Advanced Bayesian Phylogenetics: Phyloalignment

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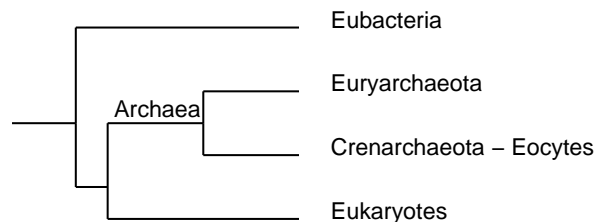
David Geffen School of Medicine at UCLA

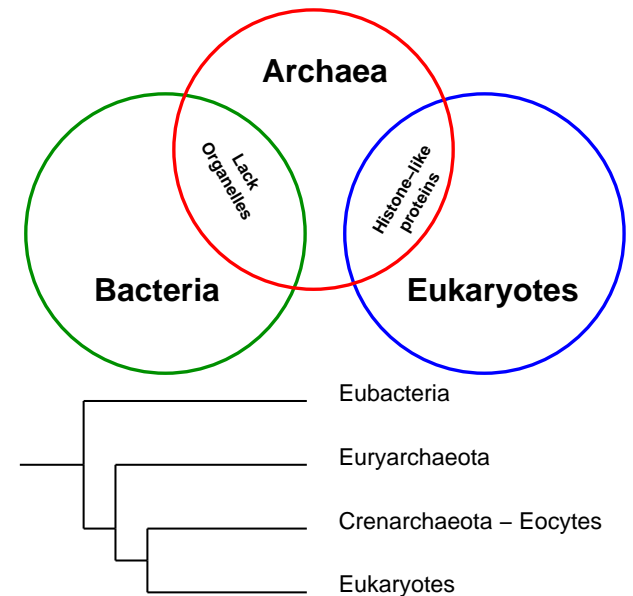Department of Biostatistics

UCLA School of Public Health

Resolving Early Branches in the Tree of Life

3? Domains of Life (Woese et al. 1990)

Contentious issue in genomics:

Do the Archaea form a single clade

(Rivera and Lake, 1992)?

Archaea / Bacteria / Eukaryotes — Lack Organelles, Histone–like proteins

Archaeal Tree

Eubacteria

Archaea

Euryarchaeota

Crenarchaeota – Eocytes

Eukaryotes

Eocyte Tree

Eubacteria

Euryarchaeota

Crenarchaeota – Eocytes

Eukaryotes

Early evidence based on phylogenetic reconstruction techniques:

- Model how biologic sequences mutated over time

- Infer branching patterns based on "shared" substitutions

Traditional Phylogenetic Reconstruction

Reconstruction Example

```
Human   – T  T  C  C  T  G  G  A  A  T
Chimp   – T  A  C  C  T  G  G  A  A  T
Mouse   – A  A  C  C  T  –  –  T  A  T
Fly     – A  A  G  A  T  C  G  T  A  T
Site:     1  2  3  4  5  6  7  8  9  10
```
Along Molecular Sequence

Human — Mouse
Chimp — Fly
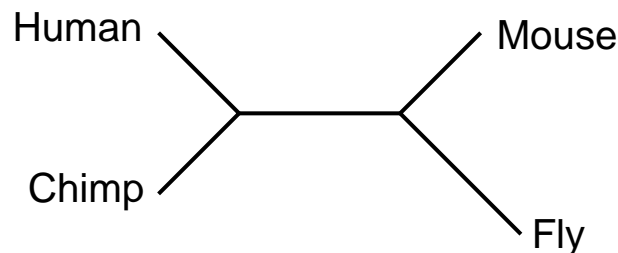
- **Substitution**: single residue replaces another

- **Insertion/deletion**: residues are inserted or deleted

Statistical Model

Assume: Homologous sites are iid and site patterns (e.g. dotted box)

$$XY \dots Z \sim \text{Multinomial}(p_{XY\dots Z})$$

where $p_{XY\dots Z}$ is determined by an unknown tree τ and a continuous-time Markov chain model (for residue substitution) given by infinitesimal rate matrix $\mathbf{Q}$

$$\mathsf{P}(X \to Y \text{ in time } t) = \left\{ e^{t\mathbf{Q}} \right\}_{XY}$$

Calculating $p_{XY\dots Z}$ integrates out unobserved states (internal nodes, gaps).

Fundamental Difficulty: Sequential Estimation

Current phylogenetic reconstruction methods:
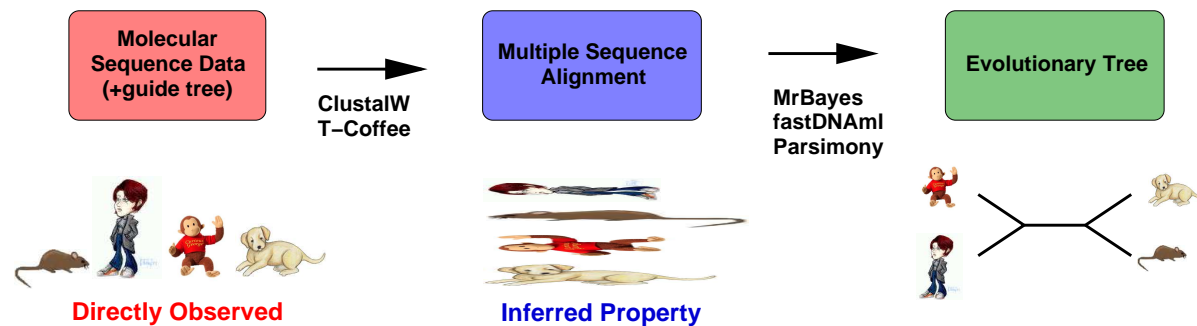
Issues: Poor alignment biases phylogeny (Lake data: EF-1α/Tu)

- Use guide tree and naive evolutionary models (**Trouble!**)

Solution: Infer alignment and phylogeny **simultaneously**

Previous approaches: Limited

- Optimization alignment, parsimony-based

- TFK91/92, forbidden positional homologies, inefficient

Alignment as a Random Variable

	Y	**M(A)**	**f**
Y_1	$= (A, T, T, C)$	$1\ 2\ -\ 3\ 4$	$A\ T\ -\ T\ C$
Y_2	$= (A, T, T, G)$	$1\ 2\ -\ 3\ 4$	$A\ T\ -\ T\ G$
Y_3	$= (T, C, T, G)$	$-\ 1\ 2\ 3\ 4$	$-\ T\ C\ T\ G$
Y_4	$= (T, C, T)$	$-\ 1\ 2\ 3\ -$	$-\ T\ C\ T\ -$
Y_5	$= (\star, \star, \star)$	$-\ 1\ 2\ 3\ -$	$-\ \star\ \star\ \star\ -$
Y_6	$= (\star, \star, \star, \star)$	$1\ 2\ -\ 3\ 4$	$\star\ \star\ -\ \star\ \star$

Observed Data: Y_1–Y_4
Missing Data: Y_5–Y_6
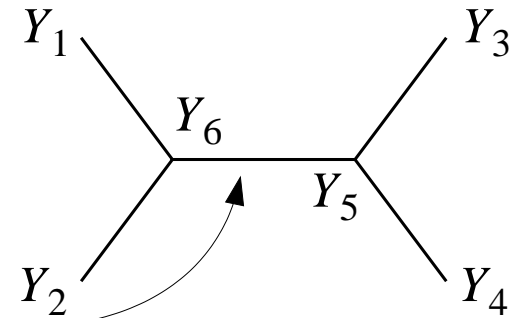
Just over **1 billion** possible alignments for $\mathbf{Y}_{obs}$

Explore space via **Forward-Backward algorithm (DP)** (Scott, 2002) to consider all possible alignments (and phylogenies) in polynomial time, weighted by posterior probability
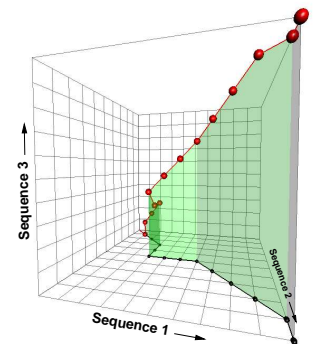
Note substitution process depends only on $\mathbf{Y}_{obs} \Rightarrow$ separates substitution and indel processes into (substitution likelihood $\times$ gap prior)

Gap Model along a Branch

Let the **multiple alignment** $\mathbf{A} = (A^{(1)}, \ldots, A^{(B)})$

- $\mathbf{A}$ is composed of pairwise alignments along each branch

- Pairwise alignment distribution follows a pair hidden Markov model (pair-HMM) **conditional** on equal sequence lengths at internal nodes
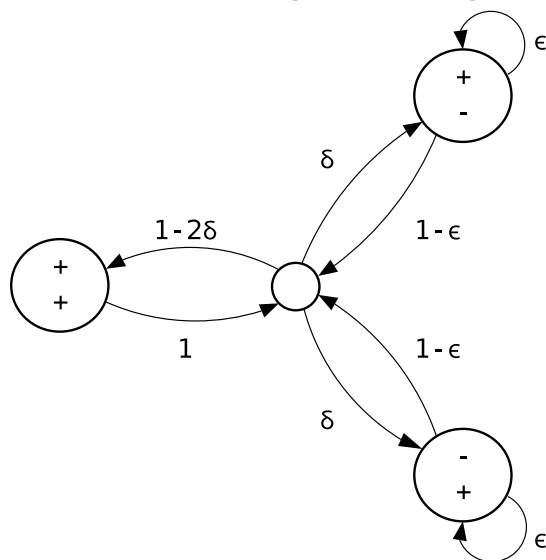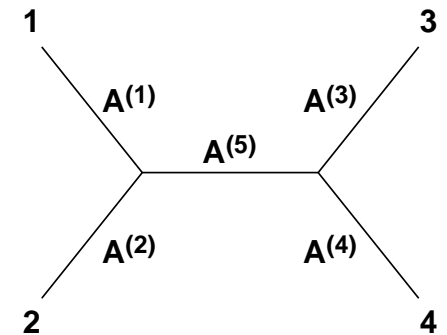
Pair-HMM parameterized by $\mathbf{\Lambda} = (\delta, \epsilon)$

- δ: Probability of indel

- ϵ: Probability of extending an indel

Affine gap penalty $\approx [\log \delta] + (\ell - 1)[\log \epsilon]$

Choosing the Blocks: Efficient Sampling

Gibbs cycle over smaller blocks in alignment $\mathbf{A}$:

$$A^{(1)}, A^{(2)}, (A^{(3)}, A^{(4)}), (A^{(5)}, A^{(6)}, A^{(7)}), \ldots$$

Let $L = $ length of alignment:

- $O(L)$, too cold (Holmes and Bruno 2001)

- $O(L^3)$, too hot (Jensen and Hein 2005)

- $O(L^2)$, just right?

O(L) O(L³) O(L²)
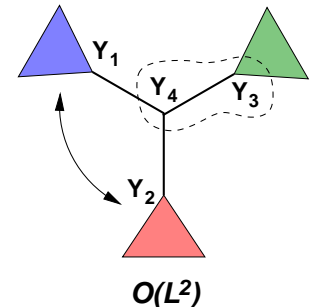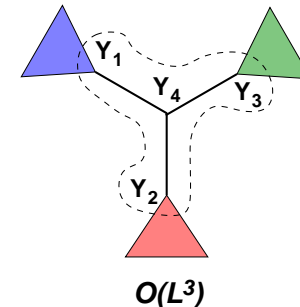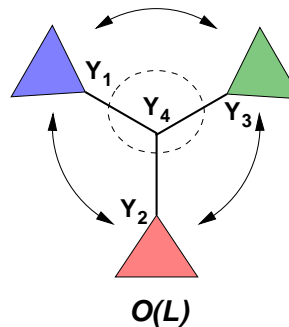
Possible **poor mixing** with $O(L)$ algorithm:

(a) 2 indels   (b) 3 indels   (c) 1 indel
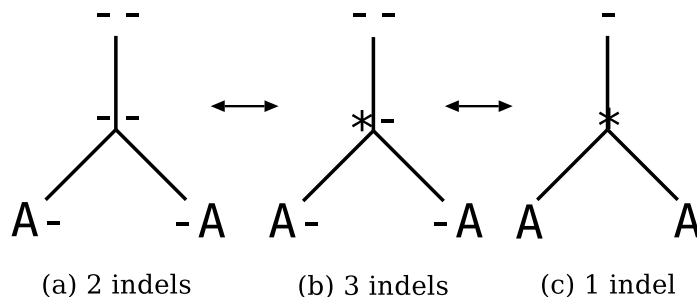
Must move through unfavorable intermediate to align/unalign sequence fragments

Improved Alignment Mixing with $O(L^2)$ Sampling
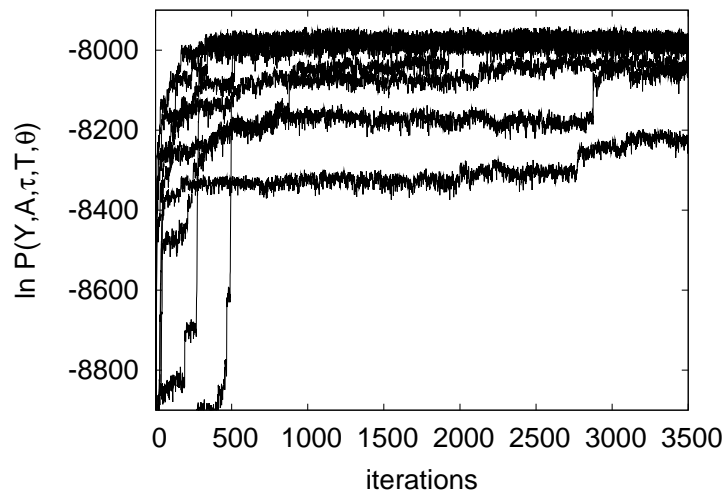
$O(L)$ **Only** $O(L)$ **and** $O(L^2)$
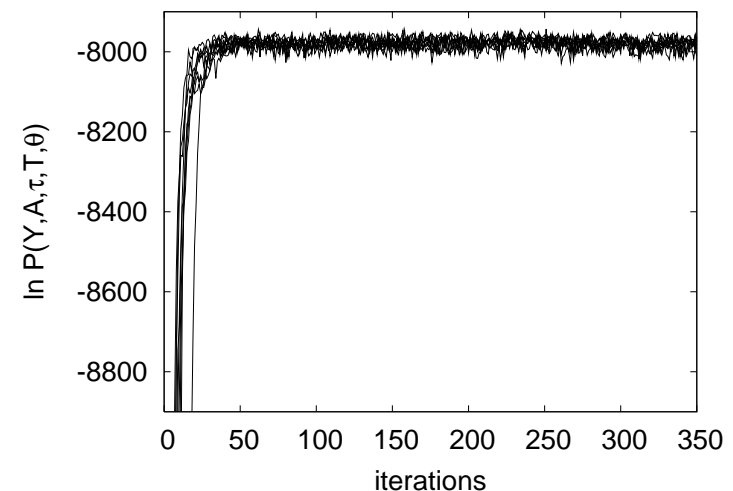
Enabling MCMC transition kernel decreases:

- Burn-in time   - Autocorrelation

Result: $> 70\times$ improvement shown here (12-taxon EF-1α/Tu dataset).

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Sequential (ClustalW) alignment of hypervariable region:

Simultaneous MAP alignment:

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Sequential (ClustalW) alignment of hypervariable region:

Sampled alignment (1):

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Sequential (ClustalW) alignment of hypervariable region:

Sampled alignment (2):

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Sequential (ClustalW) alignment of hypervariable region:

Sampled alignment (3)

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Sequential (ClustalW) alignment of hypervariable region:

Sampled alignment (4)

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Sequential (ClustalW) alignment of hypervariable region:

Sampled alignment (5)

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Sequential (ClustalW) alignment of hypervariable region:

Sampled alignment (6)

Sequential vs. Simultaneous Illustration

SIVmac251 partial *env* sequences from Cheynier et al (2001)

Displaying the posterior distribution of alignments

Alignment uncertainty (Au) plot:
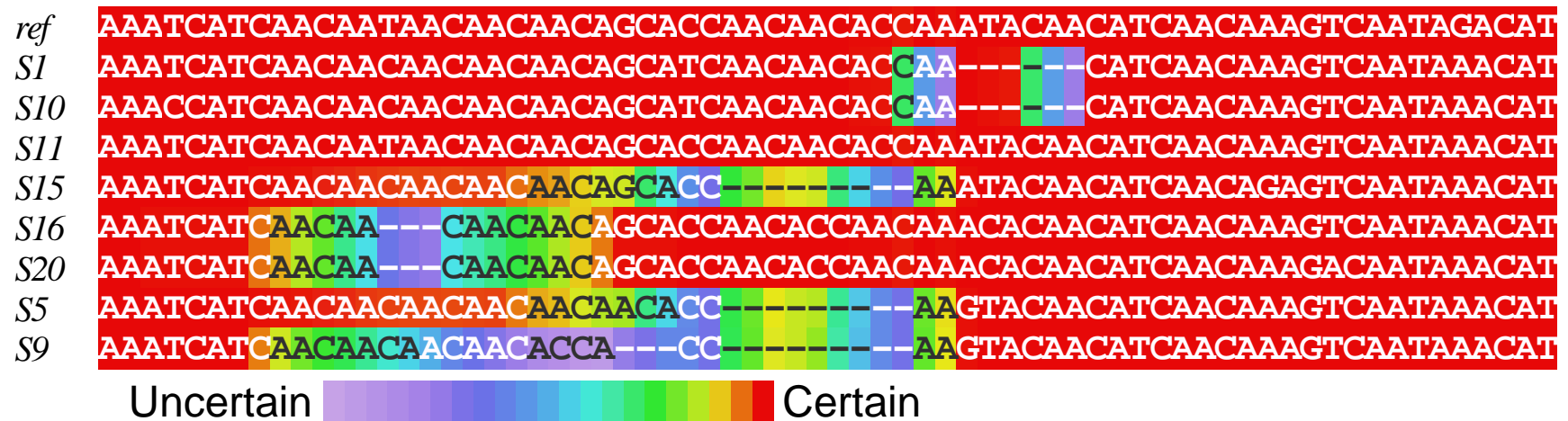
- Take "MAP" alignment as template

- Guild each residue with color reflecting probability of aligning to "root"

Trees and Alignments: Collapsed Gibbs Sampling

Problem: Tree and alignment are **highly** correlated

Further important aspect: Alignment-aware tree τ sampling

Nearest Neighbor Interchange

Propose new topology

Marginalize out alignments leading to internal nodes (5 and 6)

Resample new internal nodes
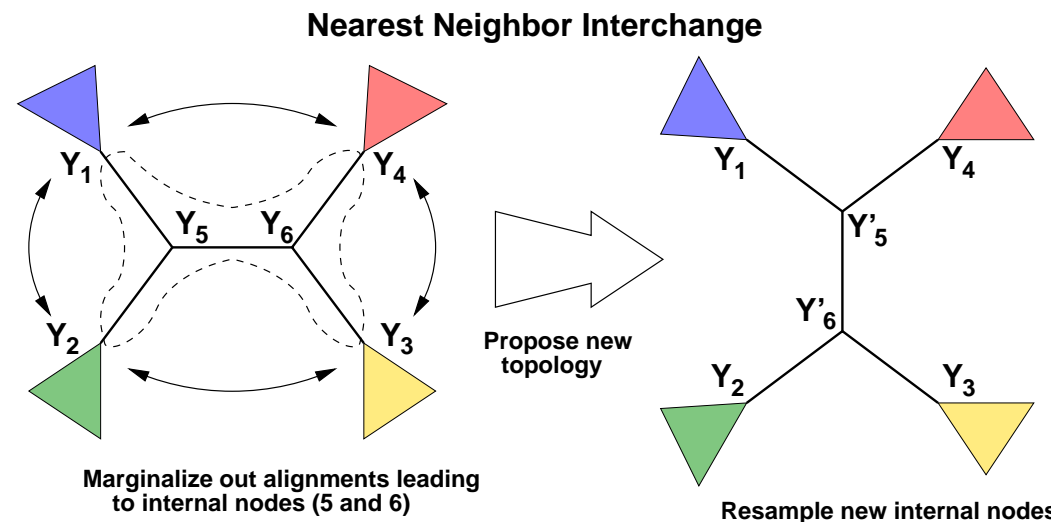
Generate $(\tau, \mathbf{A}) \mid \mathbf{Y}, \boldsymbol{\theta}$ by
1. $\tau \mid \mathbf{Y}, \boldsymbol{\theta}$ (collapsed)
2. $\mathbf{A} \mid \tau, \mathbf{Y}, \boldsymbol{\theta}$

Similar procedure available for **global changes** (SPR moves)

EF-1α/Tu Strongly Supports Eocyte Hypothesis

(*Homo*,*Sulfolobus*) clade supported at $\geq 99.9\%$ (sampling resolution):
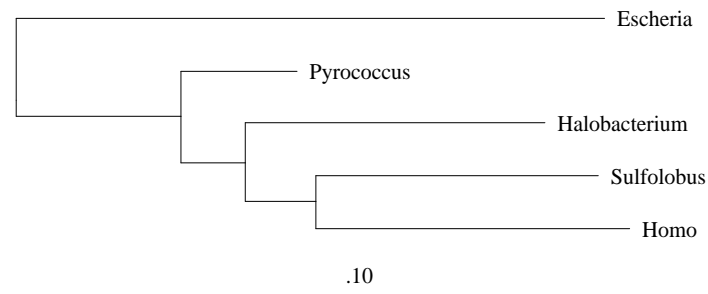
Alignment Uncertainty (Au, "gold") plot:
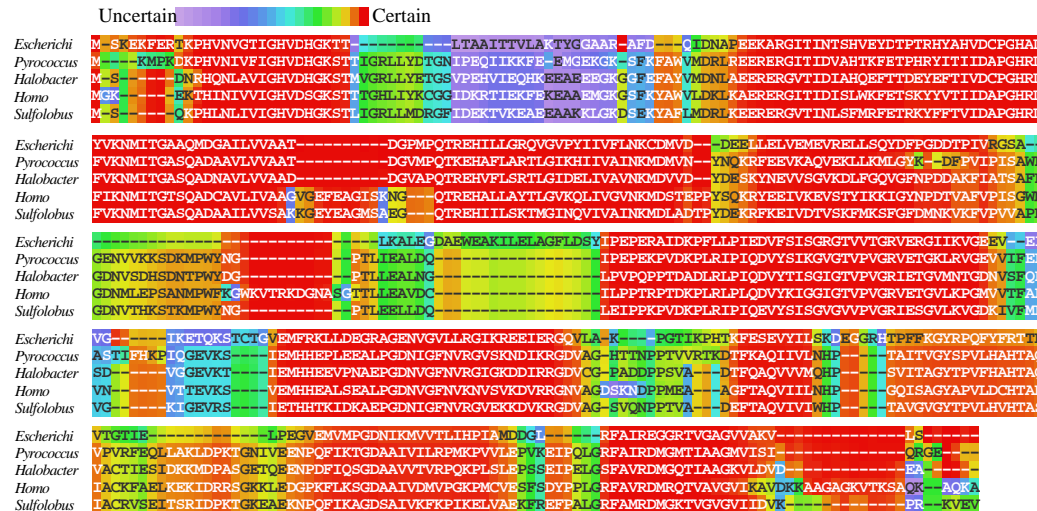
- Regions of marked homology (conservation)

- Uncertain regions

- Shared indels

EF-1α/Tu Strongly Supports Eocyte Hypothesis

(*Homo*,*Sulfolobus*) clade supported at $\geq 99.9\%$ (sampling resolution):
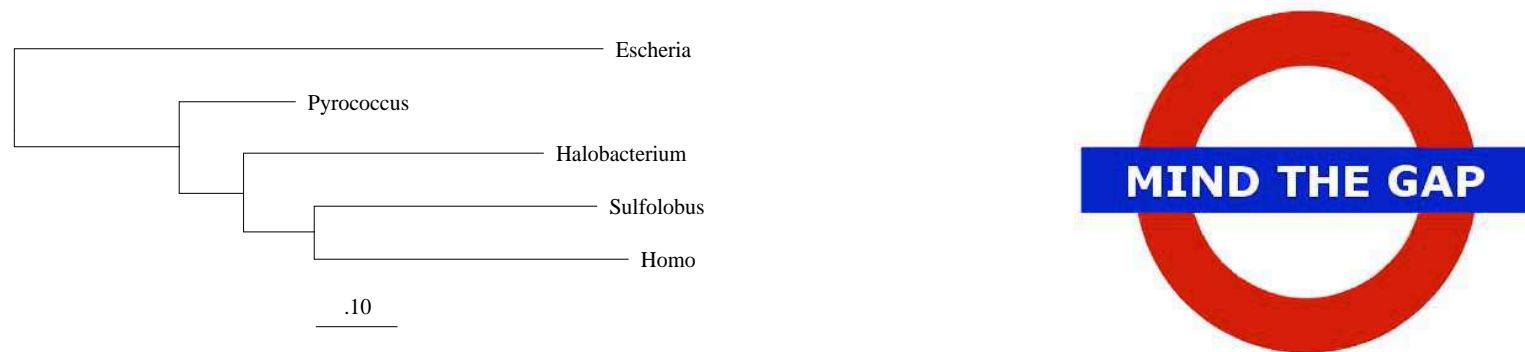
Alignment Uncertainty (Au, "gold") plot:
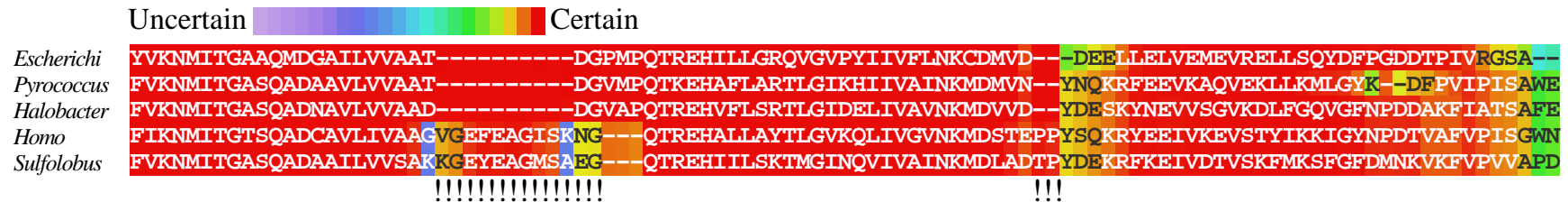
- Automatic detection of indels shared by descent vs. by state

- Two indels shared by *Homo* and *Sulfolobus* contribute support for Eocyte Hypothesis

Future Directions: Intra-Host Viral Evolution
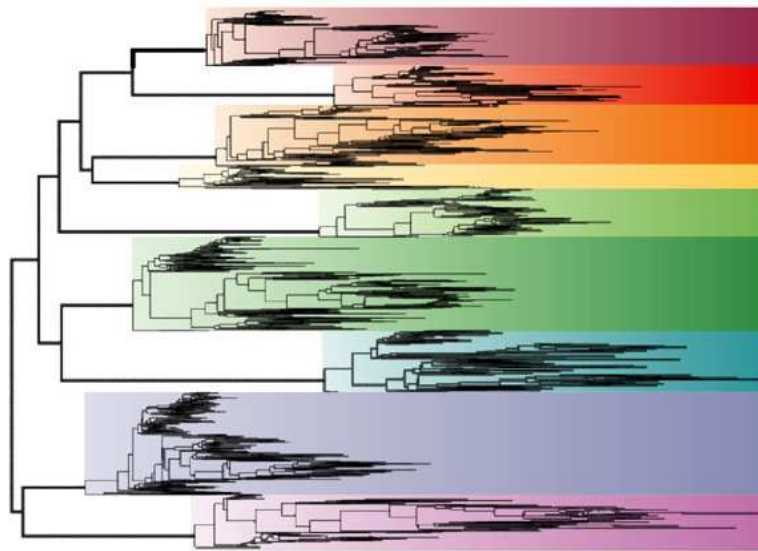
Nature Reviews | Genetics

1195 *env* sequences from 9 HIV+ patients [taken from Rambaut et al. (2004)]

Retroviruses (and HBV) exist as a **quasi-species** within infected patients:

- Shared substitutions may be insufficient to resolve intra-host phylogenies

Improve resolution using joint model:

- Indel rates $\geq$ substitution rates
- Opportunity to detect intra-host recombination

Improved Resolution – I Can See!

Shankarrapa (1999) Pt #1: 3 time-points, **90% consensus** trees
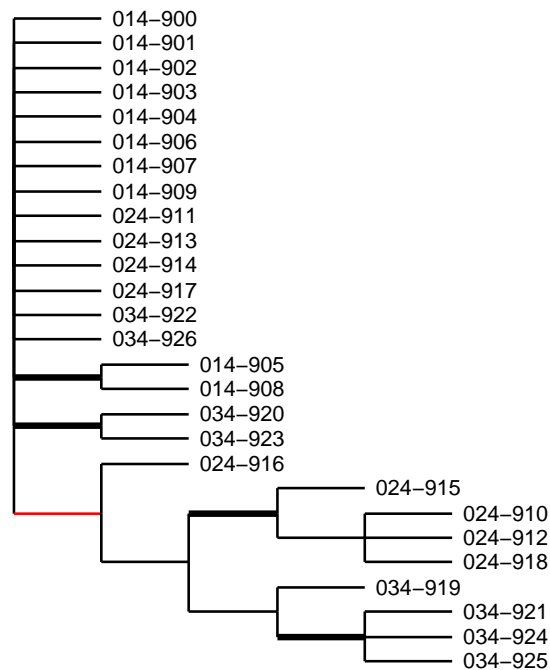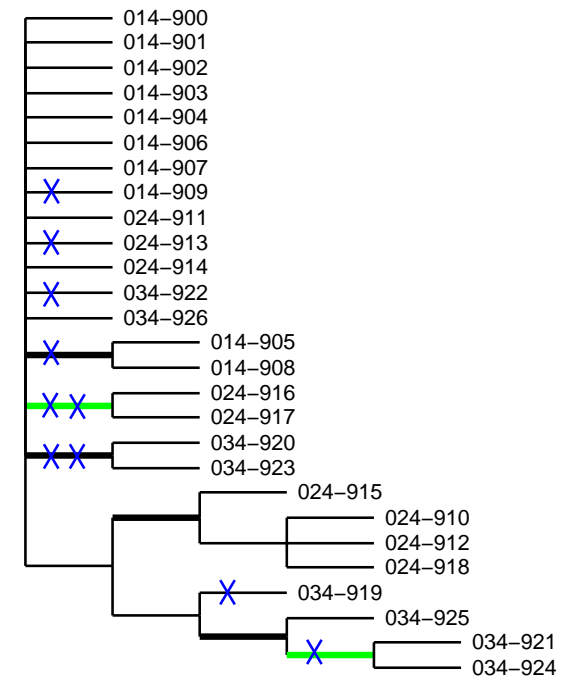
- Indel   + Indel

- Indel events ($\times$) $\Rightarrow$ **2** additional bi-partitions supported.

Codon Models: Not Always A Good Thing

```
14-00  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-00  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-02  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-02  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-03  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-03  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-04  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-04  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-07  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-07  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
24-13  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         24-13  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
34-22  AGTACTTGGGATAATAGTACTTTGAATA- - - TTACTGAA        34-22  AGTACTTGGGATAATAGTACTTTGAAT- - - ATTACTGAA
34-26  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         34-26  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-01  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-01  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-09  AGTACTTGGGATAATAGTACTATGAATAATGTTACTGAA         14-09  AGTACTTGGGATAATAGTACTATGAATAATGTTACTGAA
34-20  AGTACTTGGG- - - - - - - - - CTTTGAATAATGTTACTGAA     34-20  AGTACTTGG- - - - - - - - - GCTTTGAATAATGTTACTGAA
34-23  AGTACTTGGG- - - - - - - - - CTTTGAATAATGTTACTGAA     34-23  AGTACTTGG- - - - - - - - - GCTTTGAATAATGTTACTGAA
24-11  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         24-11  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-05  AGTACTTGGGATAATAGTACTCTGAATAATGTTACTGAA         14-05  AGTACTTGGGATAATAGTACTCTGAATAATGTTACTGAA
14-08  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-08  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
14-06  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         14-06  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
24-14  AGTACTTGGGATAATAGTACTTTAAATAATGTTACTGAA         24-14  AGTACTTGGGATAATAGTACTTTAAATAATGTTACTGAA
24-16  AGTACTTGGGATAATAGTACTTTGAATA- - - TTACTGAA        24-16  AGTACTTGGGATAATAGTACTTTGAAT- - - ATTACTGAA
24-17  AGTACTTGGGATAATAGTACTTTGAATA- - - TTACTGAA        24-17  AGTACTTGGGATAATAGTACTTTGAAT- - - ATTACTGAA
24-15  AGTATTTGGGATAATAGTACTTTGAATAATGTTACTGAA         24-15  AGTATTTGGGATAATAGTACTTTGAATAATGTTACTGAA
24-10  AGTACTTGGGATAATAGTACTTTGAATAATATTACTGAA         24-10  AGTACTTGGGATAATAGTACTTTGAATAATATTACTGAA
24-12  AGTACTTGGGATAATAGTACTTTGAATAATATTACTGAA         24-12  AGTACTTGGGATAATAGTACTTTGAATAATATTACTGAA
24-18  AGTACTTGGGATAATAGTACTTTGAATAATATTACTGAA         24-18  AGTACTTGGGATAATAGTACTTTGAATAATATTACTGAA
34-19  AGTACTTGGGATAATAGTACTTTGAATA- - - TTACTGAA        34-19  AGTACTTGGGATAATAGTACTTTGAAT- - - ATTACTGAA
34-25  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA         34-25  AGTACTTGGGATAATAGTACTTTGAATAATGTTACTGAA
34-21  AGTACTTGGGATA- - - - - - CTTTGAATAATGTTACTGAA      34-21  AGTACTTGGGAT- - - - - - ACTTTGAATAATGTTACTGAA
34-24  GGTACTTGGGATA- - - - - - CTTTGAATAATGTTACTGAA      34-24  GGTACTTGGGAT- - - - - - ACTTTGAATAATGTTACTGAA
```

HKY$\times 1$ (-1556)   **HKY**$\times 3$ (-1580)

- Codon model M0: $\omega = 1.0\,(0.9, 1, 2) \approx$ HKY$\times 3$

- **Singlet** model more likely. **Triplet** model **shifts** indels and **misaligns** residues