Advanced Bayesian Phylogenetics: Phyloalignment

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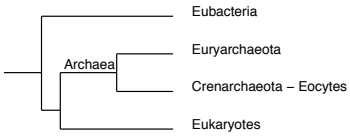
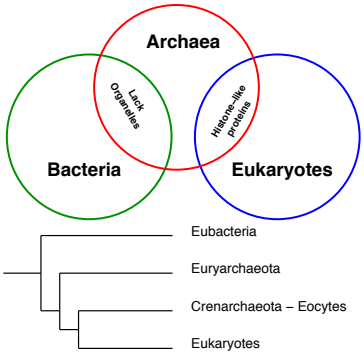
Resolving Early Branches in the Tree of Life

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

Contentious issue in genomics:
Do the Archaea form a single clade
(Rivera and Lake, 1992)?



Archaeal Tree



Eocyte Tree

Early evidence based on phylogenetic reconstruction techniques:

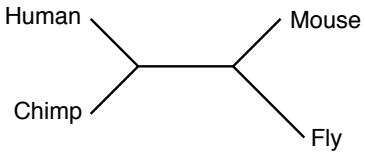
- Model how biologic sequences mutated over time
- Infer branching patterns based on “shared" substitutions

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



- **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)

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

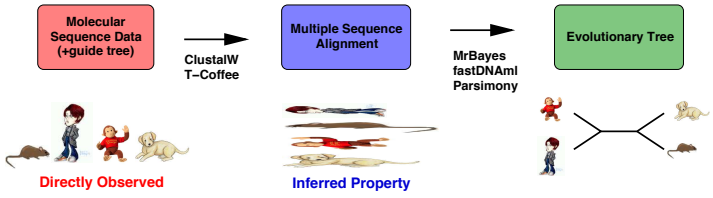
where $p_{XY \ldots Z}$ is determined by an unknown tree τ and a continuous-time Markov chain model (for residue substitution) given by infinitesimal rate matrix $\mathbf{Q}$

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

Calculating $p_{XY \ldots Z}$ 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!**)

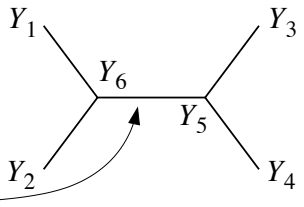
Solution: Infer alignment and phylogeny **simultaneously**

Previous approaches: Limited

- Optimization alignment, parsimony-based
- TFK91/92, forbidden positional homologies, inefficient

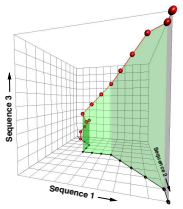
Alignment as a Random Variable

		Y	M(A)	f
Observed Data	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 –	$–\ T\ C\ T\ –$
Missing Data	Y_5	$(\star,\star,\star)$	– 1 2 3 –	$–\ \star\ \star\ \star\ –$
	Y_6	$(\star,\star,\star,\star)$	1 2 – 3 4	$\star\ \star\ –\ \star\ \star$



Just over **1 billion** possible alignments for $\mathbf{Y}_{\text{obs}}$

Explore space via **Forward-Backward algorithm (DP)** (Scott, 2002) to consider all possible alignments (and phylogenies) in polynomial time, weighted by posterior probability

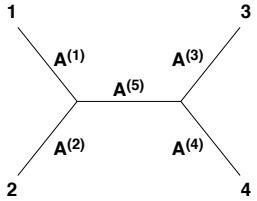


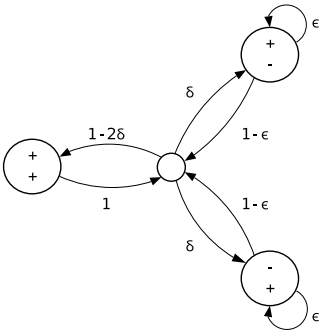
Note substitution process depends only on $\mathbf{Y}_{\text{obs}} \Rightarrow$ separates substitution and indel processes into (substitution likelihood $\times$ gap prior)

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

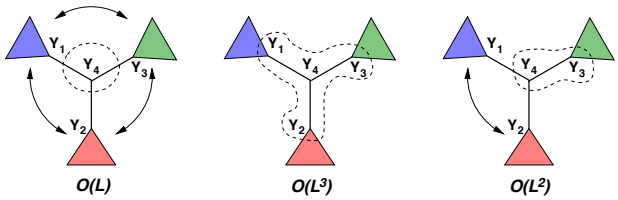
Choosing the Blocks: Efficient Sampling

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

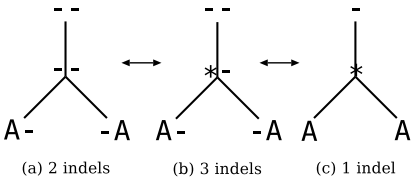
$$A^{(1)}, A^{(2)}, (A^{(3)}, A^{(4)}), (A^{(5)}, A^{(6)}, A^{(7)}), \ldots$$

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?



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

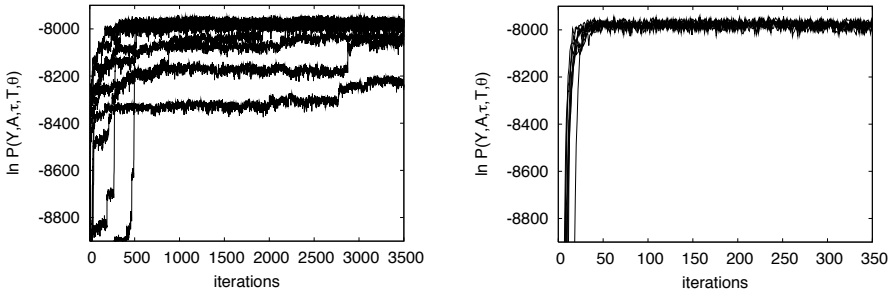


(a) 2 indels (b) 3 indels (c) 1 indel

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:

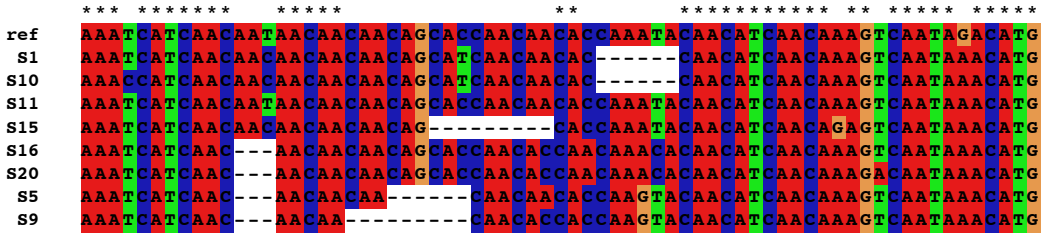
- Burn-in time
- Autocorrelation

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

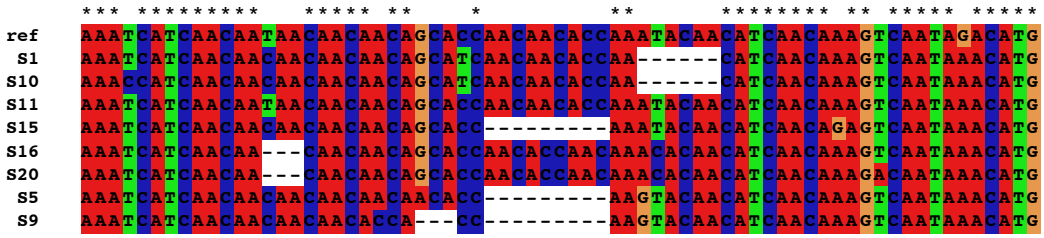
Sequential vs. Simultaneous Illustration

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

Sequential (ClustalW) alignment of hypervariable region:



Simultaneous MAP alignment:



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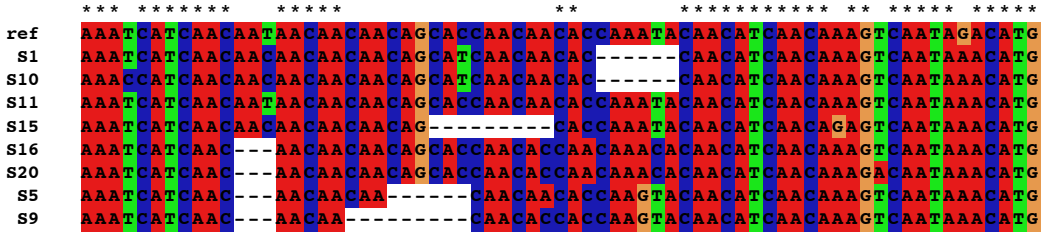
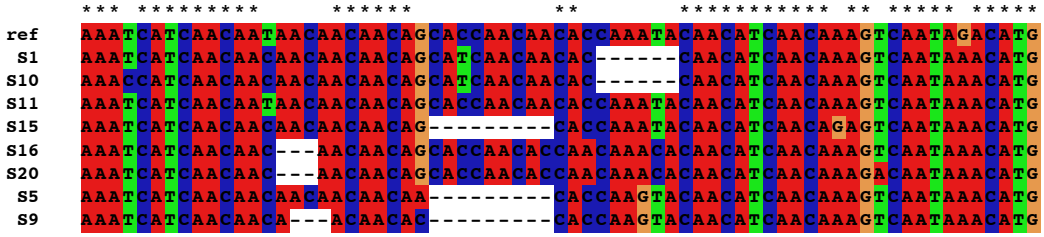


Sampled alignment (1):



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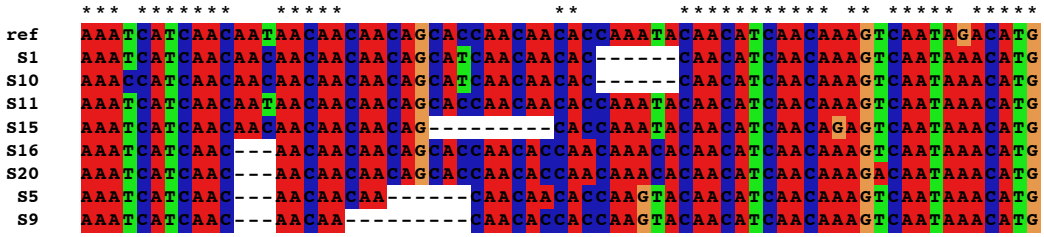
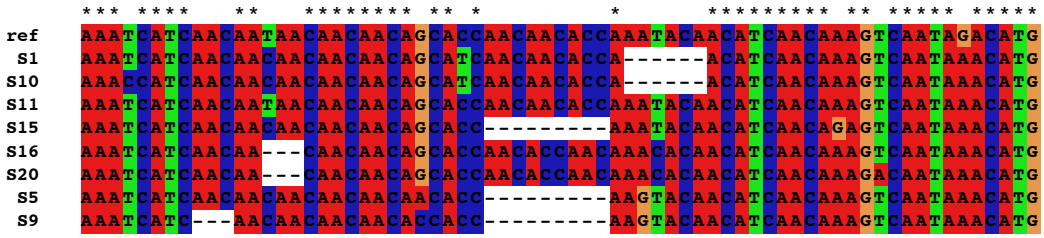


Sampled alignment (2):



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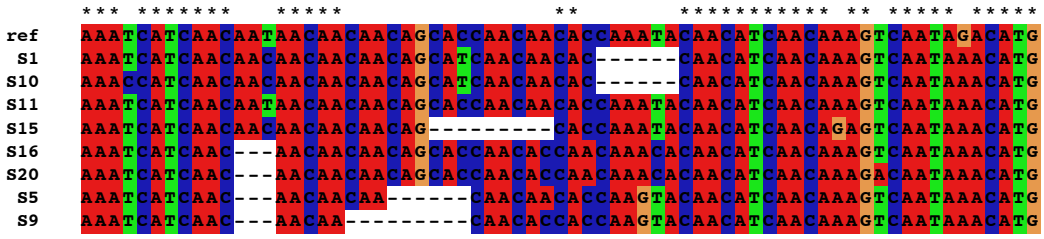
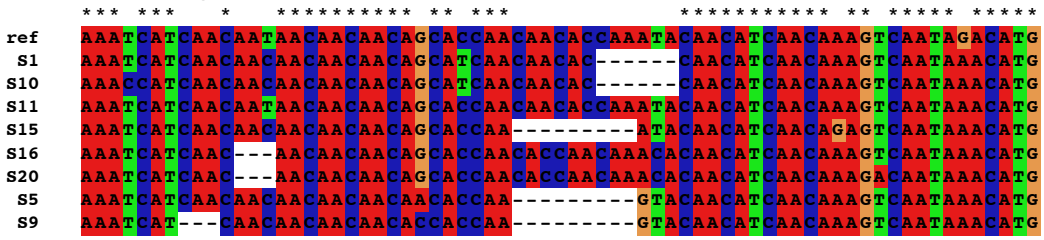


Sampled alignment (3)



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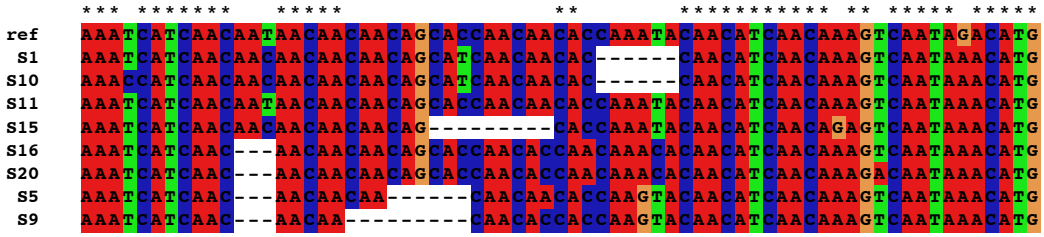
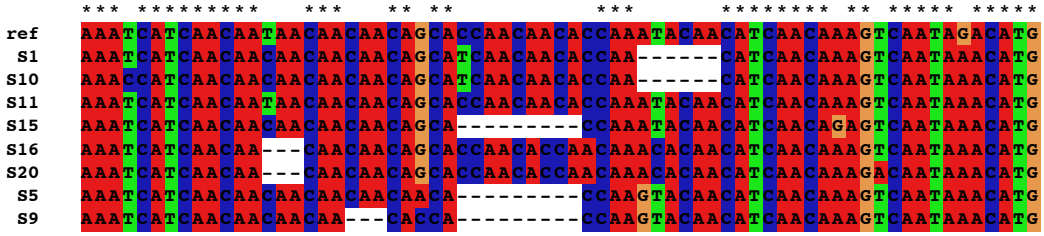


Sampled alignment (4)



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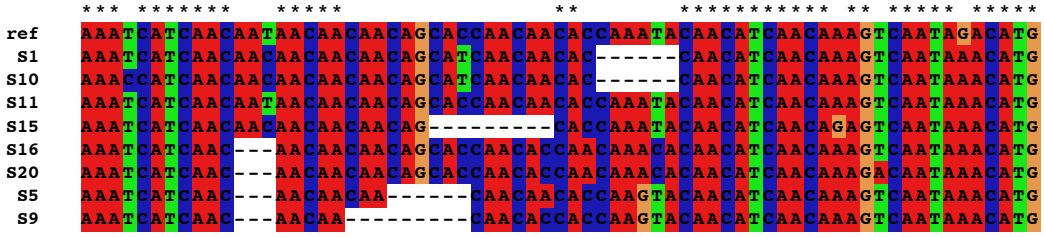
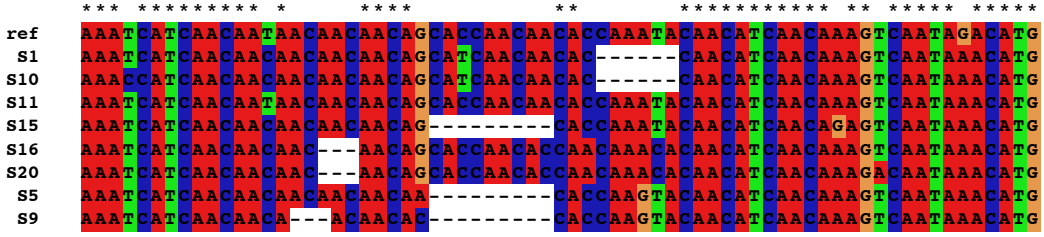


Sampled alignment (5)



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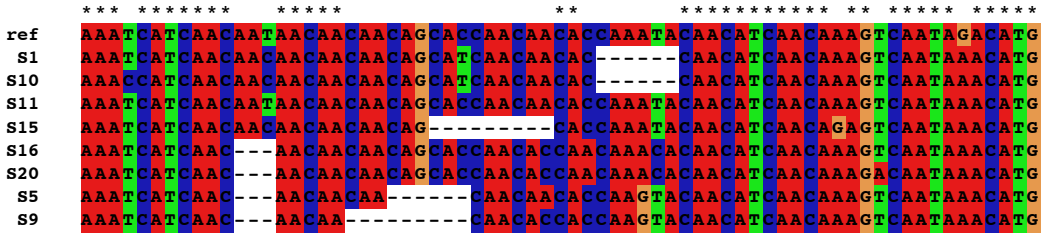
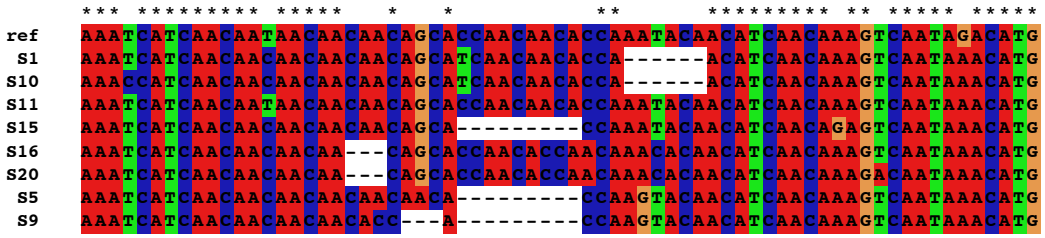


Sampled alignment (6)

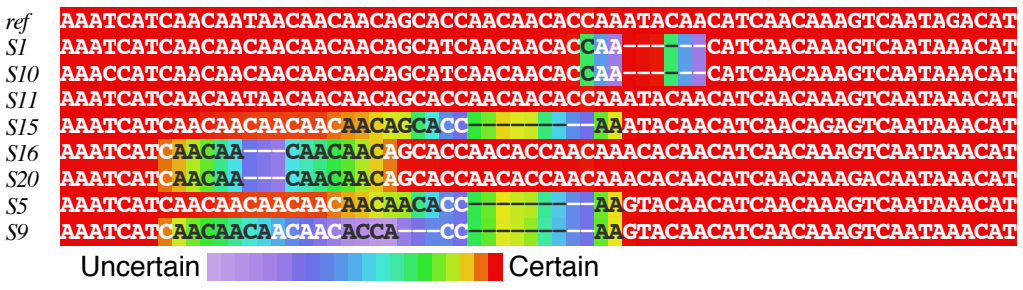


Sequential vs. Simultaneous Illustration

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

Displaying the posterior distribution of alignments

Alignment uncertainty (Au) plot:

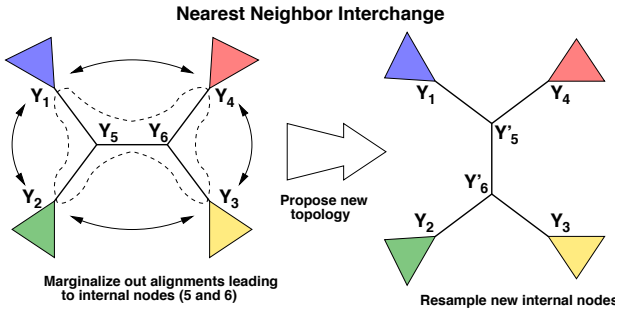


- Take “MAP” alignment as template
- Guild each residue with color reflecting probability of aligning to “root"

Trees and Alignments: Collapsed Gibbs Sampling

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

Further important aspect: Alignment-aware tree τ sampling



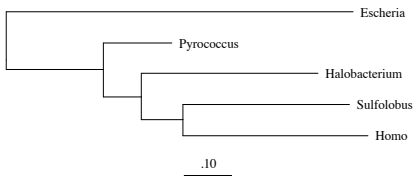
Generate $(\tau, \mathbf{A}) \mid \mathbf{Y}, \boldsymbol{\theta}$ by $1.\ \tau \mid \mathbf{Y}, \boldsymbol{\theta}$ (collapsed)

$2.\ \mathbf{A} \mid \tau, \mathbf{Y}, \boldsymbol{\theta}$

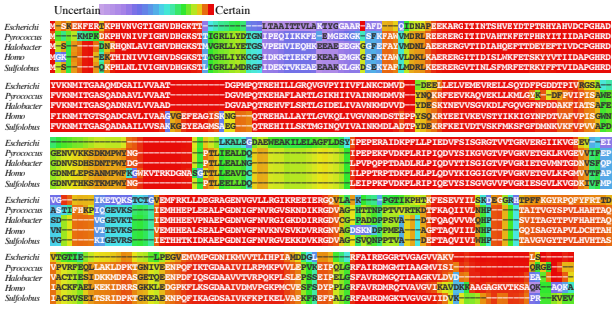
Similar procedure available for **global changes** (SPR moves)

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

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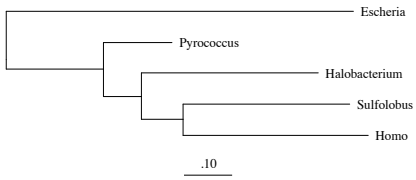

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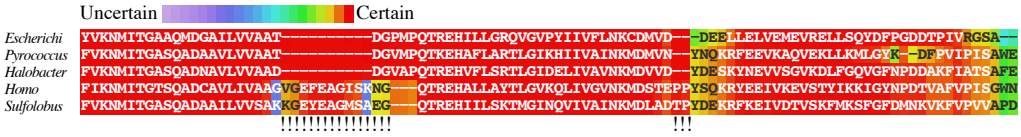
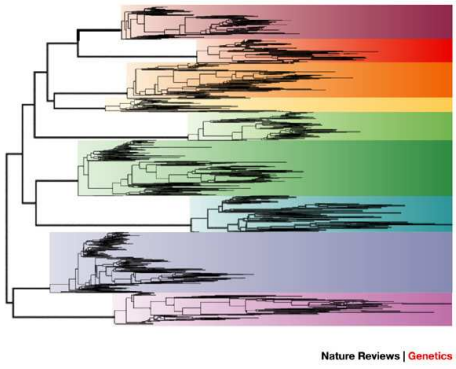


- Automatic detection of indels shared by descent vs. by state
- Two indels shared by *Homo* and *Sulfolobus* contribute support for Eocyte Hypothesis

Future Directions: Intra-Host Viral Evolution



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

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

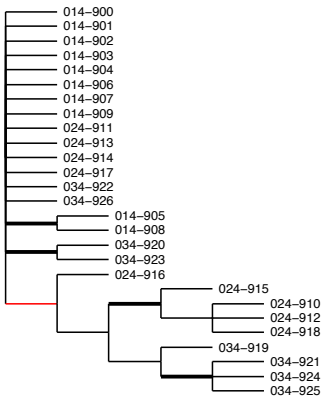
- Shared substitutions may be insufficient to resolve intra-host phylogenies

Improve resolution using joint model:

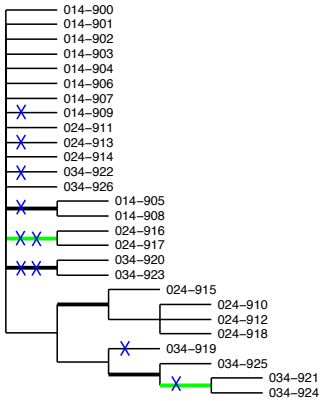
- Indel rates $\geq$ substitution rates
- Opportunity to detect intra-host recombination

Improved Resolution – I Can See!

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



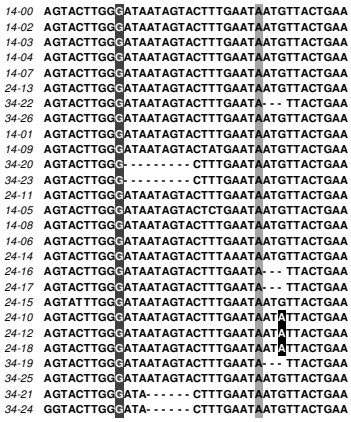
- Indel



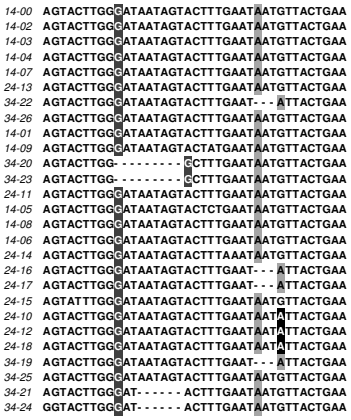
+ Indel

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

Codon Models: Not Always A Good Thing



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