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One Step Mutation (OSM) matrices

joint work with

Sequence Evolution

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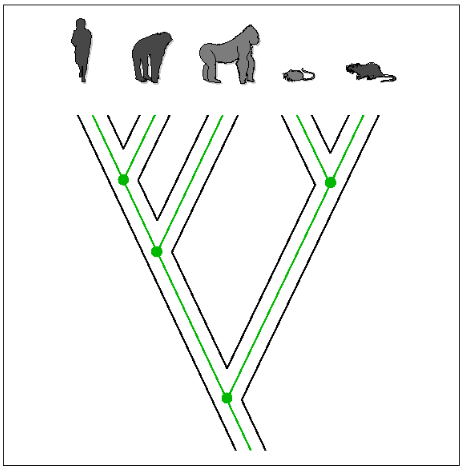

Sequence Evolution

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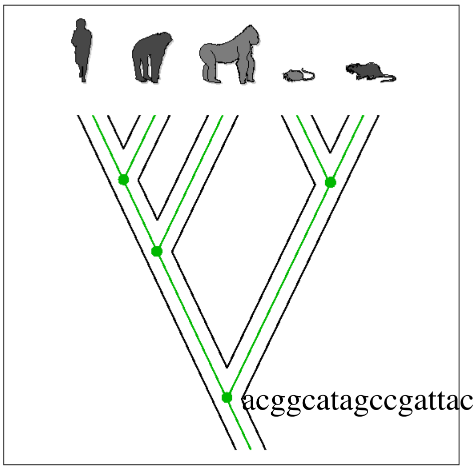

Sequence Evolution

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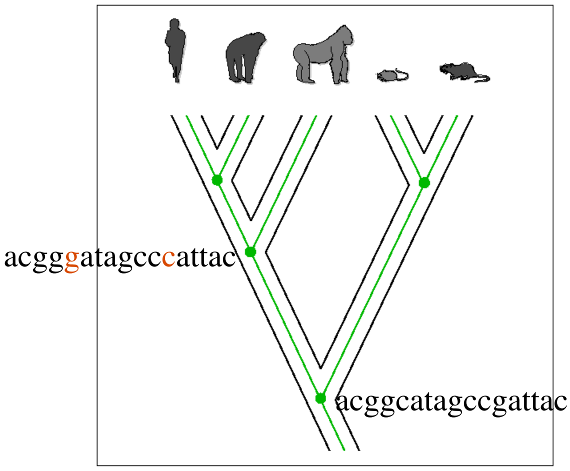

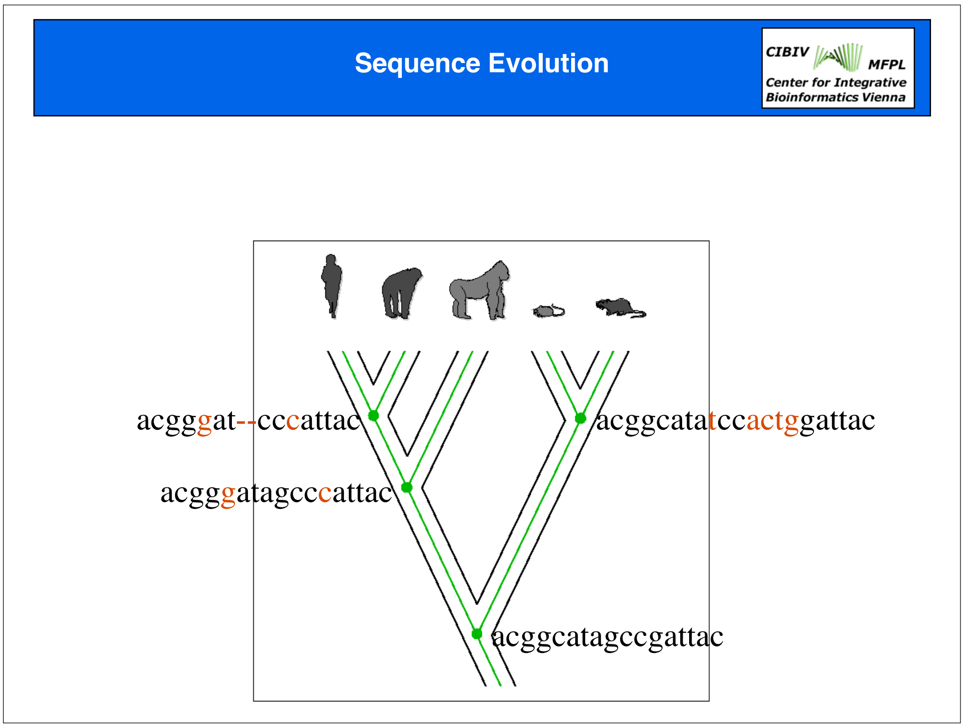
Sequence Evolution
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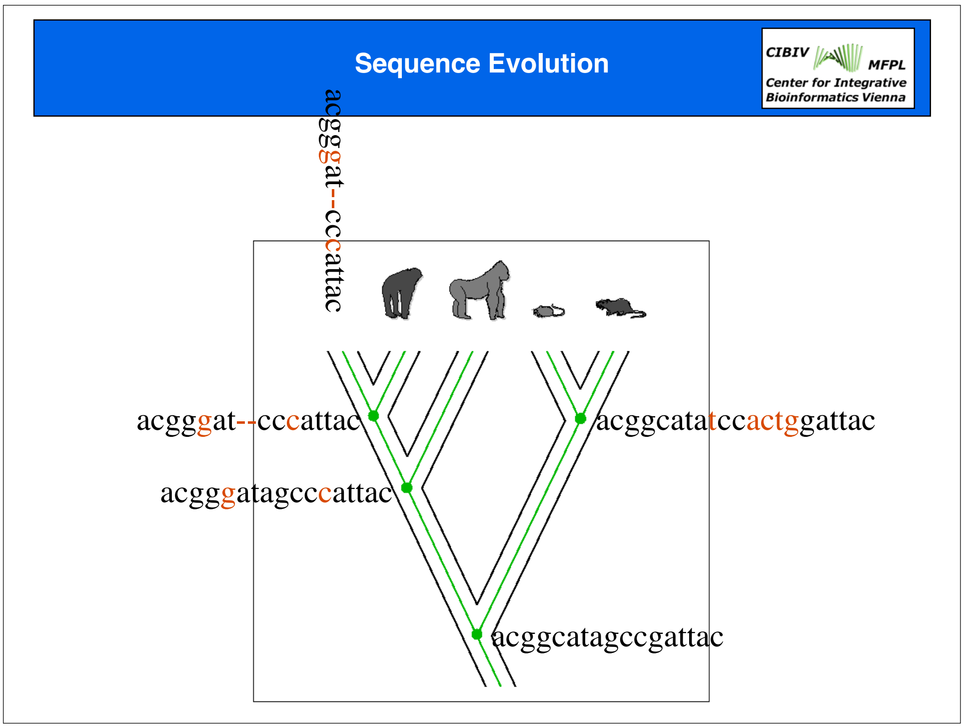
Sequence Evolution
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acgggat--cccattac
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Sequence Evolution

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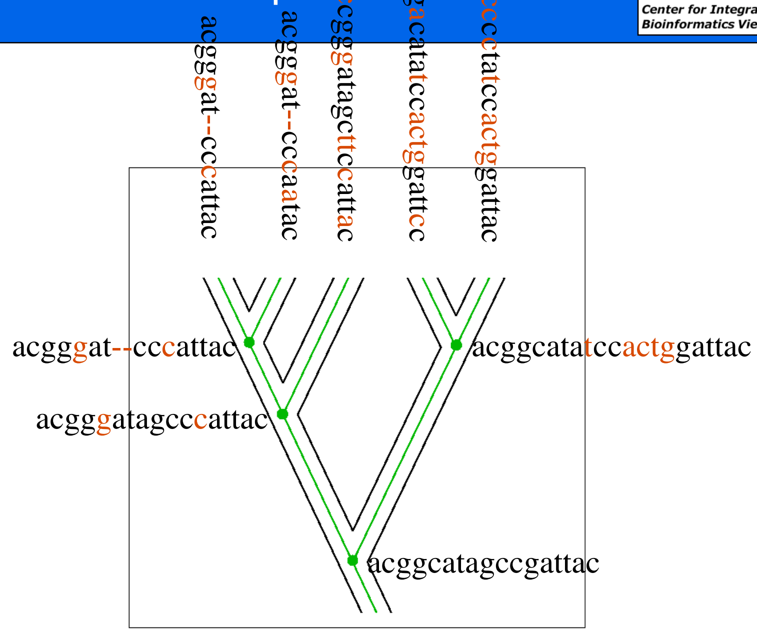

Multiple Sequence Alignment (MSA)

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seq 1	a	g	c	t	t	a	c	c	t	g	t	t	a	c	t
seq 2	c	g	t	a	a	a	t	t	t	c	c	c	g	a	t
seq 3	c	g	c	a	a	g	t	t	t	c	c	c	g	a	t
seq 4	c	a	c	t	t	a	t	t	a	g	t	c	a	a	c

Alignment column or alignment pattern

Example: Binary Alphabet {R, Y}

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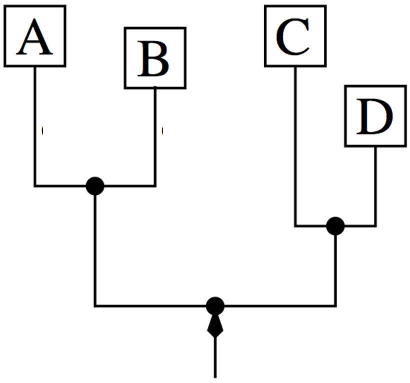

Binary Alphabet {R, Y}

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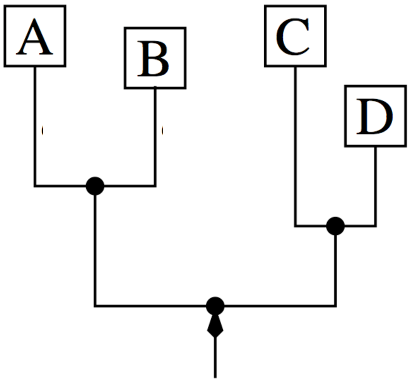
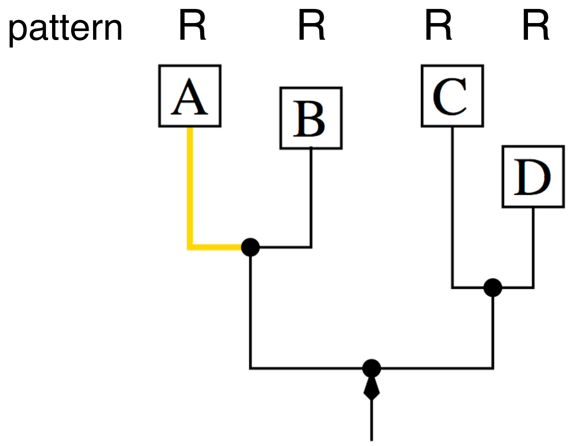
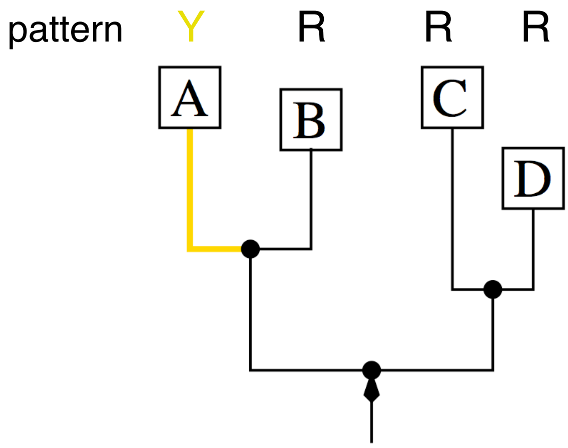
pattern R R R R



Binary Alphabet {R, Y}



Binary Alphabet {R, Y}



Binary Alphabet {R, Y}

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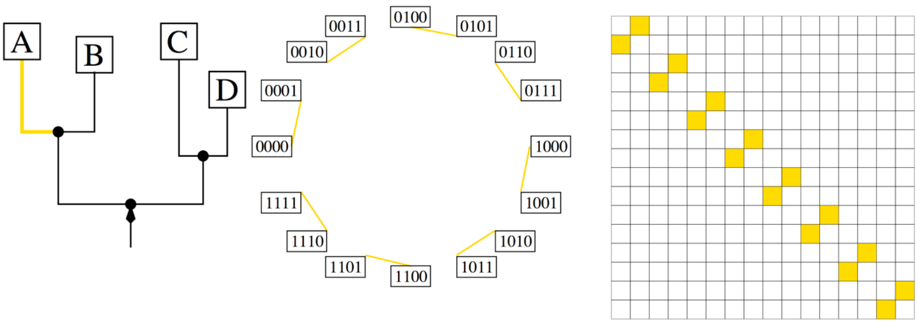
permutation matrix σ_A



Binary Alphabet {R, Y}

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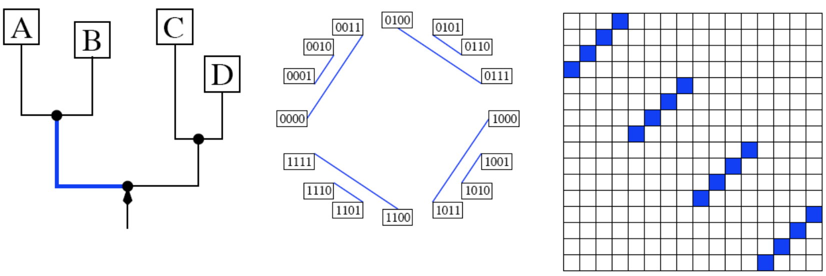
permutation matrix σ_{AB}



Internal branches

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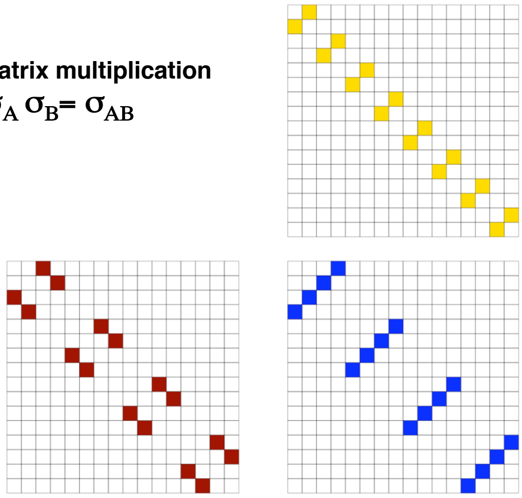
matrix multiplication

$\sigma_A \sigma_B = \sigma_{AB}$



One Step Mutation Matrix

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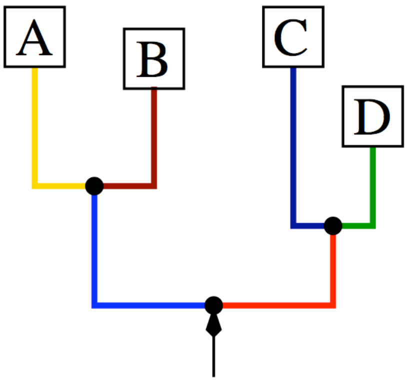

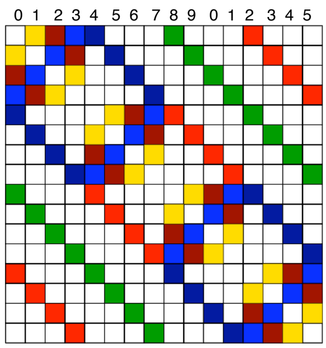

Examples of OSM-Graphs

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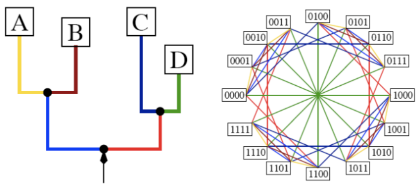

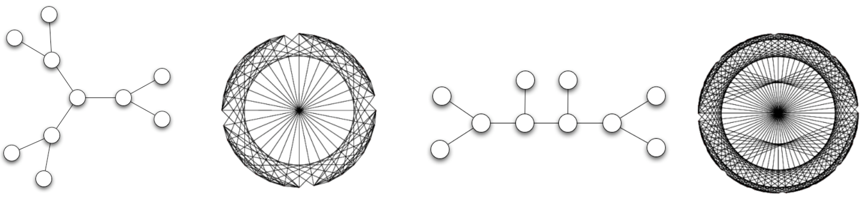

Branch Lengths:

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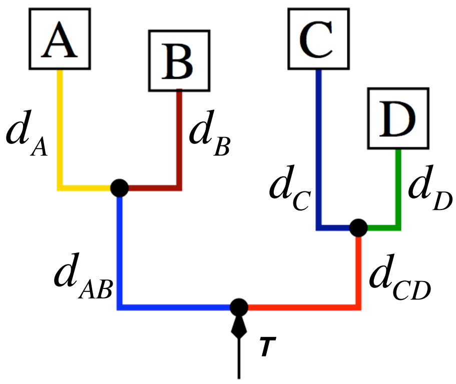


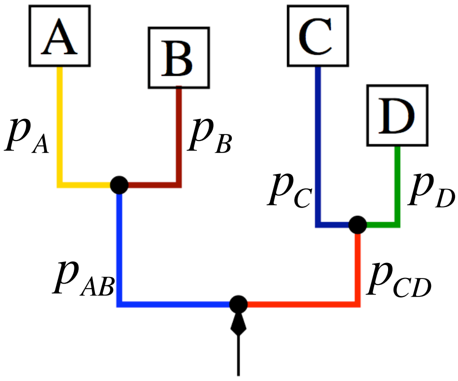
Total branch length

$$\Delta = d_A + d_B + d_C + d_D + d_{AB} + d_{CD}$$

relative edge length

$$p_{edge} = \frac{d_{edge}}{\Delta}$$

Some Formalisms:



relative branch lengths

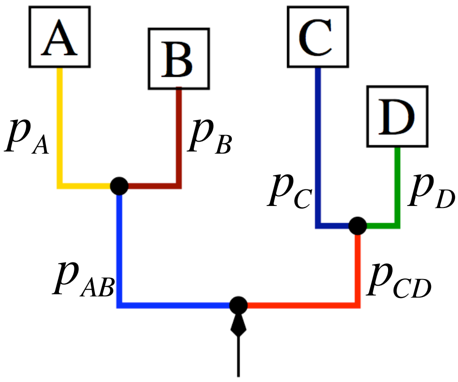
$$p_A + p_B + p_C + p_D + p_{AB} + p_{CD} = 1$$

used to assign mutation probabilities

$$p_{edge} \cdot \sigma_{edge}$$

general permutation matrix

Constructing the OSM:



$$\mathbf{M}_T = \sum_{edge} p_{edge} \cdot \sigma_{edge}$$

Many Substitutions:

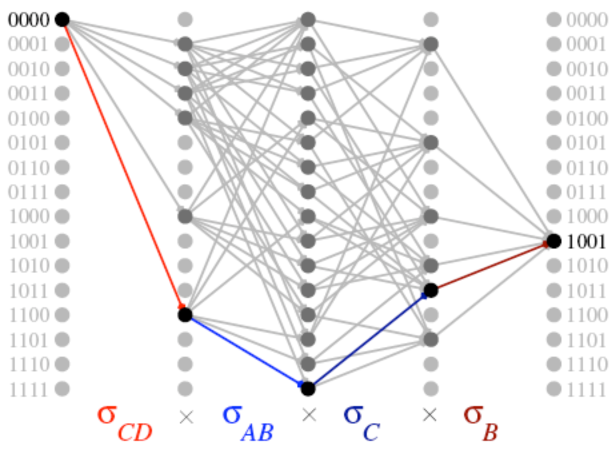
$$\mathbf{M}_T = \sum_{edge} p_{edge} \cdot \sigma_{edge}$$

One substitution

$$\mathbf{M}_T^k = \left(\sum_{edge} p_{edge} \cdot \sigma_{edge} \right)^k$$

***k* substitutions**

Many Substitutions: Random walk



Maximum Parsimony (MP)

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$$\underset{k}{\mathrm{Min}}\left\{\mathbf{M}_T^k(i,j) > 0 \,\middle|\, k \in N\right\}$$

describes the minimal number of mutations to move from pattern *i* to *j*

MP: For a tree *T* and pattern *j* compute:

$$\underset{k}{\mathrm{Min}}\left\{\mathbf{M}_T^k(R...R,j) > 0 \text{ or } \mathbf{M}_T^k(Y...Y,j) > 0 \,\middle|\, k \in N\right\}$$

Maximum Likelihood

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We assume that the number of substitutions is Poisson distributed with parameter Δ. Then we compute, the expected OSM as

$$\overline{\mathbf{M}_T} = \sum_{k=0}^{\infty} \frac{\exp(-\Delta)\Delta^k (\mathbf{M}_T)^k}{k!}$$

$$\overline{\mathbf{M}_T} = \exp(-\Delta) \cdot \exp(\Delta \cdot \mathbf{M}_T)$$

$$\overline{\mathbf{M}_T} = \exp(-\Delta) \cdot \mathbf{H}_{2^n} \cdot \exp(\Delta \cdot \mathbf{D}_T) \cdot \mathbf{H}_{2^n}$$

where $\mathbf{D}_T = \mathbf{H}_{2^n} \cdot \mathbf{M}_T \cdot \mathbf{H}_{2^n}$

and $\mathbf{H}_{2^n} = \underbrace{\mathbf{H}_2 \otimes \mathbf{H}_2 \otimes \ldots \otimes \mathbf{H}_2}_{n \text{ times}}$ $\qquad \mathbf{H}_2 = \begin{pmatrix} 1 & 1 \\ 1 & -1 \end{pmatrix}$

Maximum Likelihood

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$$\overline{\mathbf{M}_T} = \exp(-\Delta) \cdot \mathbf{H}_{2^n} \cdot \exp(\Delta \cdot \mathbf{D}_T) \cdot \mathbf{H}_{2^n}$$

The likelihood of a tree *T* with branch length Δ, given an alignment of length *L* is then

$$\Pr(T,\Delta) = \prod_{i=1}^{L} \overline{\mathbf{M}_T}(\{R...R,Y...Y\}, pattern(i))$$

Another View at the Mutations

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$$\overline{\mathbf{M}_T} = \exp(-\Delta) \cdot \mathbf{H}_{2^n} \cdot \exp(\Delta \cdot \mathbf{D}_T) \cdot \mathbf{H}_{2^n}$$

From the above formula, we can **analytically** compute the posterior probability of the number of mutations that have occurred on a fixed tree.

$$\Pr(k \text{ mutations} \mid \text{pattern}) = \frac{\exp(-\Delta)\Delta^k}{k!} \frac{(\mathbf{M}_T(R,\ldots,R,\text{pattern}))^k}{\overline{\mathbf{M}_T}(R\ldots,R,\text{pattern})}$$

similar work by Rasmus Nielsen, John Huelsenbeck, Jonathan Bollback (2002, 2003, 2005)

Posterior probabilities:clock-like tree

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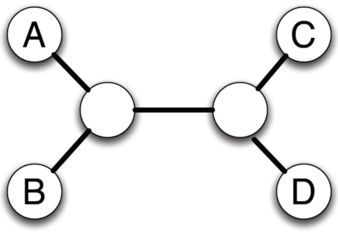
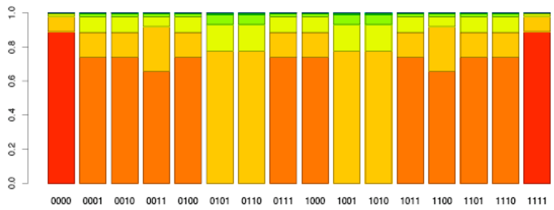
$$\mathrm{ppd}[k \mid \mathbf{a}] = \frac{\exp[-\Delta]\Delta^k\left(\pi_0 \mathbf{M}_T^k(\mathbf{0},\mathbf{a}) + \pi_1 \mathbf{M}_T^k(\mathbf{1},\mathbf{a})\right)}{\pi_0 \overline{\mathbf{M}_T}(\mathbf{0},\mathbf{a}) + \pi_1 \overline{\mathbf{M}_T}(\mathbf{1},\mathbf{a})}$$

Δ=1.0





Posterior probabilities: five Taxa Tree

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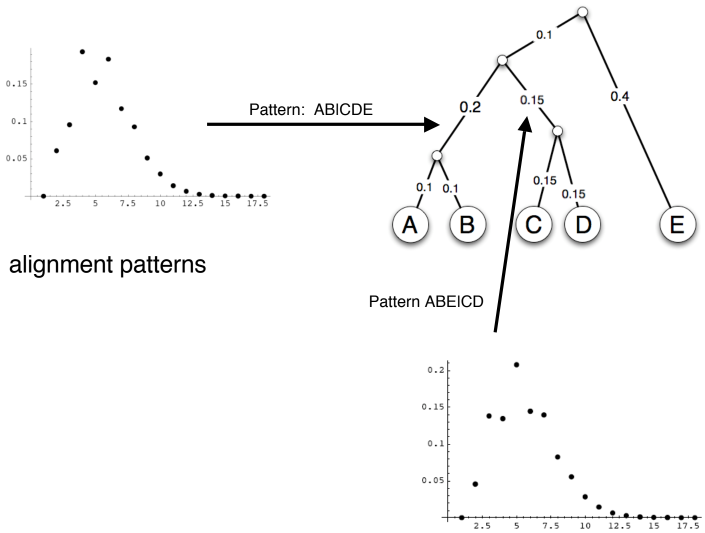

Summary and Outlook

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Developed an evolutionary model that describes the action of a single substitution on an alignment pattern.

This leads to a tree-topology mediated random walk on the space of words of length *n*.

Maximum Parsimony and Maximum Likelihood are “extreme” cases within this framework.

Practical Aspect: Analytical formula for the posterior probabilities of the number of substitutions for a pattern.

Open Questions:

•Connection between OSM and Hadamard transform (Hendy, Penny 1989) and its generalization, the Fourier calculus on evolutionary trees (Szekely, Steel, Erdös 1993).

•Other type of substitution distributions?

•Computational issues

The real stuff

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```
..GUCAUAGAGGGUGAGAAUCCCGUG..
..GCCGGAGAGGGUGACAGCCCCAUC..
..CCCGUGGACGGUGUGAGGCCGGUA..
..GUGAUACAGGGUGACAACCCCGUA..
..ACCAGAGAAGGUGAAAGUCCUGUA..
..GCGAUACAGGGUGACAGCCCCGUA..
```

The real stuff

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```
..GUCAUAGAGGGUGAGAAUCCCGUG..
..GCCGGAGAGGGUGACAGCCCCAUC..
..CCCGUGGACGGUGUGAGGCCGGUA..
..GUGAUACAGGGUGACAACCCCGUA..
..ACCAGAGAAGGUGAAAGUCCUGUA..
..GCGAUACAGGGUGACAGCCCCGUA..
```

Observed pattern count

$$\mathbf{O}\left(d_1,\ldots,d_{4^n}\right)$$

The real stuff

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```
..GUCAUAGAGGGUGAGAAUCCCGUG..
..GCCGGAGAGGGUGACAGCCCCAUC..
..CCCGUGGACGGUGUGAGGCCGGUA..
..GUGAUACAGGGUGACAACCCCGUA..
..ACCAGAGAAGGUGAAAGUCCUGUA..
..GCGAUACAGGGUGACAGCCCCGUA..
```

Observed pattern count

$$\mathbf{O}\left(d_1,\ldots,d_{4^n}\right)$$

Maximum likelihood etc.

The real stuff

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```
..GUCAUAGAGGGUGAGAAUCCCGUG..
..GCCGGAGAGGGUGACAGCCCCAUC..
..CCCGUGGACGGUGUGAGGCCGGUA..
..GUGAUACAGGGUGACAACCCCGUA..
..ACCAGAGAAGGUGAAAGUCCUGUA..
..GCGAUACAGGGUGACAGCCCCGUA..
```

→ Observed pattern count

$$\mathrm{O}\left(d_1,\ldots,d_{4^n}\right)$$

↓ Maximum likelihood etc.

$$\mathrm{E}\left(p_1,\ldots,p_{4^n}\right)$$

$$\hat{T}$$

The real stuff

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```
..GUCAUAGAGGGUGAGAAUCCCGUG..
..GCCGGAGAGGGUGACAGCCCCAUC..
..CCCGUGGACGGUGUGAGGCCGGUA..
..GUGAUACAGGGUGACAACCCCGUA..
..ACCAGAGAAGGUGAAAGUCCUGUA..
..GCGAUACAGGGUGACAGCCCCGUA..
```

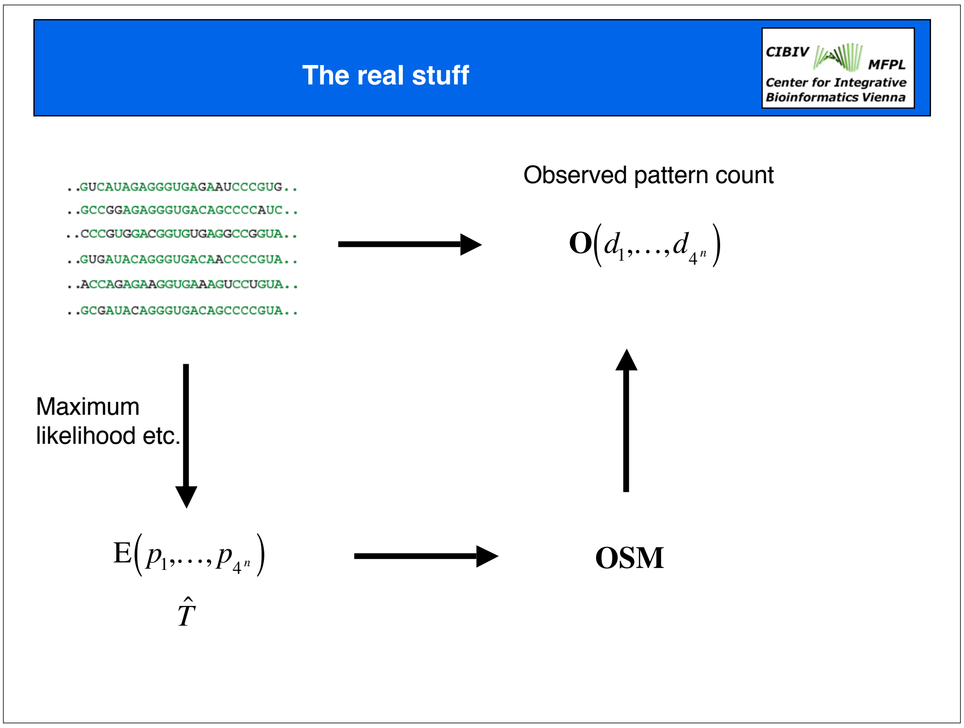
→ Observed pattern count

$$\mathrm{O}\left(d_1,\ldots,d_{4^n}\right)$$

↓ Maximum likelihood etc.

$$\mathrm{E}\left(p_1,\ldots,p_{4^n}\right) \rightarrow \textbf{OSM}$$

$$\hat{T}$$


The real stuff
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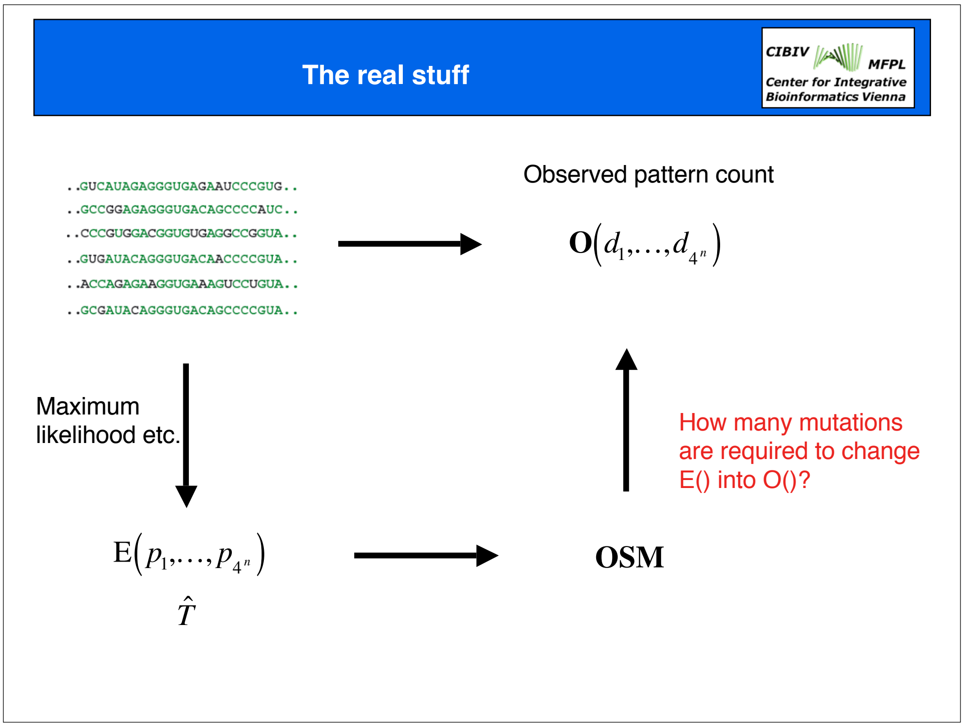
..GUCAUAGAGGGUGAGAAUCCCGUG..
..GCCGGAGAGGGUGACAGCCCCAUC..
..CCCGUGGACGGUGUGAGGCCGGUA..
..GUGAUACAGGGUGACAACCCCGUA..
..ACCAGAGAAGGUGAAAGUCCUGUA..
..GCGAUACAGGGUGACAGCCCCGUA..
Observed pattern count
$O(d_1,\ldots,d_{4^n})$
Maximum likelihood etc.
$E(p_1,\ldots,p_{4^n})$
$\hat{T}$
OSM


The real stuff
CIBIV
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..GUCAUAGAGGGUGAGAAUCCCGUG..
..GCCGGAGAGGGUGACAGCCCCAUC..
..CCCGUGGACGGUGUGAGGCCGGUA..
..GUGAUACAGGGUGACAACCCCGUA..
..ACCAGAGAAGGUGAAAGUCCUGUA..
..GCGAUACAGGGUGACAGCCCCGUA..
Observed pattern count
$O(d_1,\ldots,d_{4^n})$
Maximum likelihood etc.
How many mutations are required to change E() into O()?
$E(p_1,\ldots,p_{4^n})$
$\hat{T}$
OSM