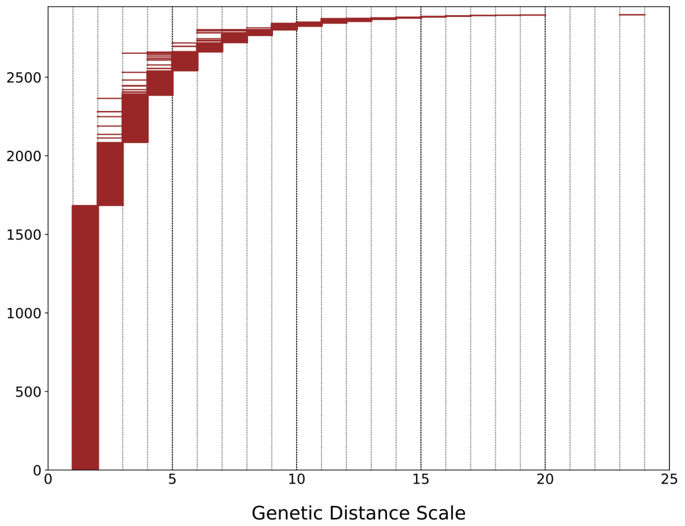
Replication apparatus can switch RNA template.
Co-infection can lead to recombination into a hybrid genome.

Convergence

independent emergence of similar traits.

$\Rightarrow$ **cycles in phylogenetic network at different scales.**

Persistent Homology of SARS-CoV-2



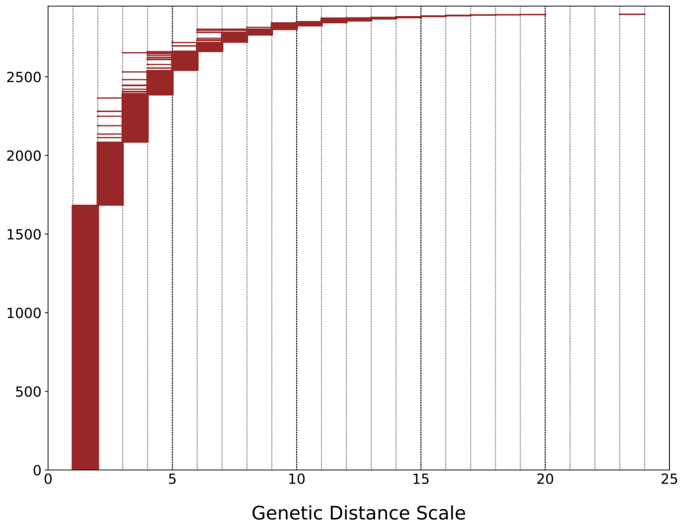
February 28th, 2021

$\sim 450,000$ isolates

$\sim 160,000$ unique sequences

$\Rightarrow |H_1| \sim 2,900$

Persistent Homology of SARS-CoV-2



February 28th, 2021

$\sim 450,000$ isolates
$\sim 160,000$ unique sequences

$\Rightarrow |H_1| \sim 2,900$

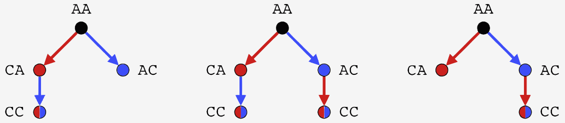
How? Luck and patience.

Signal or Noise?

Back-of-the-envelope

$p \simeq 2/30,000 \simeq \mathcal{O}(10^{-4})$
#unique sequences $= \mathcal{O}(10^6)$

$\Rightarrow$ expect $\mathcal{O}(100)$ cycles are noise



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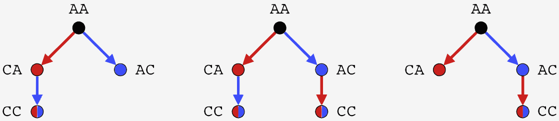
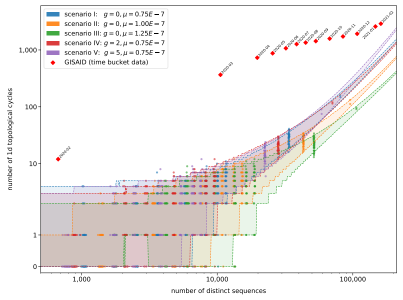


Simulations of neutral evolution

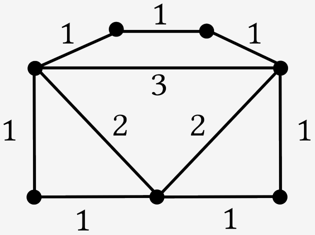
- uniform mutation probability
- no fitness advantages
- no recombinations

$\Rightarrow$ expect 350-400

(at worst: $1,200 \sim 50\%$)



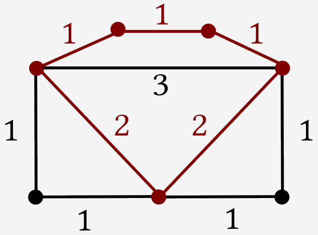
The topological Recurrence Index (tRI)



example: $[1, 3)$-persistent class

Which mutations are responsible for homology?

The topological Recurrence Index (tRI)



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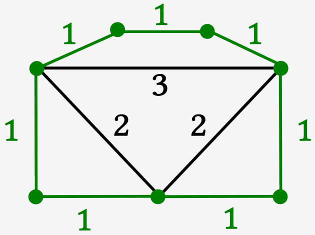
The topological Recurrence Index (tRI)



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Which mutations are responsible for homology?

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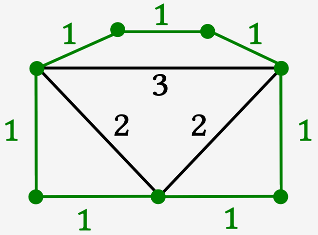
from **exhaustive** reduction

Every edge of length 1 corresponds to a unique single neucleotide variation (SNV).

The topological Recurrence Index (tRI)



example: $[1,3)$-persistent class

Which mutations are responsible for homology?

use cycle representatives
from **exhaustive** reduction

Every edge of length 1 corresponds to a unique single neucleotide variation (SNV).

SNV-cycles := Exhaustive representatives of $[1,d)$ classes

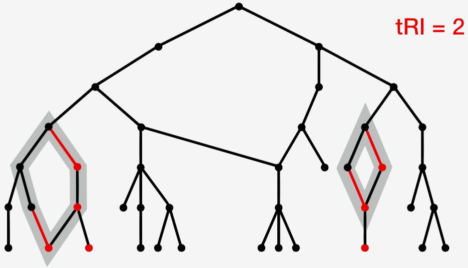
The topological Recurrence Index (tRI)

Z_{SNV} – set of all SNV-cycles in H_1

μ – mutation of interest

(notation: **RefPosAlt**, e.g. **D614G**)

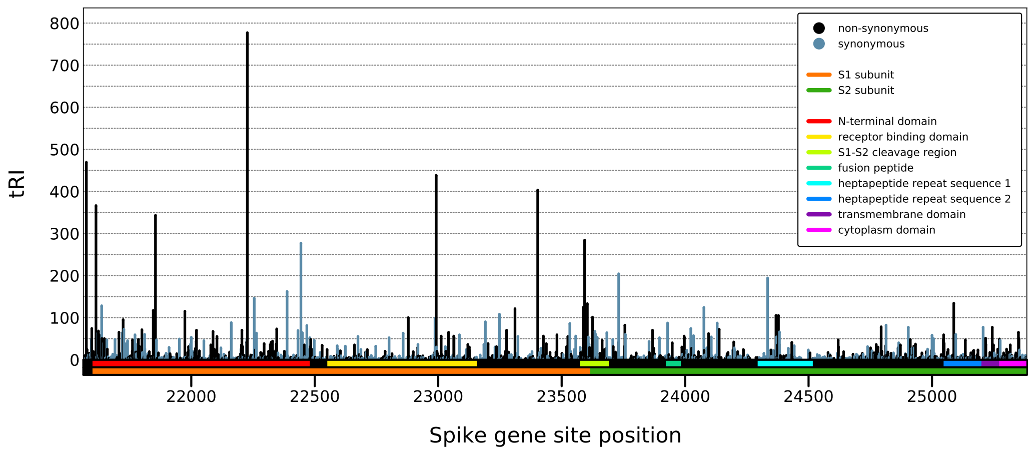
$$\mathrm{tRI}(\mu) := \#\{\gamma \in Z_{\mathrm{SNV}} \mid \mu \in \gamma\}$$



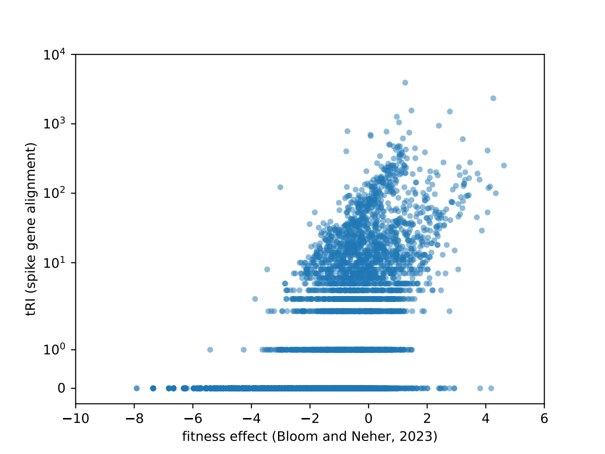
$\Longrightarrow$ **tRI is a measure for convergence**

(and thus fitness)

Topological Recurrence of Spike mutations

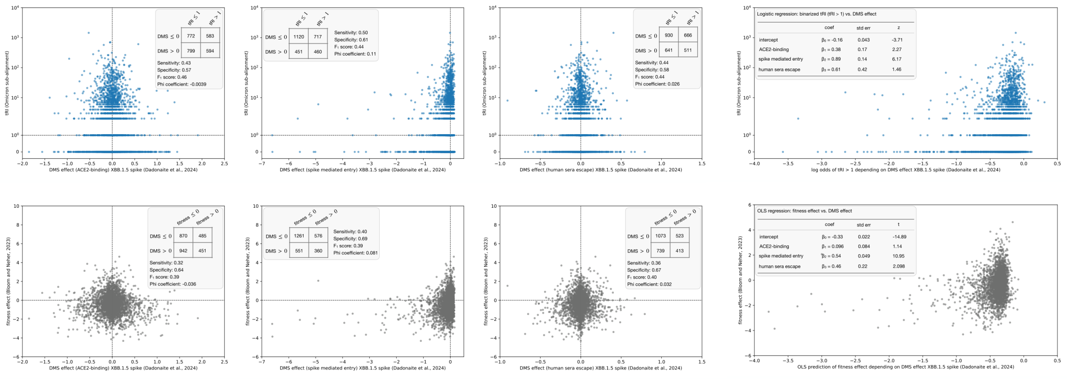


Comparison with Established Fitness Measures



tRI is correlated with tree-based fitness index (Bloom & Neher, 2022)

Comparison with Established Fitness Measures



	tRI ≤ 1	tRI > 1
DMS ≤ 0	772	583
DMS > 0	799	594

Sensitivity: 0.43
Specificity: 0.57
F_1 score: 0.46
Phi coefficient: -0.0039

	tRI ≤ 1	tRI > 1
DMS ≤ 0	1120	717
DMS > 0	451	460

Sensitivity: 0.50
Specificity: 0.61
F_1 score: 0.44
Phi coefficient: 0.11

	tRI ≤ 1	tRI > 1
DMS ≤ 0	930	666
DMS > 0	641	511

Sensitivity: 0.44
Specificity: 0.58
F_1 score: 0.44
Phi coefficient: 0.026

Logistic regression: binarized tRI (tRI > 1) vs. DMS effect

	coef	std err	z
intercept	$\beta_0 = -0.16$	0.043	-3.71
ACE2-binding	$\beta_1 = 0.38$	0.17	2.27
spike mediated entry	$\beta_2 = 0.89$	0.14	6.17
human sera escape	$\beta_3 = 0.61$	0.42	1.46

	fitness ≤ 0	fitness > 0
DMS ≤ 0	870	485
DMS > 0	942	451

Sensitivity: 0.32
Specificity: 0.64
F_1 score: 0.39
Phi coefficient: -0.036

	fitness ≤ 0	fitness > 0
DMS ≤ 0	1261	576
DMS > 0	551	360

Sensitivity: 0.40
Specificity: 0.69
F_1 score: 0.39
Phi coefficient: 0.081

	fitness ≤ 0	fitness > 0
DMS ≤ 0	1073	523
DMS > 0	739	413

Sensitivity: 0.36
Specificity: 0.67
F_1 score: 0.40
Phi coefficient: 0.032

OLS regression: fitness effect vs. DMS effect

	coef	std err	t
intercept	$\beta_0 = -0.33$	0.022	-14.89
ACE2-binding	$\beta_1 = 0.096$	0.084	1.14
spike mediated entry	$\beta_2 = 0.54$	0.049	10.95
human sera escape	$\beta_3 = 0.46$	0.22	2.098

tRI is correlated with experimental measures of fitness increase.

Time, Multipersistence, and a Computational Trick

Include time series information

→ **2-parameter persistence**

Good News: Get all SNV-cycles from restriction to 1d subfiltration @ $r = 1$.

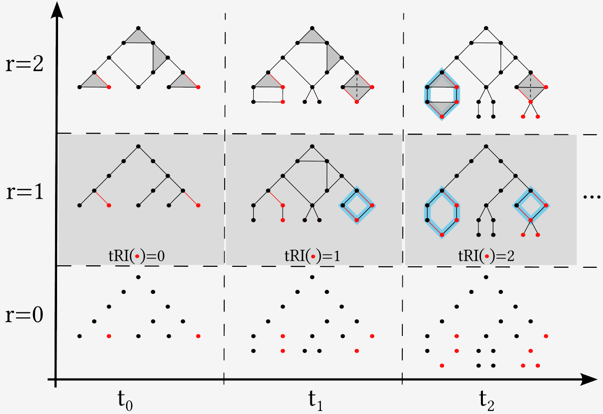
Trick: Equivalent to deformation of metric

→ **Ripser "Add-on":** `MuRiT`

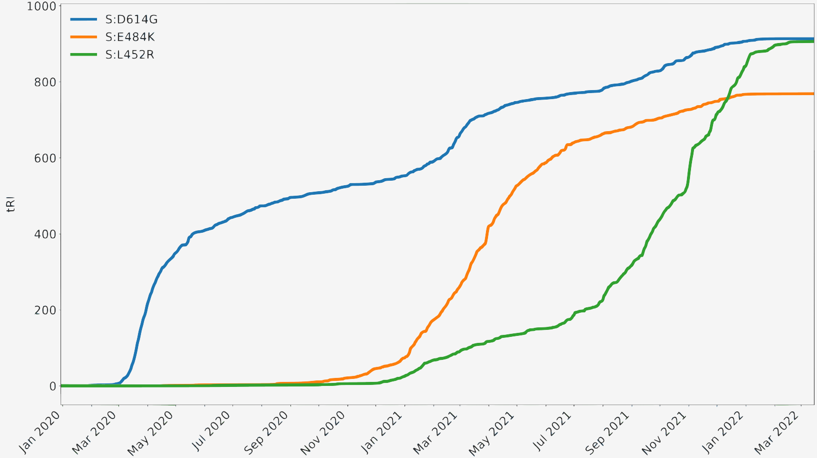
Multipersistence through Rips Transformations

calculates pathwise persistence from

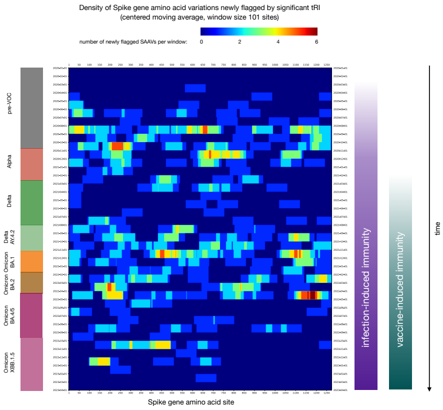
distance matrix + additional filtration



EvotRec.py – Evolution of topological Recurrence



Dynamic Fitness Landscape and Epistasis


Density of Spike gene amino acid variations newly flagged by significant tRI
(centered moving average, window size 101 sites)

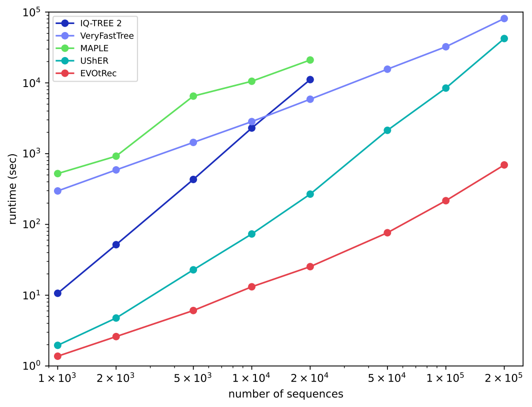
time-resolved tRI activity along the genome shows surprising amount of time-dependence.

Looks like tRI measures *epistasis*:
influence of current mutational background on fitness of newly acquired mutations.

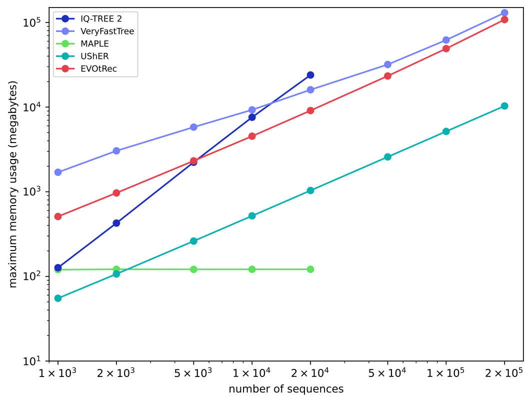
This is possible because SNV-cycles are *localized* in a particular genetic background.

Computational Benchmarks

Runtime

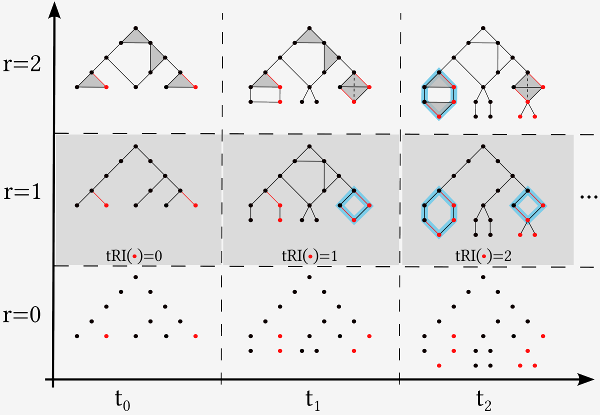


Memory



Summary

- Persistent homology measures evolutionarily relevant phenomena
- topological Recurrence Index (tRI) is sensitive to fitness effects
- `EvotRec` computations are fast and efficient
- tRI activity might allow study of epistasis
- Differentiation between beneficial and deleterious mutations must rely on experiments, but persistent homology can tell us where to look



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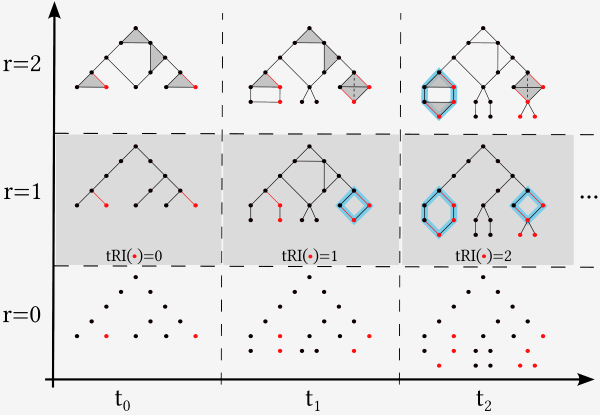

Thank you!