Split Scores on Phylogenetic Trees and Applications

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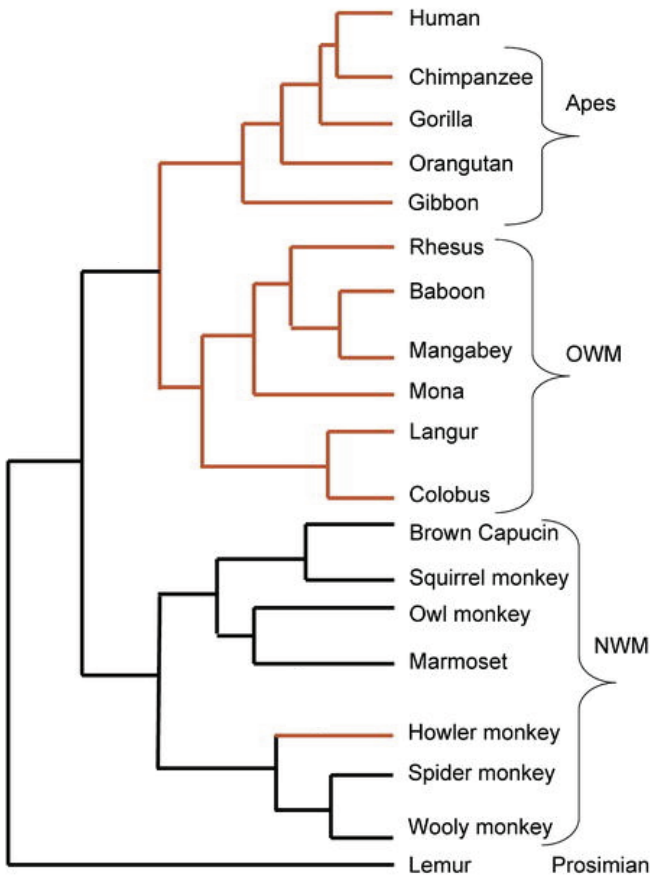
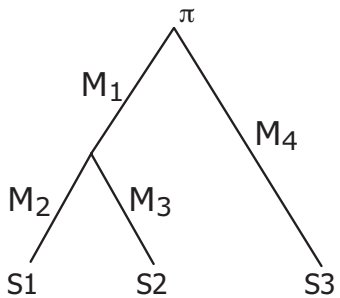
Theory: Split scores



Phylogenetic Tree of Primates

Under the general Markov model on phylogenetic trees, one can associate a score with an edge in the tree.

General Markov model on T



Model parameters =

$$\begin{cases} \text{tree topology} \\ \text{root distribution vector } \boldsymbol{\pi} = (\pi_i) \\ \text{Markov matrix on each edge } M_e \end{cases}$$

Under the iid assumption, one can compute the

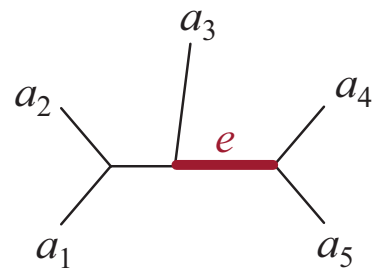
expected site pattern frequencies, e.g. p_{AAAAA}

```
Gorilla      AAGCTTCACCGGCGCAGTTGTTCTTATAATTGCCCACGGACTTACATCAT...
Orangutan    AAGCTTCACCGGCGCAACCACCCTCATGATTGCCCATGGACTCACATCCT...
Human        AAGCTTCACCGGCGCAGTCATTCTCATAATCGCCCACGGGCTTACATCCT...
Chimpanzee   AAGCTTCACCGGCGCAATTATCCTCATAATCGCCCACGGACTTACATCCT...
Gibbon       AAGCTTTACAGGTGCAACCGTCCTCATAATCGCCCACGGACTAACCTCTT...
```

Data: *empirical* $\widehat{p}_{AAAAA}$. Ideally, $\widehat{p}_{AAAAA} \approx p_{AAAAA}$.

Idea: Associate score to edge in tree.

Pattern frequency array has a natural 'flattening' according to splits in the tree:



$\mathbf{a_1a_2a_3 \mid a_4a_5}$.

The flattening for this split is the matrix

$$\mathbf{AAA} \rightarrow \begin{pmatrix} p_{\mathbf{AAA}AA} & p_{\mathbf{AAA}AC} & p_{\mathbf{AAA}AG} & \cdots & p_{\mathbf{AAA}TT} \\ p_{AACAA} & p_{AACAC} & p_{AACAG} & \cdots & p_{AACTT} \\ p_{AAGAA} & p_{AAGAC} & p_{AAGAG} & \cdots & p_{AAGTT} \\ p_{AATAA} & p_{AATAC} & p_{AATAG} & \cdots & p_{AATTT} \\ p_{ACAAA} & p_{ACAAC} & p_{ACAAG} & \cdots & p_{ACATT} \\ p_{ACCAA} & p_{ACCAC} & p_{ACCAG} & \cdots & p_{ACCTT} \\ p_{ACGAA} & p_{ACGAC} & p_{ACGAG} & \cdots & p_{ACGTT} \\ p_{ACTAA} & p_{ACTAC} & p_{ACTAG} & \cdots & p_{ACTTT} \\ \vdots & & & \ddots & \vdots \end{pmatrix} \quad \mathbf{TT} \downarrow$$

Rows and columns are indexed by states at conglomerate variables $a_1a_2a_3$ and a_4a_5.

A 16×64 matrix is defined analogously for the split $a_1a_2 \mid a_3a_4a_5$.

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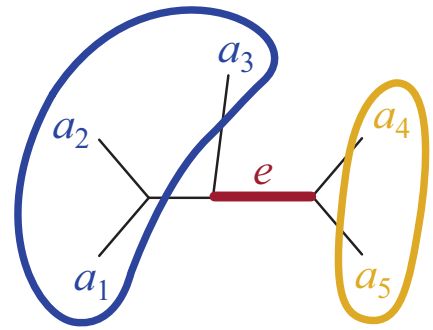

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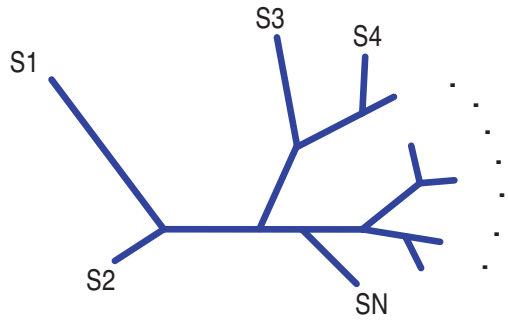
Theorem:

Given GM on an n-taxon tree, each matrix flattening corresponding to an edge of the tree has rank 4.

Otherwise the rank > 4.



Germ of idea:

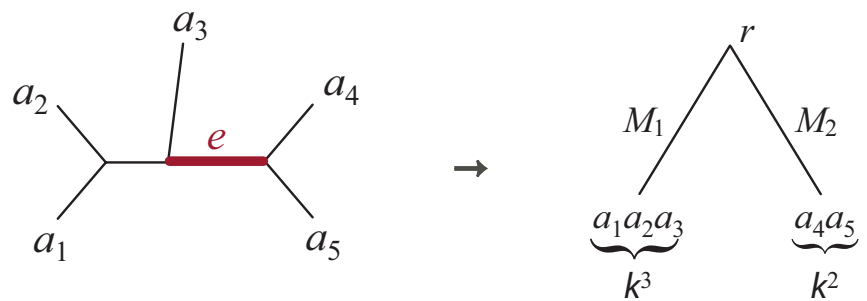
$$\text{matrix flattening rank} = 4 \iff \text{edge in tree}$$

$$\Updownarrow$$

$$\text{singular value decomposition}$$

Theorem: Given GM on an n-taxon tree, each matrix flattening corresponding to an edge of the tree has rank 4. Otherwise the rank > 4.

Focusing on edge e leads to a 'simpler' graphical model:



$$\text{5-dim tensor} \quad \rightsquigarrow \quad 4^3 \times 4^2 \text{ matrix}$$

$$P = \left(p_{AAAAA,\, etc}\right) \text{ flattens to a matrix } P_e$$

with a matrix factorization $P_e = M_1^T \operatorname{diag}(\boldsymbol{\pi}_\mathbf{r}) M_2$.

Connections to tensor rank, latent class models, ...

Other applications of result

- Ideals and Varieties:

  Allman-Rhodes: "Phylogenetic Ideals and Varieties for the general Markov model on trees"

  Draisma-Kuttler: Ideal theoretic version of theorems

- Parameter identifiability results: (Covarion models, mixture models, ...)

- Tree reconstruction algorithms:

  Eriksson 2005: Tree construction algorithm using SVD (GM)

  Kubatko and Chifman 2014: `SVDquartets` (GTR)

  Casanellas and Fernández-Sánchez 2016: `Erik+2` quartet-based (GM)

How can we use these ideas for inference?

- **Software in C:** `SplitSup`
  - Input: aligned sequences, splits to be tested
  - Steps:

    Construct the matrix flattening for current split
    (sparse matrix, binary encoding of patterns)

    Compute four largest singular values
    (svdlibc package)

    Compute **score** and write to file. Repeat.
- $\rightsquigarrow$ *EXTREMELY FAST*
- Our **score** based on the SVD is in the range $[0, 1]$ with 0 good. For the split $A \mid B$ with matrix flattening $P_{A|B}$, the score is

$$\sqrt{\frac{\sum_{i=5}^{k} \sigma_i^2}{\sum_{i=1}^{k} \sigma_i^2}} = \frac{\sqrt{\sum_{i=5}^{k} \sigma_i^2}}{\|P_{A|B}\|_F}$$

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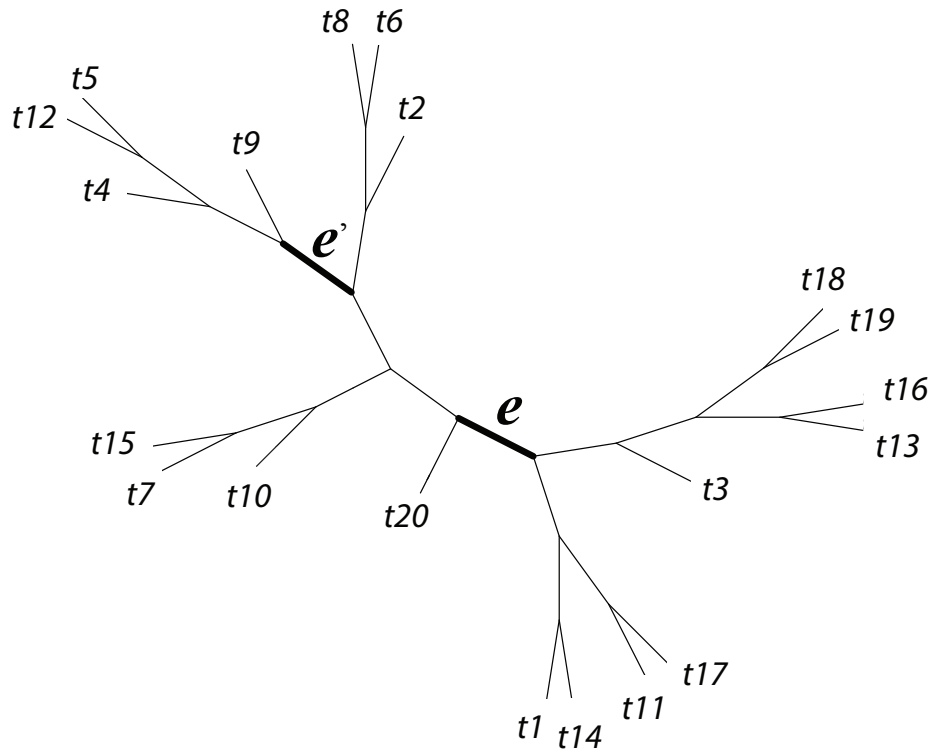
Properties of splits scores

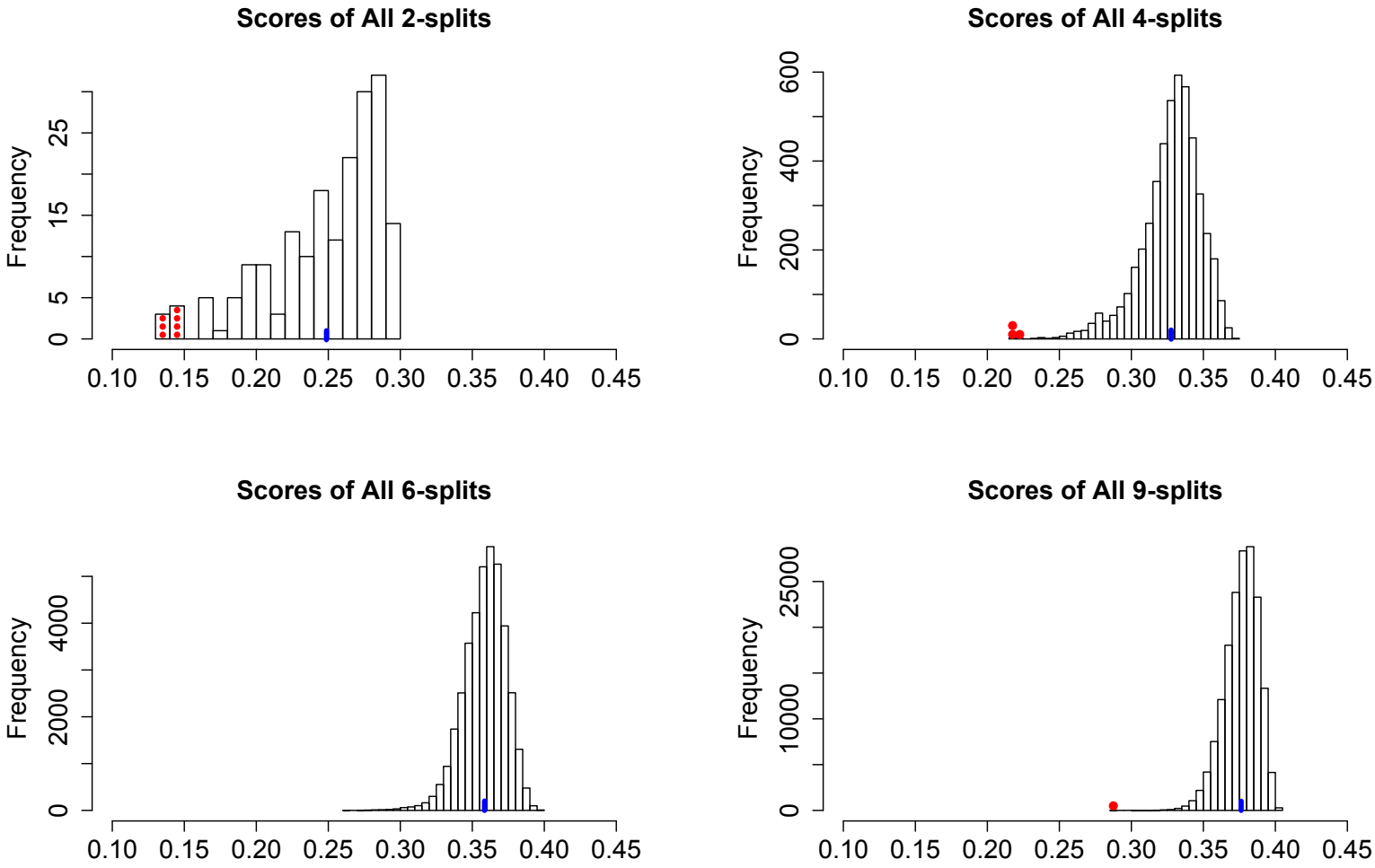
20 taxon tree used for simulations



Simulations: Jukes-Cantor model

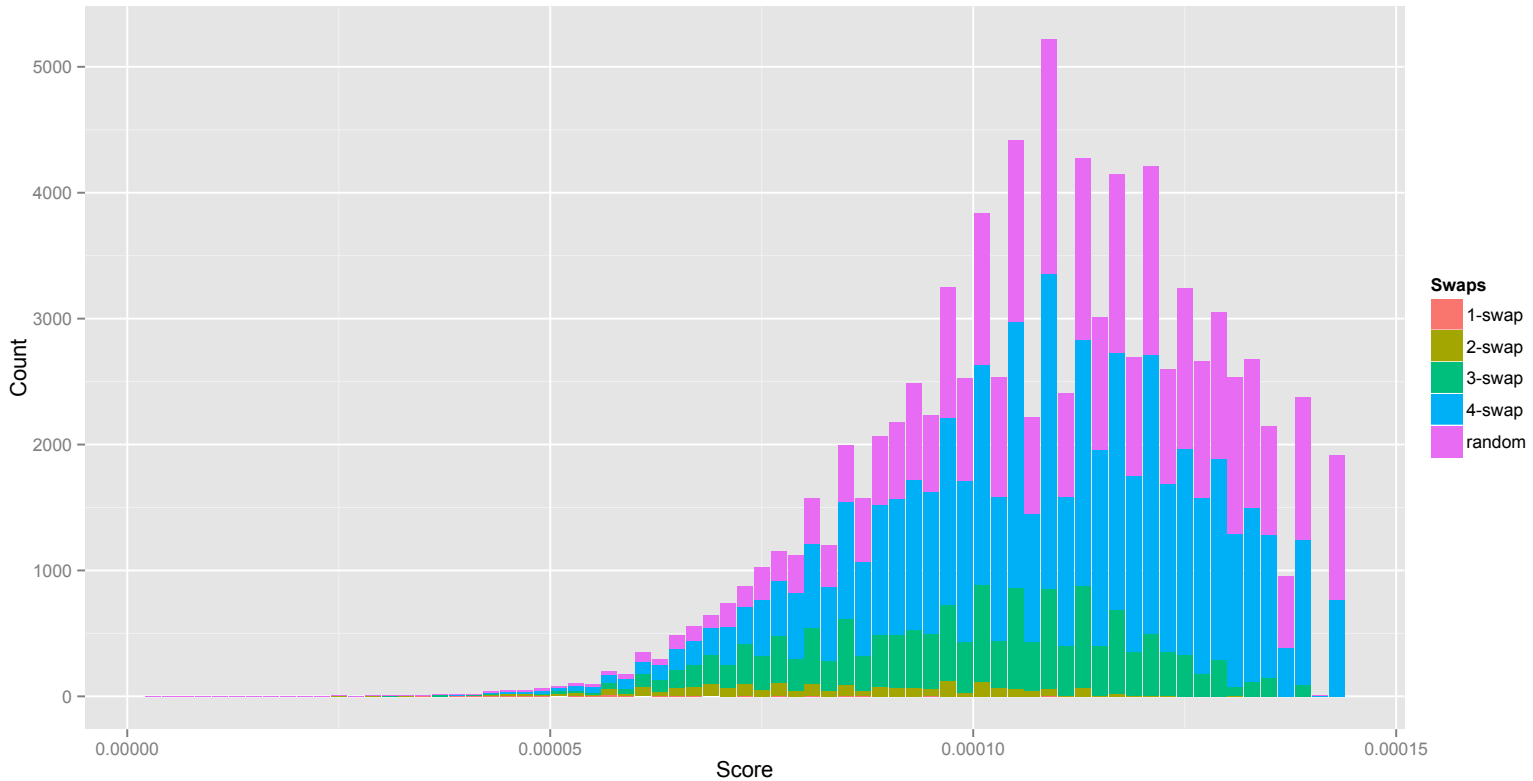
e' = 4-split, e = 9-split, false splits

Application 1: Identify true phylogenetic splits



True splits in tree shown with red dots. Smallest scores.

Application 1: Identify close to true phylogenetic splits

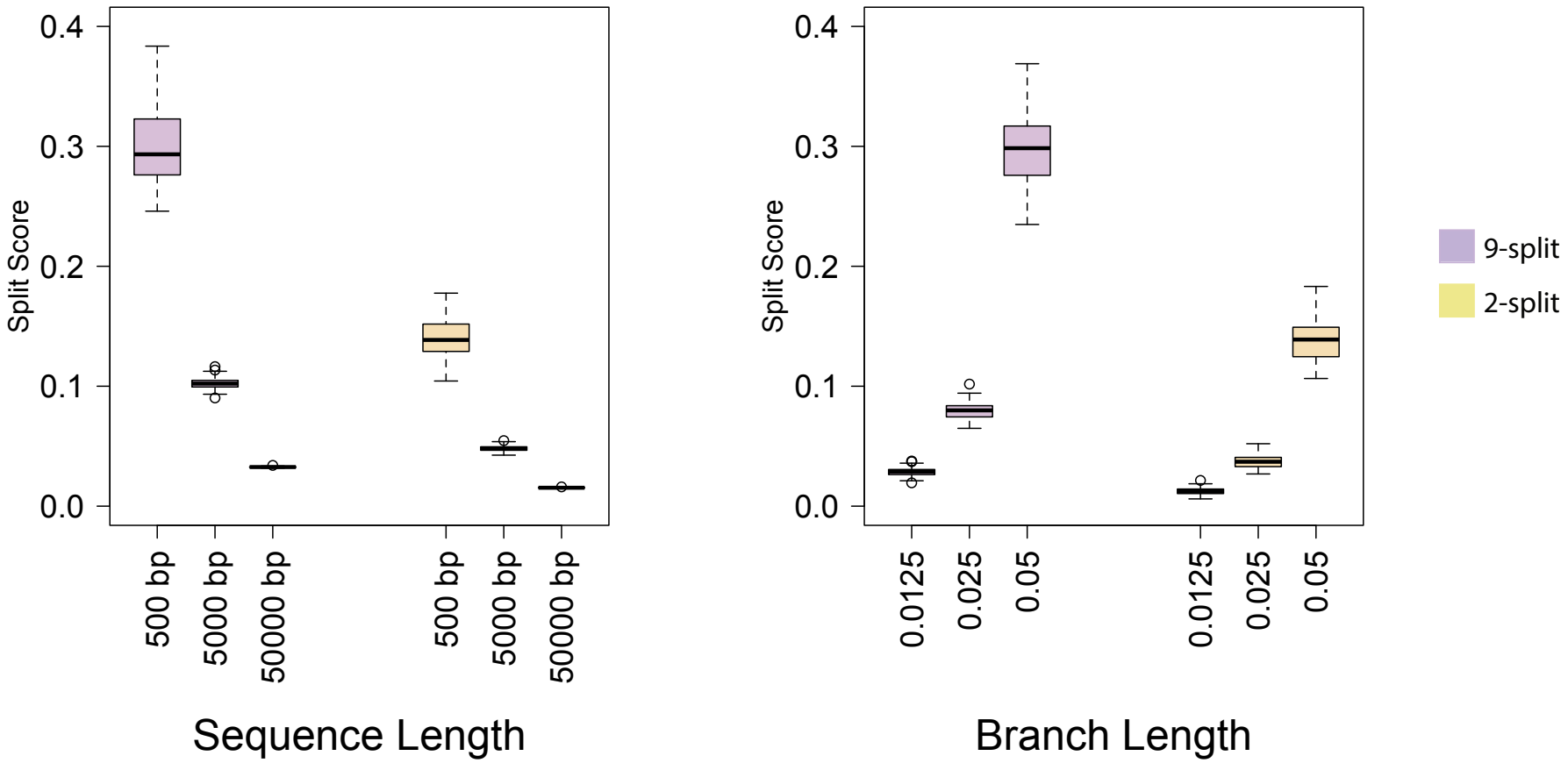


Fix true 10-split and plot scores for 10-splits that differ by 1 taxon, 2 taxa, ...

Properties: Sequence length and branch length effects

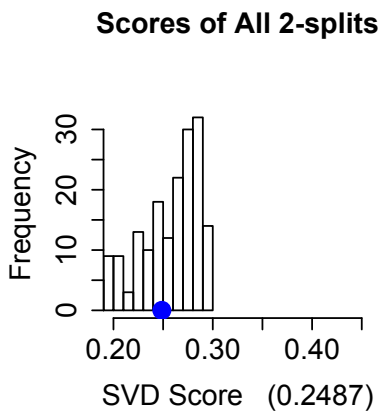
(L) Split scores for true splits decrease with sequence length.

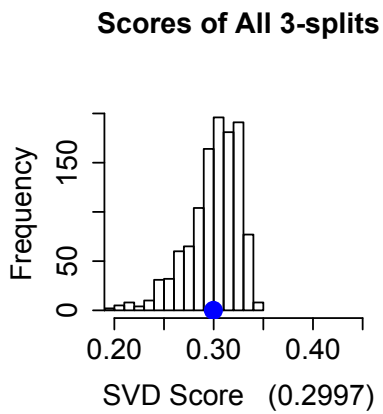
(R) Split scores scale with tree diameter.

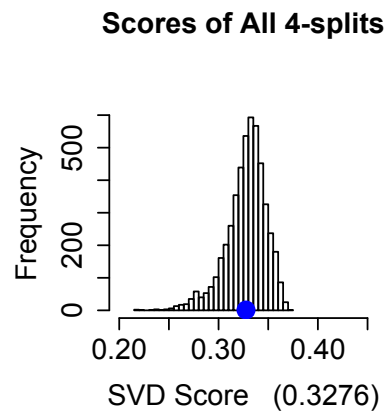


Properties: Split size effect

Split scores increase with split size.





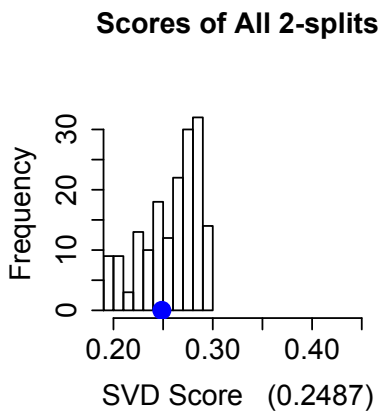


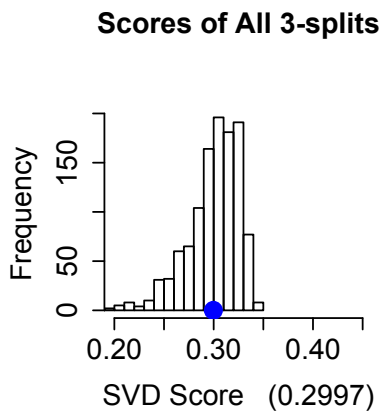
Mean of the observed distribution of split scores for a fixed size $k \,\big|\, (N-k)$ increases with k. Standard deviation decreases.

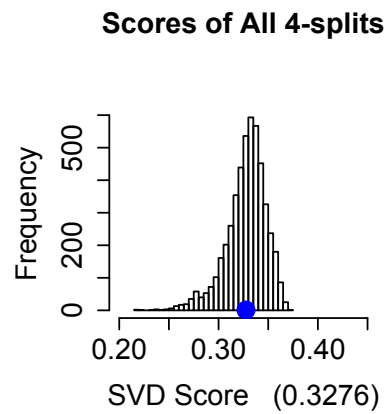
Caution: For use with data, comparisons should be made among splits of same size $k \,\big|\, N-k$.

Properties: Split size effect

Split scores increase with split size.







Dimension of rank varieties $4(4^k + 4^{N-k}) - 16$

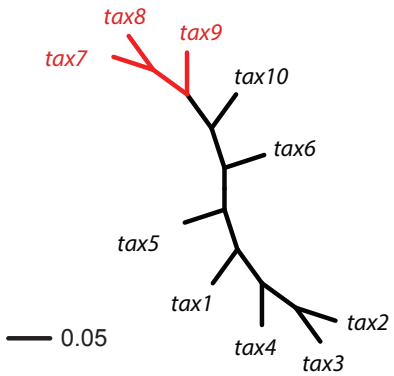
$$\min \text{ at } k = \frac{\lfloor N \rfloor}{2}, \quad \max \text{ at } k = 2$$

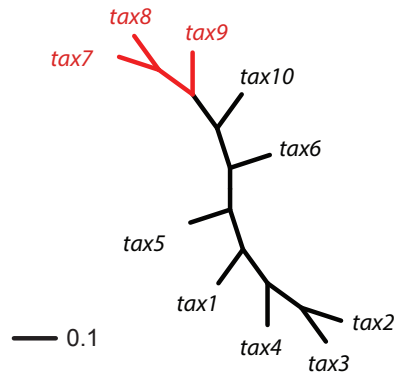
$\rightsquigarrow$ why Eriksson algorithm performs poorly in practice

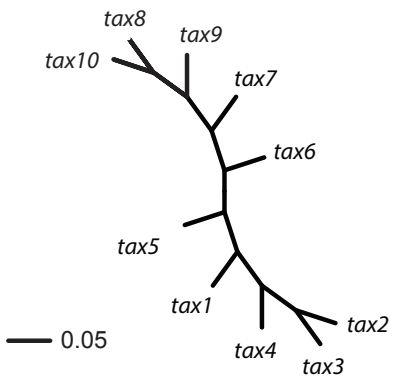
Application 2: Detecting shifts in evolutionary process along a chromosome

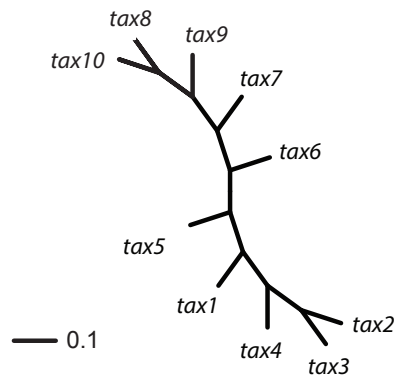
'Sliding Window Analysis'

Four phylogenies along a chromosome







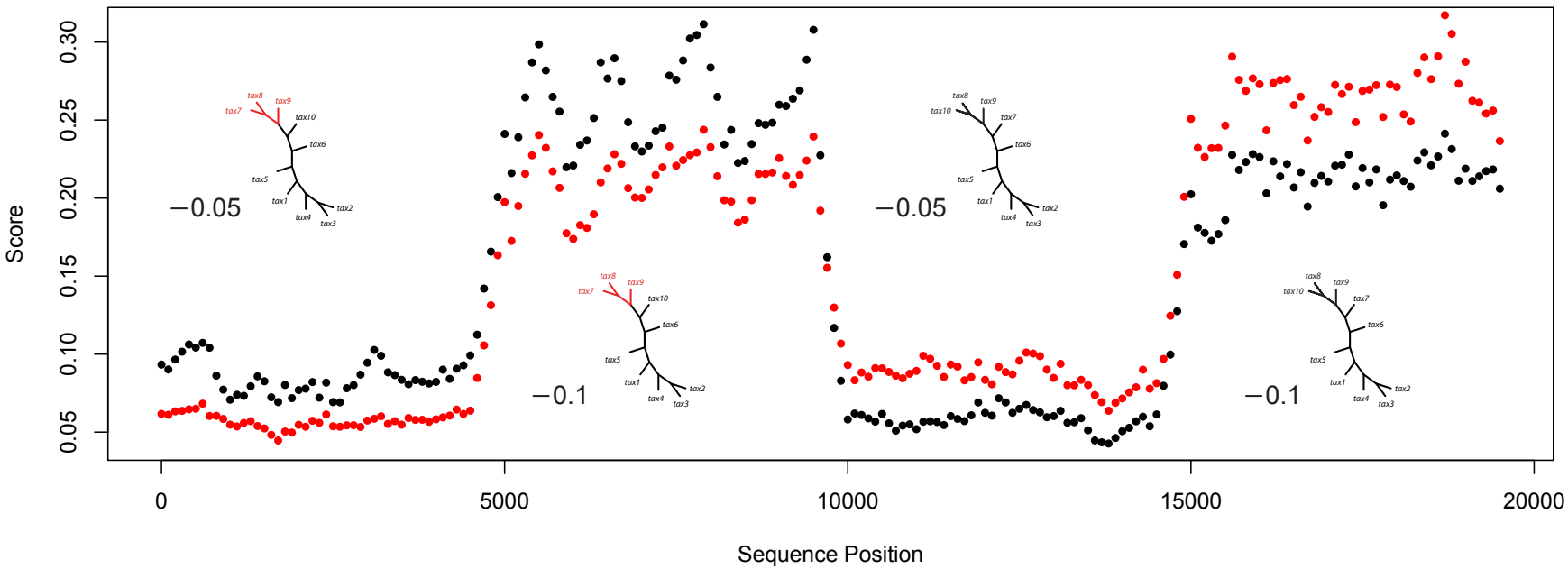


5000 bp were simulated for each model tree, JC model, then concatenated

Application 2: Detecting shifts in evolutionary process along a chromosome

7-8-9 split

8-9-10 split



Lower scores indicate better fit. 'Best' score shifts with model tree.

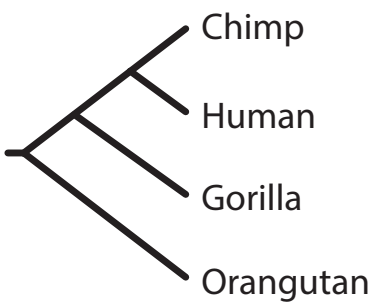
Methods: JC model 5000 bp per tree, concatenated block size: 500 bp, offset: 100 bp

Application 2: Detecting shifts in evolutionary process along a chromosome

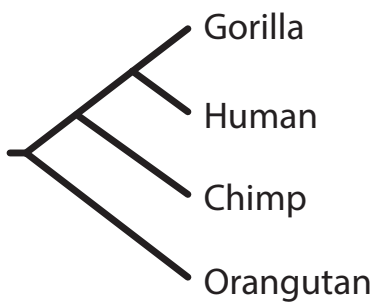
How does this perform for empirical data?

Consider the chromosome 7 data of Patterson et al. *Nature* (2006), used here to examine the relationships among human-chimp-gorilla.

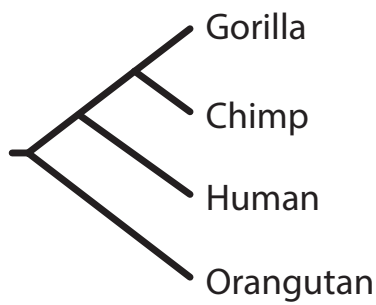
Three possible gene trees:



(HC)G



(GH)C



(GC)H

Species trees $\neq$ gene trees.

Application 2: Detecting shifts in evolutionary process along a chromosome

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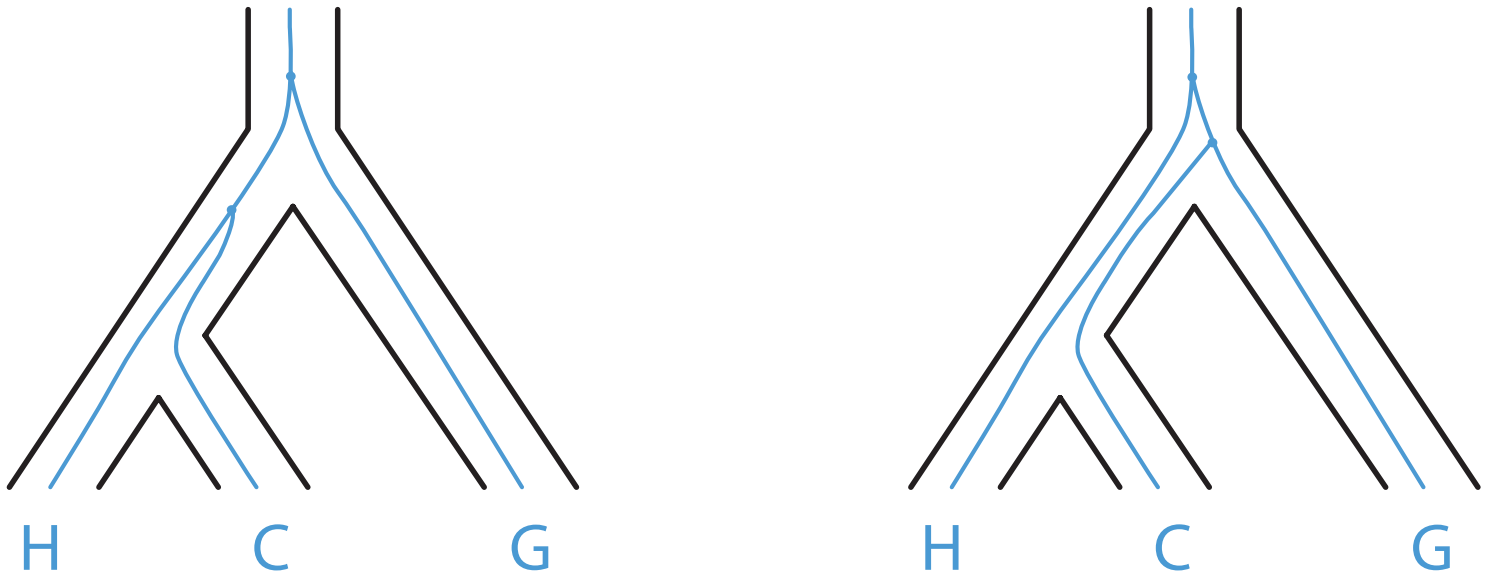

Gene trees $((H, C), G)$ and $(H, (C, G))$

in species tree $((h, c), g)$

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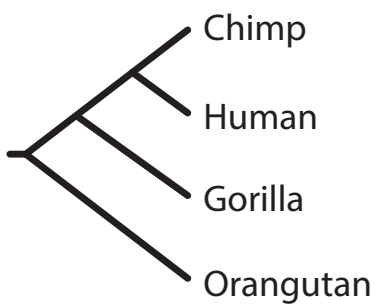

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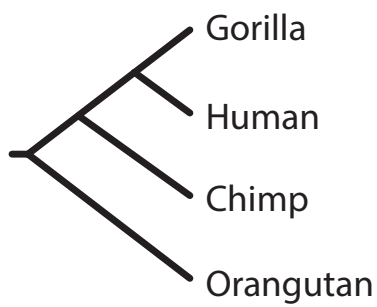

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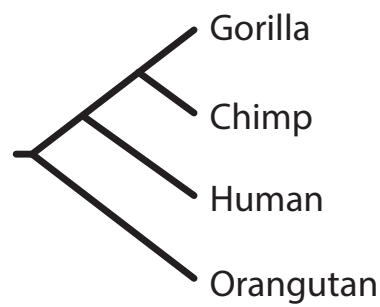

(GC)H

QUICK scan of Chromosome 7 in blocks of size 2000 bp

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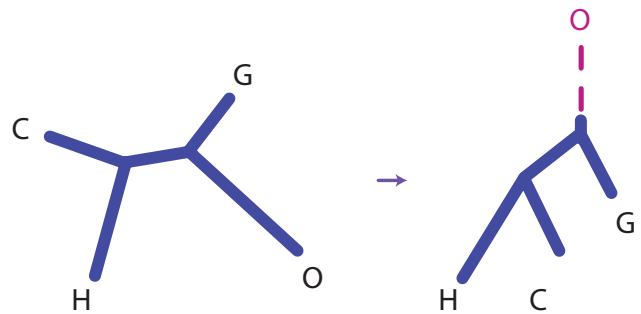
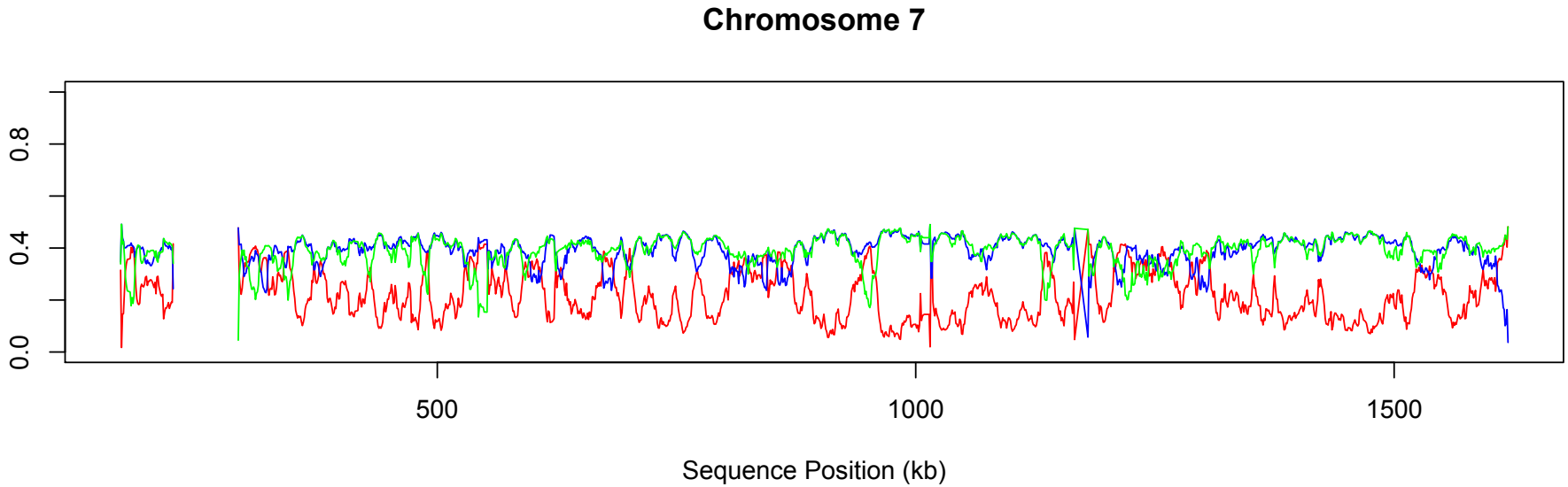


Outgroup is used to root tree, then deleted.

QUICK scan of Chromosome 7 in blocks of size 2000 bp

Application 2: Detecting shifts in evolutionary process along a chromosome

Empirical data of Patterson et al. (2006):



(HC)G (GH)C (GC)H

Chr 7 has
1,903,271 bp

window size:	2000 bp
slide size:	1000 bp
min no of sites required:	500 bp

Application 2: Detecting shifts in evolutionary process along a chromosome

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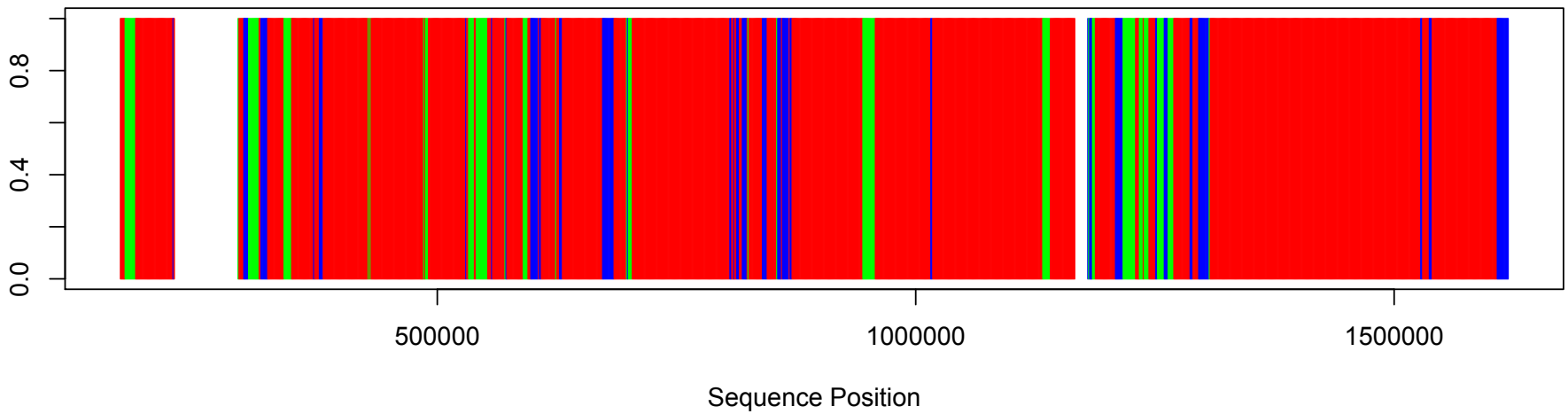

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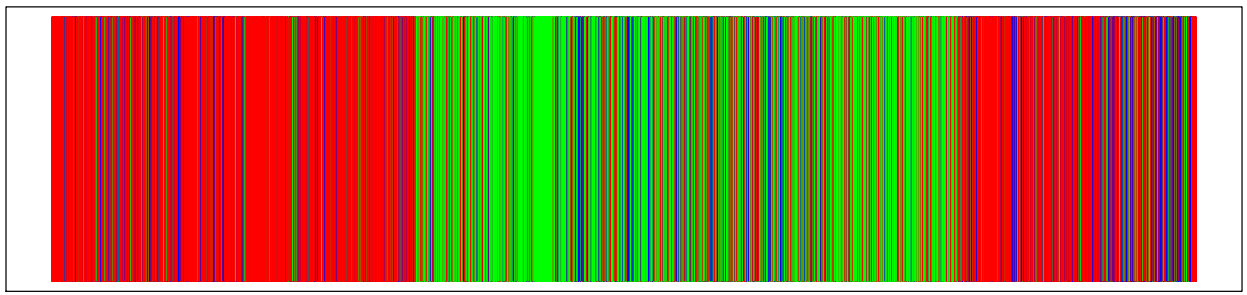
Application 2: Detecting shifts in evolutionary process along a chromosome

Mosquito Data – Fontaine et al. (2015): phylogenomic analysis of whole genomes from *Anopheles gambiae* species complex.



Sequence Position

Sliding window method picks out rough location of known chromosome 2L inversion as a shift in the phylogeny.

Chr 2L has $\sim$ 37.5-million bp

window size:	10,000 bp
slide size:	1000 bp
min no of sites required:	500 bp

red vertical line = *An. gambiae-An. coluzzii* clade (known sister species)
green vertical line = *An. coluzzii-An. arabiensis* clade

Application 2: Detecting shifts in evolutionary process along a chromosome

Viral Data — Alicai et al. (2016):

Whole-genome alignment of the 10 distinct genes for all 29 individual samples (3 new).

$$\begin{cases} \text{14 samples of Cassava Brown Streak Virus (CBSV)} \\ \text{15 samples of Ugandan Cassava Brown Streak Virus (UCBSV)} \end{cases}$$

Phylogenetic analysis:

Strong support for CBSV | UCBSV split.

CBSV has an accelerated rate of evolution compared to UCBSV, matching field observations of increased virulence for these strains.

Sliding window analysis: Do changes in the score across the genome indicate which genes may be involved in the shift in evolutionary rate of CBSV?

Application 2: Detecting shifts in evolutionary process along a chromosome

Viral Data — Alicai et al. (2016):

Whole-genome alignment of the 10 distinct genes for all 29 individual samples (3 new).

$$\begin{cases} \text{14 samples of Cassava Brown Streak Virus (CBSV)} \\ \text{15 samples of Ugandan Cassava Brown Streak Virus (UCBSV)} \end{cases}$$

Phylogenetic analysis:

Strong support for CBSV | UCBSV split.

CBSV has an accelerated rate of evolution compared to UCBSV, matching field observations of increased virulence for these strains.

Sliding window analysis: Do changes in the score across the genome indicate which genes may be involved in the shift in evolutionary rate of CBSV?

Application 2: Detecting shifts in evolutionary process along a chromosome

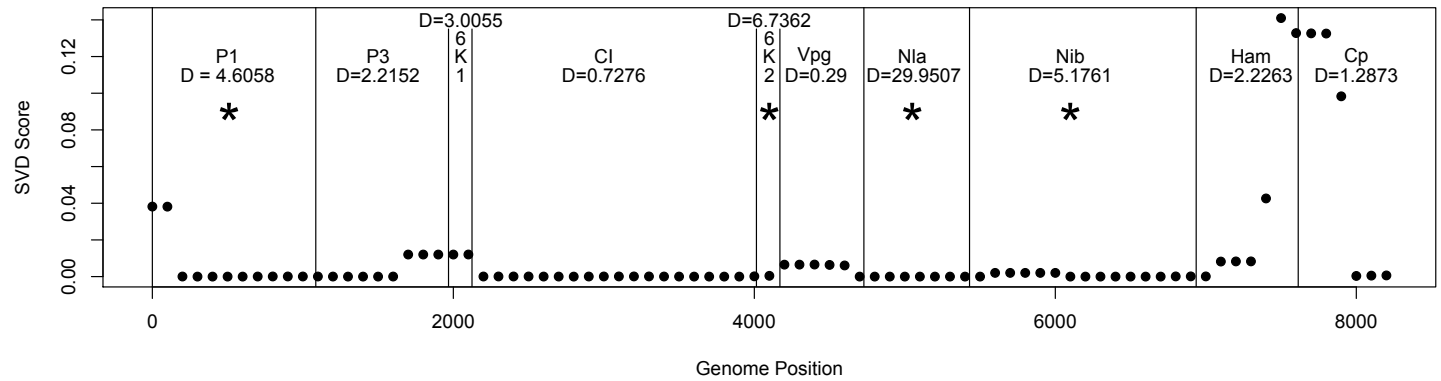
Viral Data — Alicai et al. (2016):

14 samples CBSV
15 samples UCBSV

Consider 14-split CBSV | UCBSV:

alignment is $\sim$ 8.8k bp

window size: 500 bp
slide size: 100 bp
min no of sites required: 100 bp



- indicates score.

$*$ indicates significant difference in evolutionary rate across split.

Gene boundaries are given by black vertical lines.

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