Comparison of Minisatellites

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Outline

1. Tandem repeats evolution, and minisatellite maps.
2. Evolutionary model.
3. Arches.
4. Alignment algorithm.
5. Applications.

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Minisatellites (ms): what are they?

- Class of tandem repeat: Satellites, Minisatellites, Microsatellites.
- Example of a tandem repetition:

  $\cdots$ cggcgat cggcgac cggagat cggcgat cggcgat cggagat cgacgat $\cdots$

- A minisatellite unit measures between 7-100 bp, and their overall length is greater than 0.5kb.
- ms undergo amplifications and contractions $\Rightarrow$ variation in their number of unit.
- ms also undergo point-mutations and homogenization.

Interests in Minisatellites

- Implication in diseases: insulin-dependent diabetes, several cancers, epilepsy, and others [Buard, Jeffreys 97].
- Phylogeny and population studies:
  - Micro-evolution in small range of evolutionary time.
  - Migration of population: out-of-Africa hypothesis [Armour et al 96].
  - Evolution of the Y chromosome [Jobling, Tyler 00].
- Individual or species identification: forensic studies, genetic markers, identification of bacteria [Jeffreys 93]
- Theoretical interest: Why such sequences exist? How do they evolve?

Minisatellites maps

- Difficulty to sequence and assemble minisatellites.
- There is a specific method to obtain the sequence of variants of the unit, **Minisatellite Variant Repeat PCR** [Jeffreys et al. 91].
  MVR-PCR yields a **ms map**: a sequence of symbols, each representing a different variant of the repeated unit.
- Example of a minisatellite map:
  - s = cggcgat cggcgac cggagat cggcgat cggcgat cggagat cgacgat
  - New alphabet: A = cggcgat B = cggcgac C = cggagat D = cgacgat
  - Corresponding map: A B C A A C D

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Example of evolution of ms

Ancestor map: AAAAA

Today's variants: A,B,C,D,E

Trace of the evolution in individual 1:

	A	A	A	A	A					
Mutation	A	A	A	**B**	A					
5 Amplifications	A	A	A	B	**B**	**B**	**B**	**B**	**B**	A
Mutation	A	A	A	B	B	**C**	B	B	B	A
Mutation	A	A	A	B	B	C	B	**D**	B	A
Amplification	A	A	A	B	B	C	B	D	**D**	B	A

Example of evolution of ms (2)

Trace of the evolution in individual 2:

	A	A	A	A	A	
Mutation	A	**E**	A	A	A	
Amplification	A	E	A	A	**A**	A
Contraction	A	E	A	A	A	

We would like to compute an optimal alignment:

I1:	A	A	A	B	B	C	B	D	D	B	A
	|	[	|	[	/		/		/	/	|
I2:	A	E	A	A	-	-	-	-	-	-	A

Single Step Evolutionary Model

- Unitary operations
  - **Amplification(A)/Contraction(C)** duplicates/removes a variant which is next to an identical variant.
  - **Mutation(M)** mutates one variant in another.
  - **Insertion(I)/Deletion(D)** inserts/removes a variant, but without constraint.
- Non-unitary operations:
  - **Generation(G)/Compression(K)** generates/compresses an **arch** from/to its single ancestor variant.
- A cost is associated to each operation. Alignment cost is the sum of its operations costs.

Operations costs

- The model is symmetric: I = D and A = C.
- Observed much higher relative frequency of amplifications and contractions compared to other events $\Rightarrow$ A, C $<$ M, D, I.
- A deletion can also be obtained by a mutation plus a contraction. We have either:
  1. Hypothesis 1 **(H1)**: D $>$ M + C and I $>$ A + M
  2. Hypothesis 2 **(H2)**: D $\leq$ M + C and I $\leq$ A + M
- **Theorem**: Under H1 or H2, alignment cost is a metric distance.

Problem definition

Problem: Let s and r be two ms maps of length n and m, find an *optimal global* alignment between s and r under the single step evolutionary model.

Related works

- Alignment with duplication [Benson 97]:
  - Alignment of two sequences that may contain several tandem repeats; operations are substitutions, indels and duplications.
  - Differences with our approach: duplication relates the two sequences while for us a duplication is internal to one map; repeated units are unknown.
- Duplication history reconstruction [Benson et Dong 99, Elemento al 01, Tang al 01, Elemento 02, Jaitly 02].

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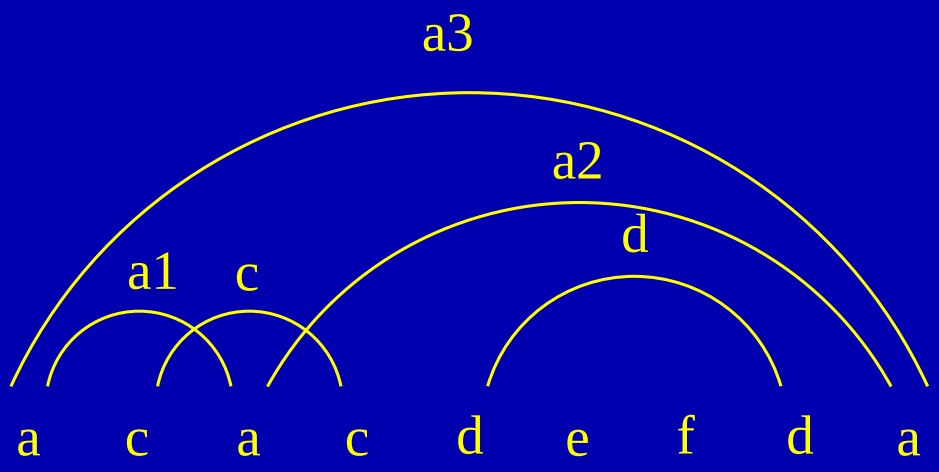
Arches

Let s be a map.

Def: an **arch** of s is a subsequence of s whose first and last variants are identical.

Def: an arch is **simple** if its internal variants occur only once and **complex** otherwise.

Ex: s=acacdefda



Def: two arches are **compatible** if they do not cross or share a same first foot or a same last foot.

Generate/Compress an Arch

- Generation and Compression are symmetrical.
- Generate a simple arch: from A to ABCA

First method					Second method				
	A					A			
Amplification	A	A			Amplification	A	A		
Mutation	A	B			Amplification	A	A	A	
Amplification	A	B	B		Amplification	A	A	A	A
Mutation	A	B	C		Mutation	A	B	A	A
Amplification	A	B	C	C	Mutation	A	B	C	A
Mutation	A	B	C	A					

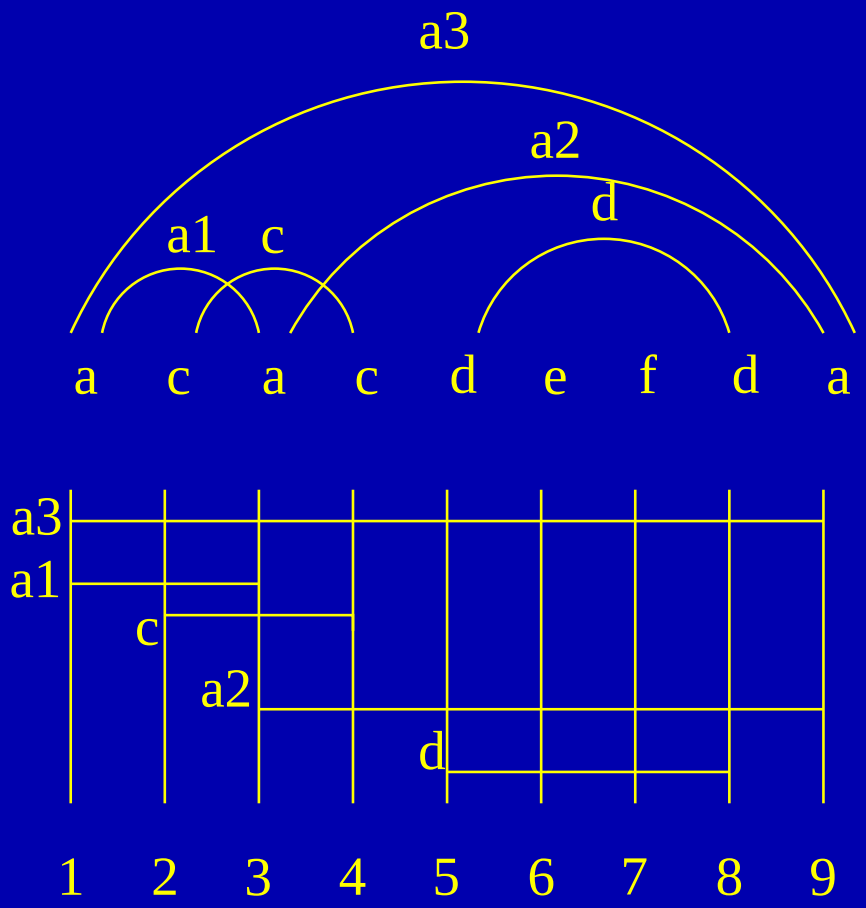
Identical variants at the extremities allow to avoid one mutation.

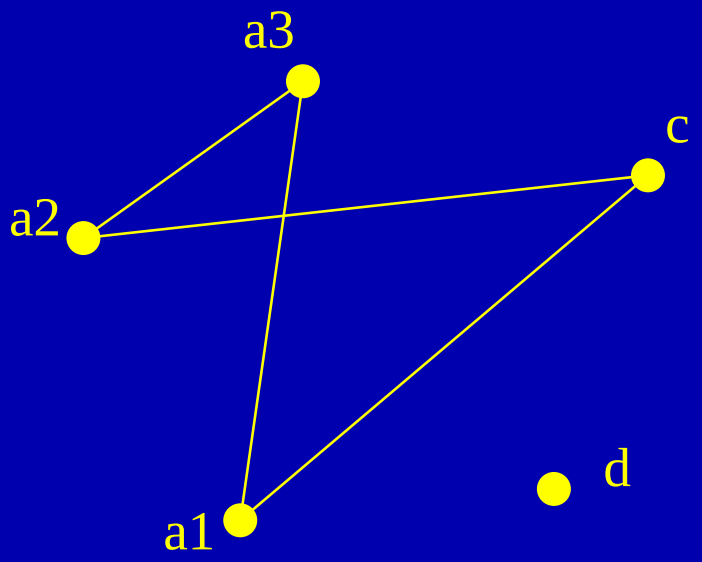
- Non-commutativity of operations.
- **Theorem:** the optimal generation/compression of an arch uses the largest subset of compatible inner arches.

Overlap graphs

- Map of size n, arches are subintervals in [1,n].
- Compatibility relation defines an overlap graph.
- **Theorem**: Finding the largest subset of compatible inner arches is equivalent to finding the max stable in an overlap graph.
- Complexity of this procedure is $O(V^2)$ with V the number of vertices of the graph [Apostolico et al. 92].
- Maximal number of arches is $\Theta(n^2)$.

Example





How to convert the problem of finding the max subset of compatible arches in the problem of finding the max stable set in an overlap graph

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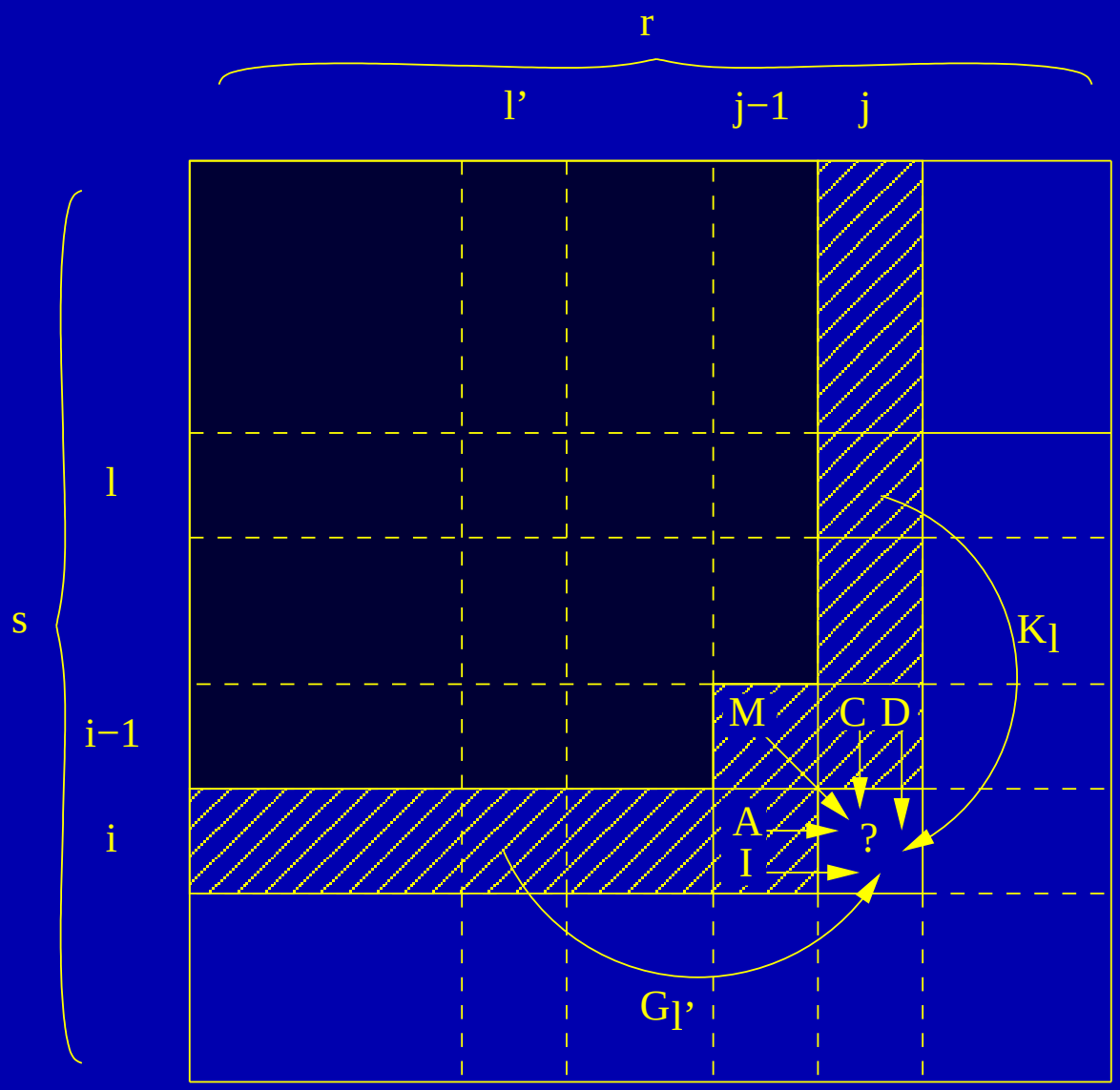
Dynamic Programming Dependencies



Recurrence

$$\mathscr{A}[i, j] = min \begin{cases} \mathscr{A}[i - 1, j - 1] + M(s[i],r[j]) & \text{Mute} \\ \mathscr{A}[i - 1, j] + C & \text{Contract} \\ \quad \textbf{iff } s[i - 1] = s[i] \textbf{ or } s[i]=r[j] & \\ \mathscr{A}[i - 1, j] + S & \text{Delete} \\ \mathscr{A}[i, j - 1] + A & \text{Amplify} \\ \quad \textbf{iff } r[j - 1] = r[j] \textbf{ or } s[i]=r[j] & \\ \mathscr{A}[i, j - 1] + I & \text{Insert} \\ \mathscr{A}[l, j] + K(s[l, i]) & \text{Compress an arch} \\ \quad \forall\, \textbf{l} \in \textbf{[1, i - 2] such that s[l] = s[i]} & \\ \mathscr{A}[i, l'] + G(r[l',j]) & \text{Generate an arch} \\ \quad \forall\, \textbf{l'} \in \textbf{[1, j - 2] such that r[l'] = r[j]} & \end{cases}$$

Complexity

Theorem: If p = max(n, m), overall complexity is $O(p^4)$ time.

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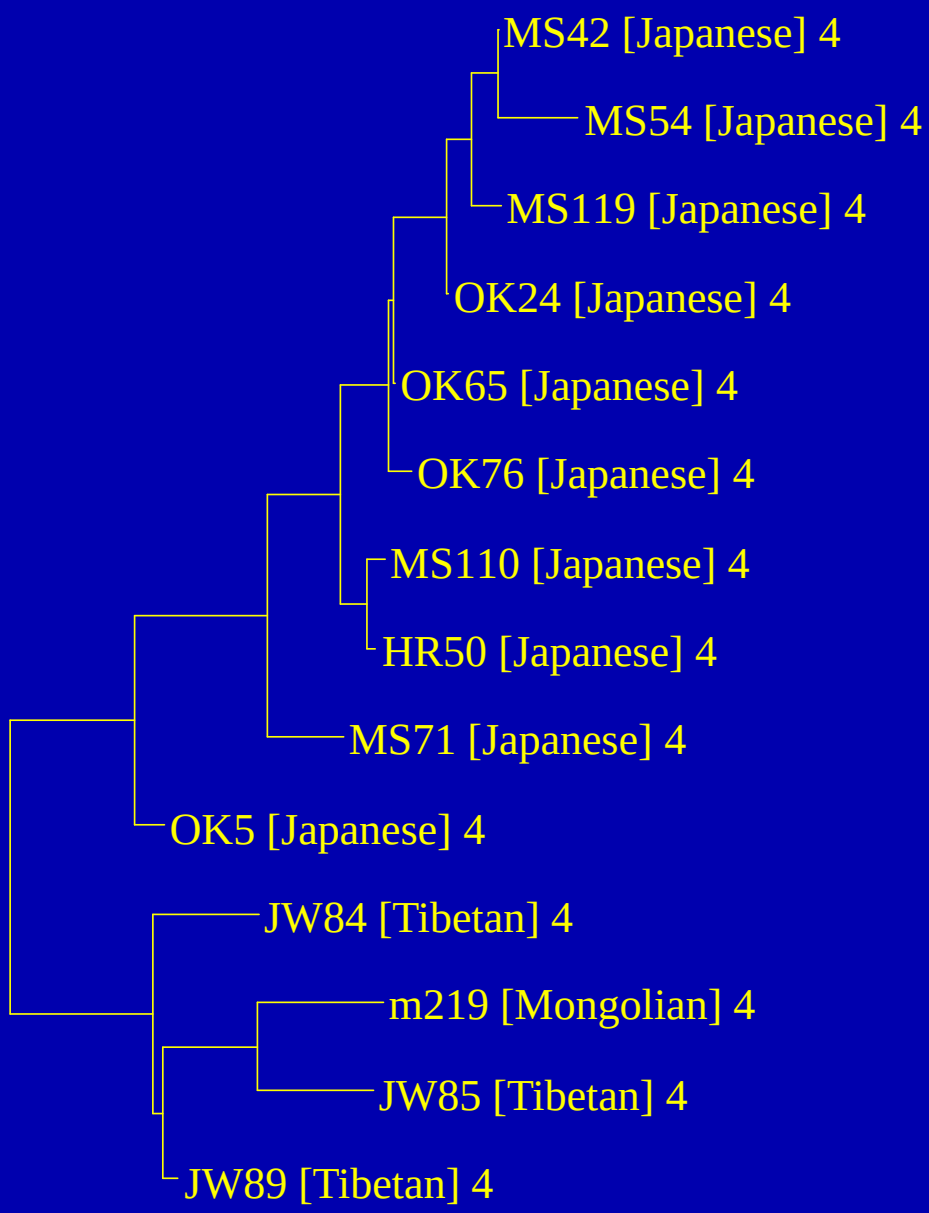
Minisatellite MSY1

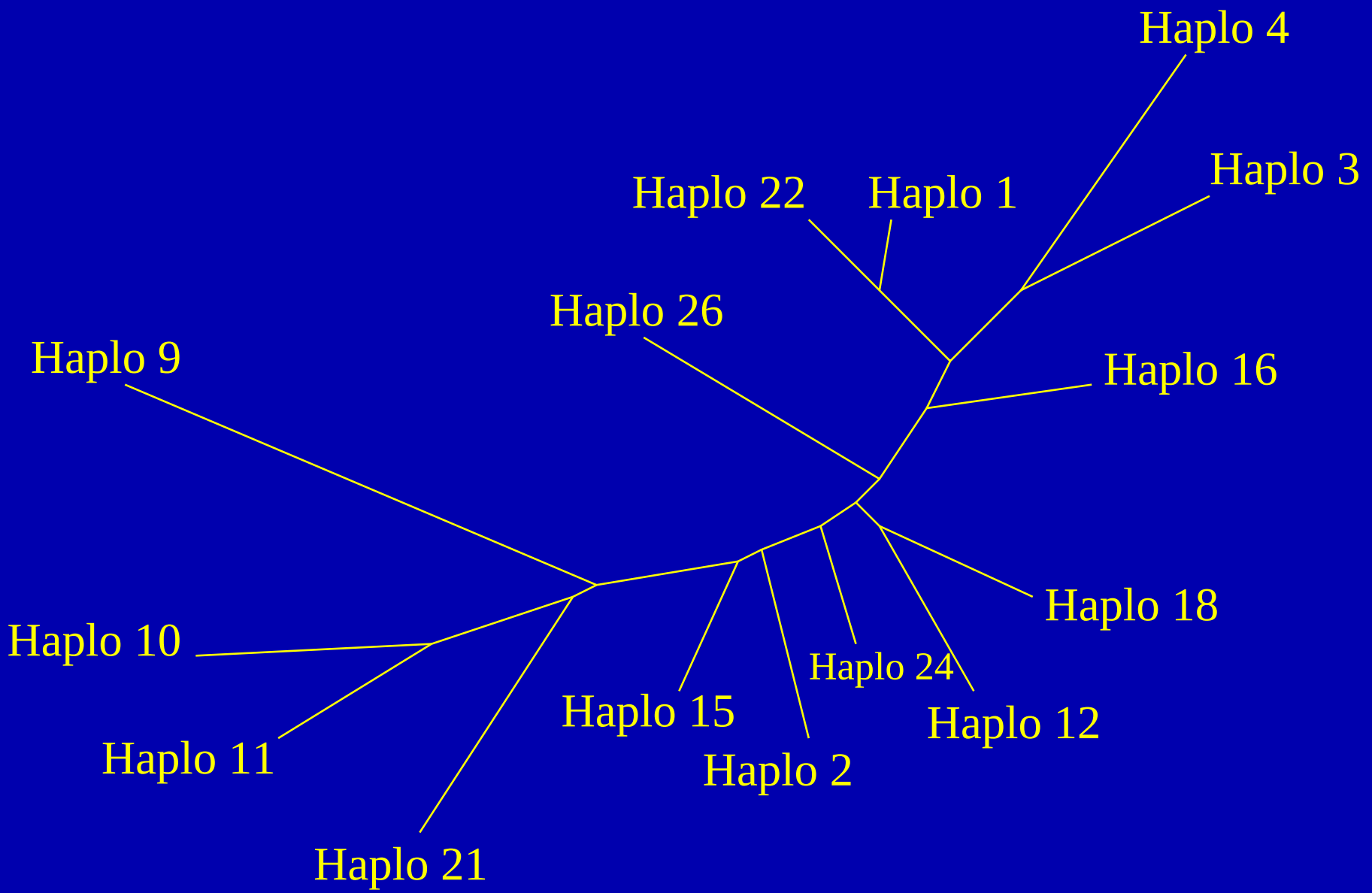
- MSY1 is a ms on the Y chromosome. Unit length 25bp, 5 variants differ by at most 4 residues. Evolution simplified: no exchange between alleles [Jobling et al 98].
- Maps for 690 men taken in $\neq$ populations distributed in 24 haplogroups.
- Is MSY1 an appropriate marker to study the evolution of these haplogroups? or of the subpopulations in an haplogroup? or of individuals?
- Experiments: Compute all pairwise alignments and construct a phylogenetic tree with BioNJ from our distance matrix.

Example of a phylogenetic tree

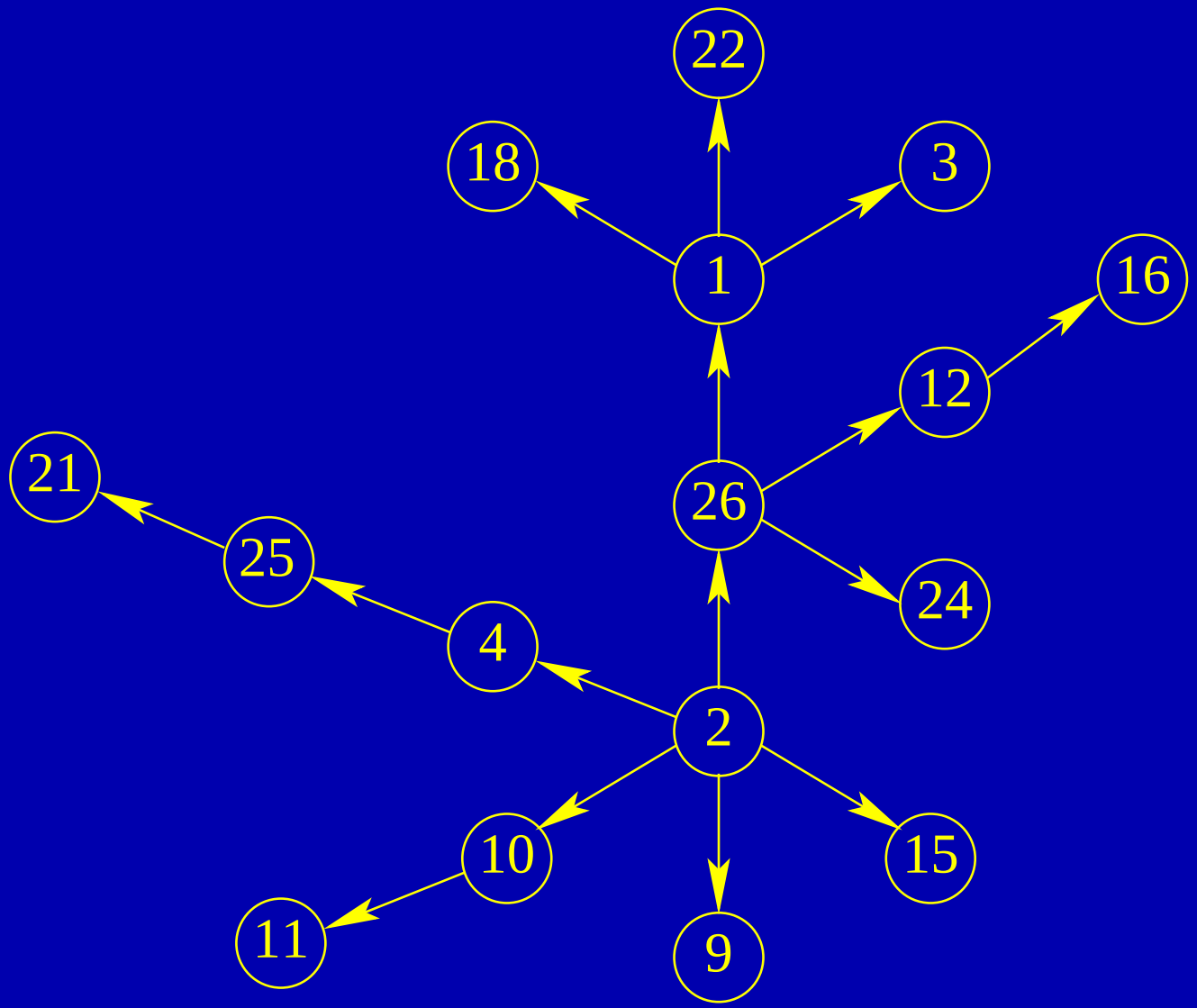


Haplogroup 4 phylogenetic tree.

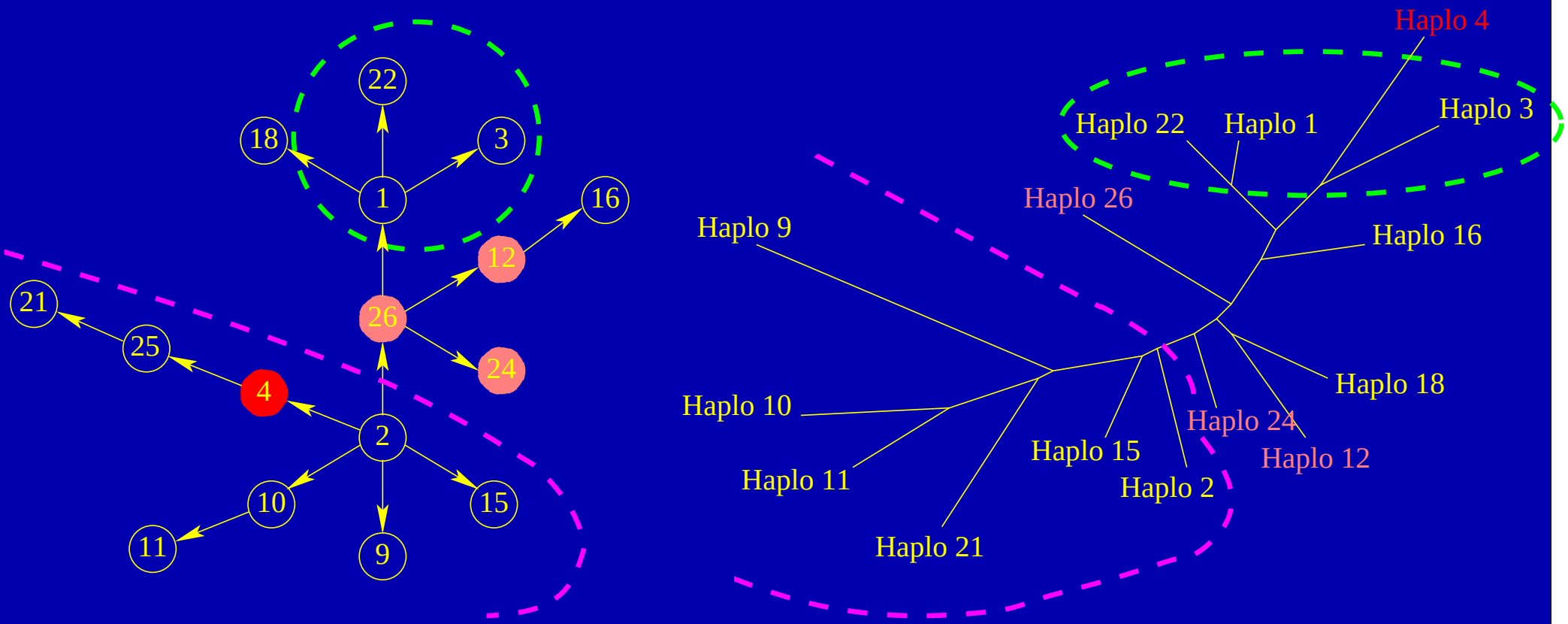
Haplogroups tree



Haplogroups tree (2)



Haplogroups trees comparison



Conclusion and future works

- A new and specific alignment method for minisatellites maps.
- Extensions: multiple amplification/contraction.
  1. arity > 1: $\cdots$ cgg <u>att</u> tga $\cdots \longrightarrow \cdots$ cgg **att att att** tga $\cdots$
  2. order > 1: $\cdots$ cgg <u>att tga</u> $\cdots \longrightarrow \cdots$ cgg **att tga att tga** $\cdots$
- Applicability for different biological purposes and on different ms.