

Deciphering viral RNA structure with ViennaRNA

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viruses *in silico* lecture series
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Part I

RNA structure prediction

with

ViennaRNA

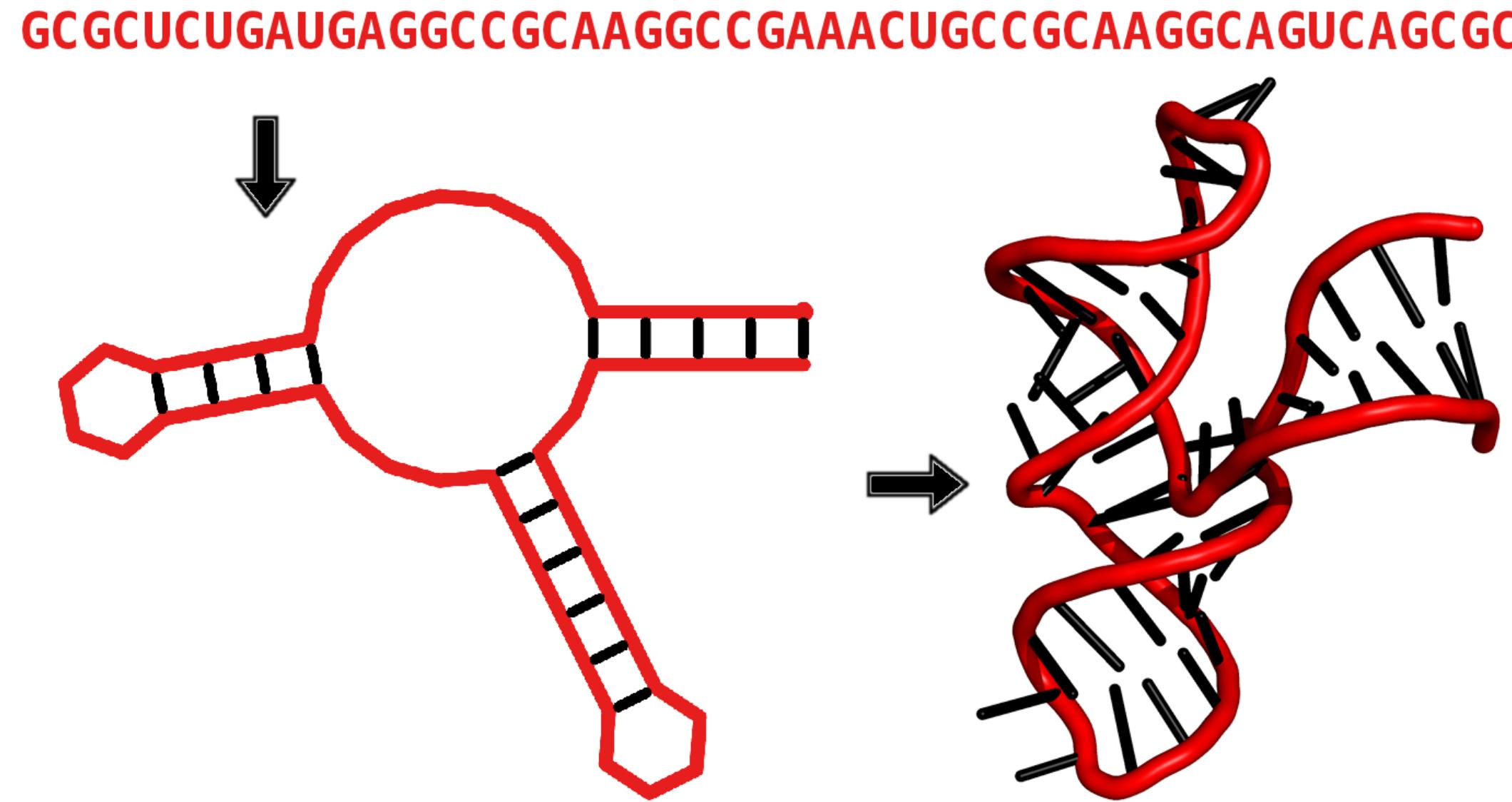
Part II

RNA structure conservation

in

Tick-borne encephalitis virus

The RNA folding problem

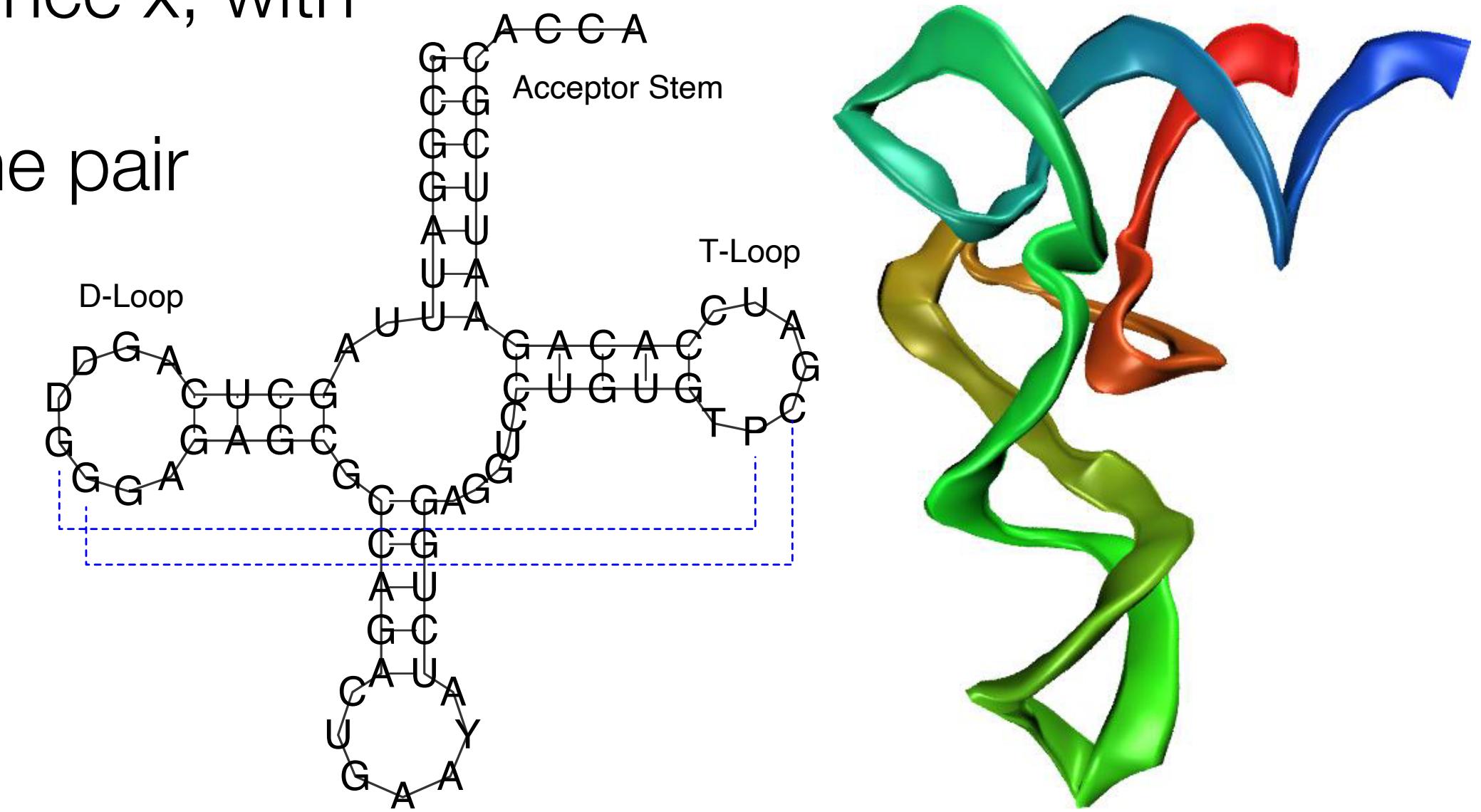


- Hierarchical folding: Secondary structure forms first then helices arrange to form tertiary structure
- Secondary structure captures a majority of stabilising interactions
- Convenient and biologically useful description: Many thermodynamic properties can be predicted
- Starting point for RNA 3D structure prediction
- Tertiary structure prediction needs knowledge of secondary structure

RNA secondary structures

A **secondary structure** is a list of base pairs (i,j) on a sequence x , with

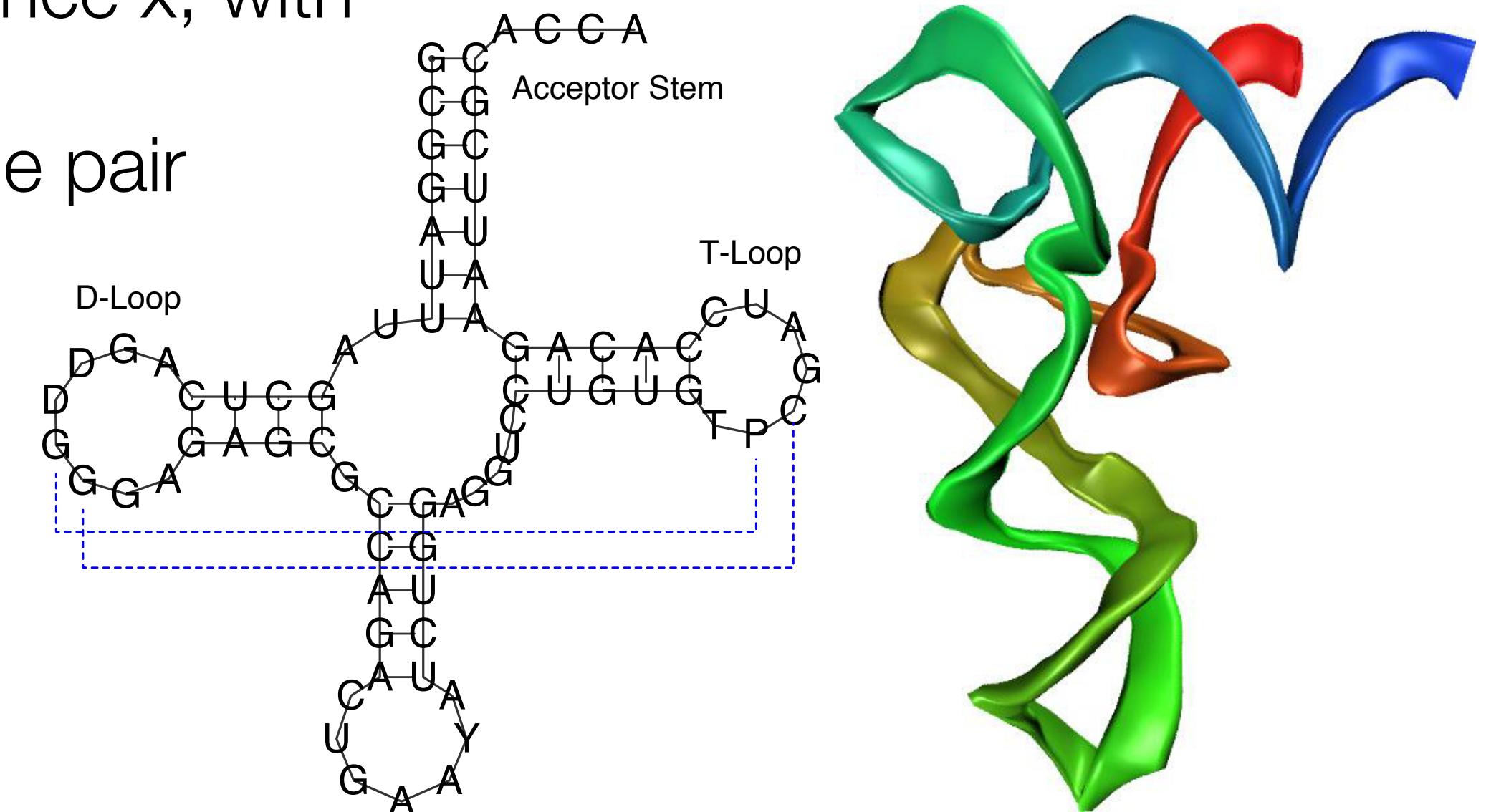
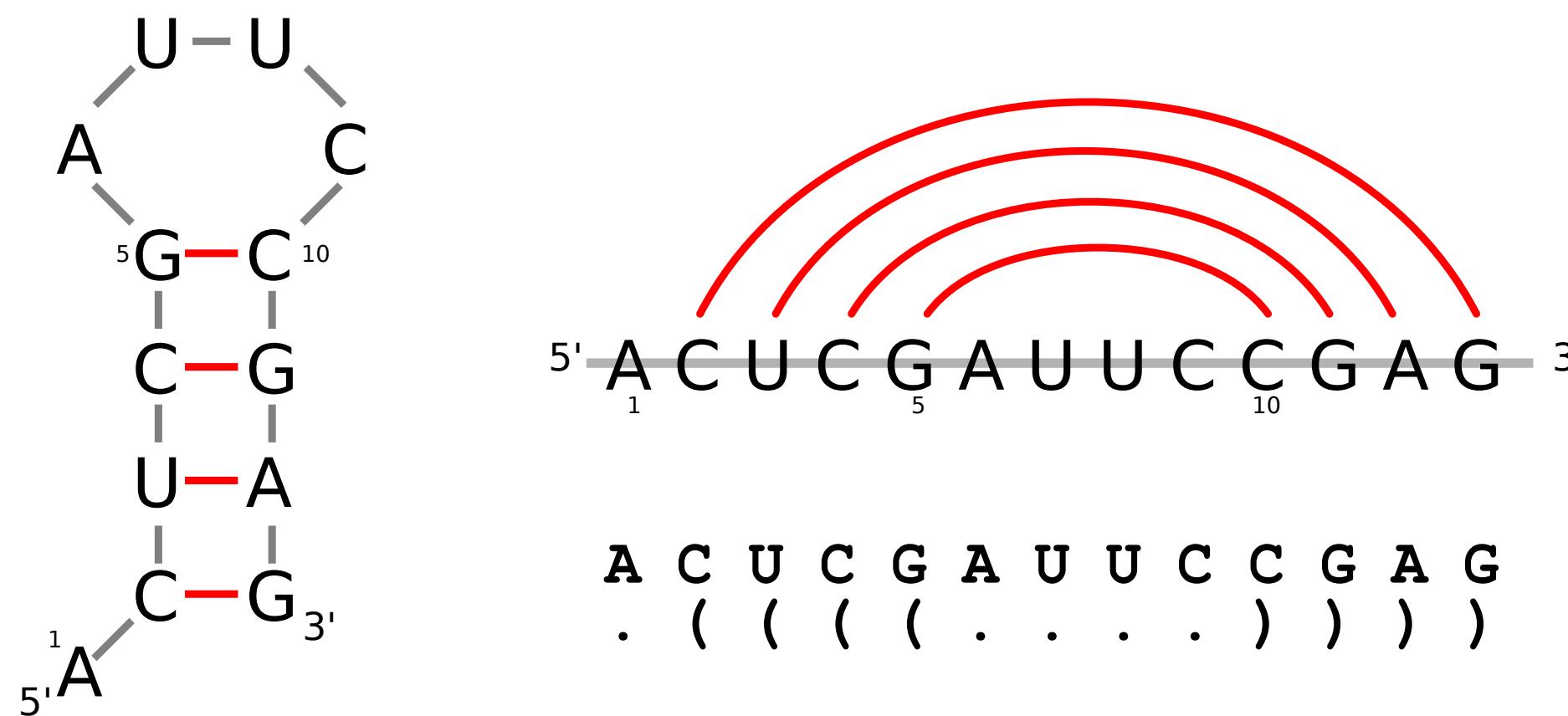
- Any nucleotide (sequence position) can form at most one pair
- If (i,j) is a pair then $x_i x_j \in \{GC, CG, AU, UA, GU, UG\}$
- If (i,j) is a base pair, then $j - i > 3$
- No pseudo-knots: No pairs (i,j) and (k,l) with $i < k < j < l$



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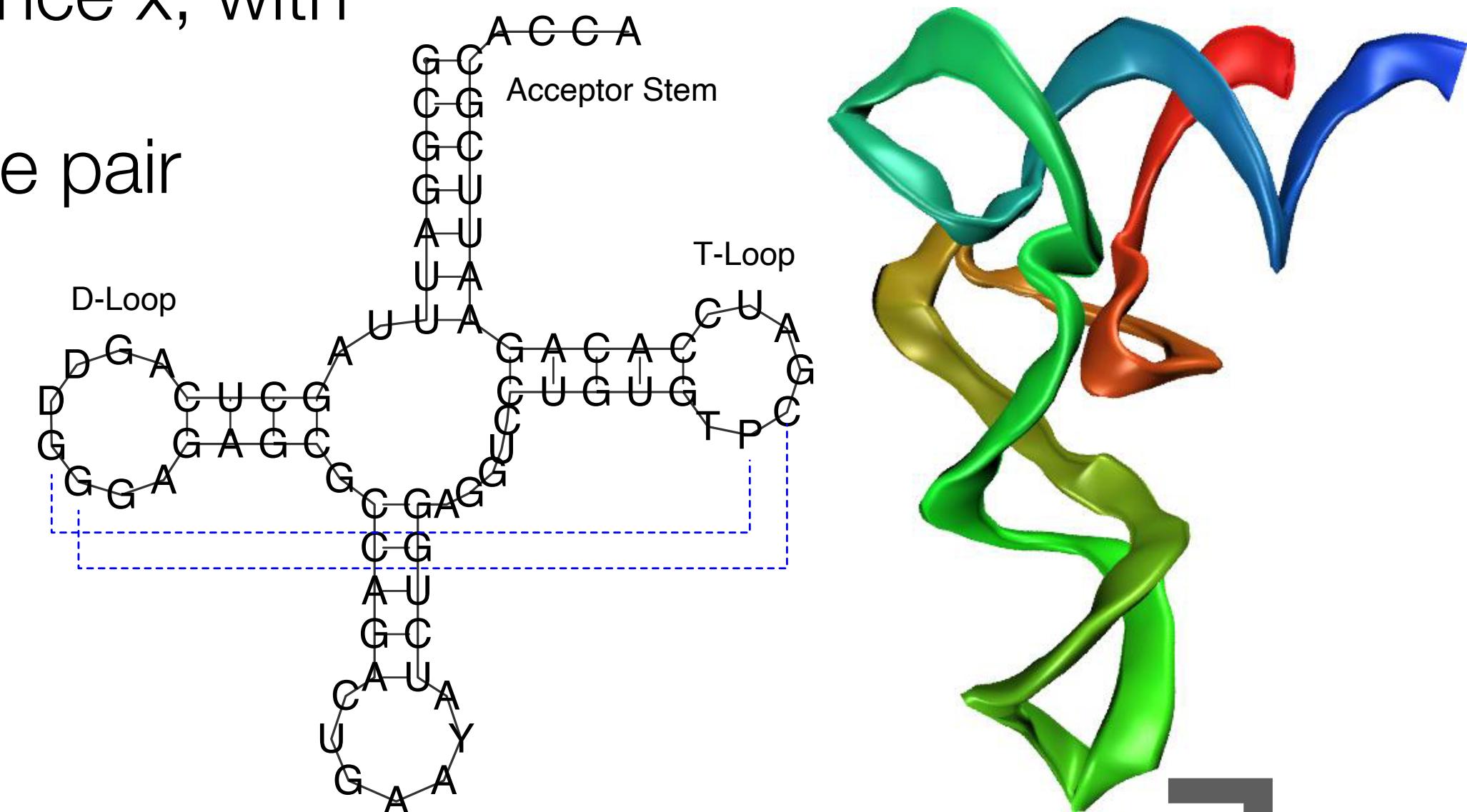
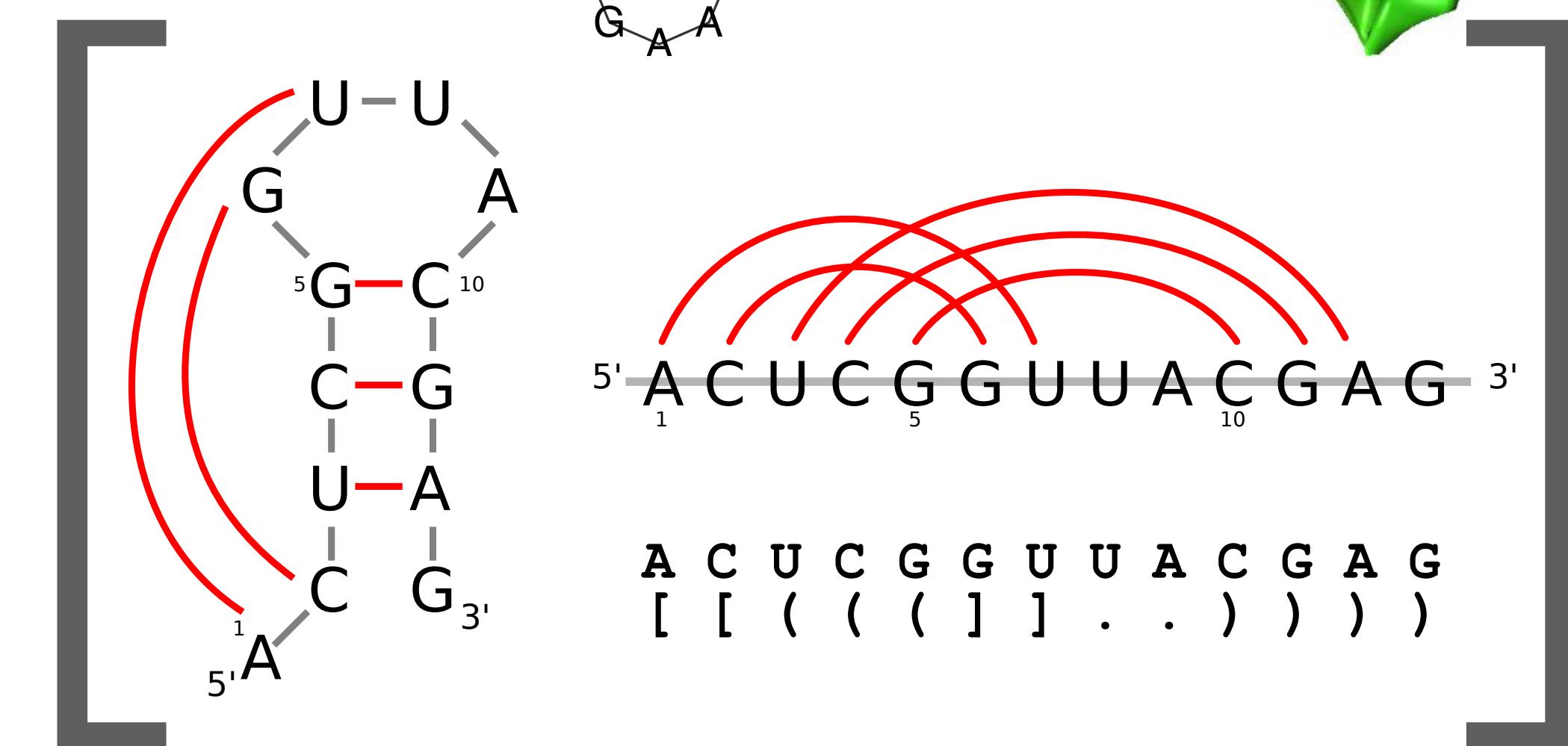
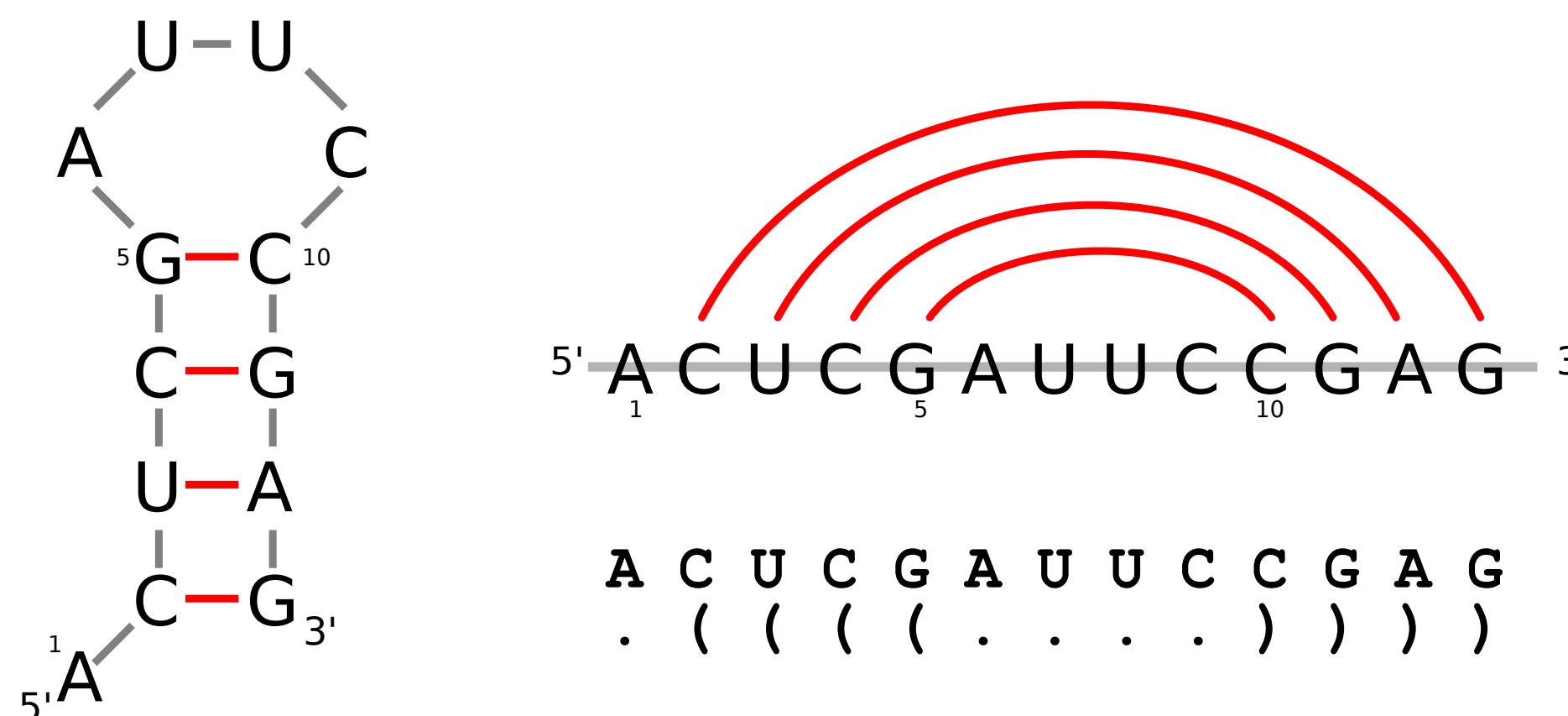
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Solving the RNA folding problem

Toy model for RNA folding: assign energies to base pairs $\varepsilon(x, y)$

Easily solved by **Dynamic Programming**: recursive computation with tabulation of intermediate results



$$E_{ij} = \min_{i < k \leq j} \left\{ E_{i+1,j}; \left(E_{i+1,k-1} + E_{k+1,j} + \varepsilon(x_i, x_k) \right) \right\}$$

- E_{1n} is the best possible energy for our sequence
- Backtracing through the E table yields the corresponding structure
- The algorithm requires $\mathcal{O}(n^2)$ memory and $\mathcal{O}(n^3)$ CPU time

In practice this toy model is not good enough !
We need loop-dependent energies for serious predictions

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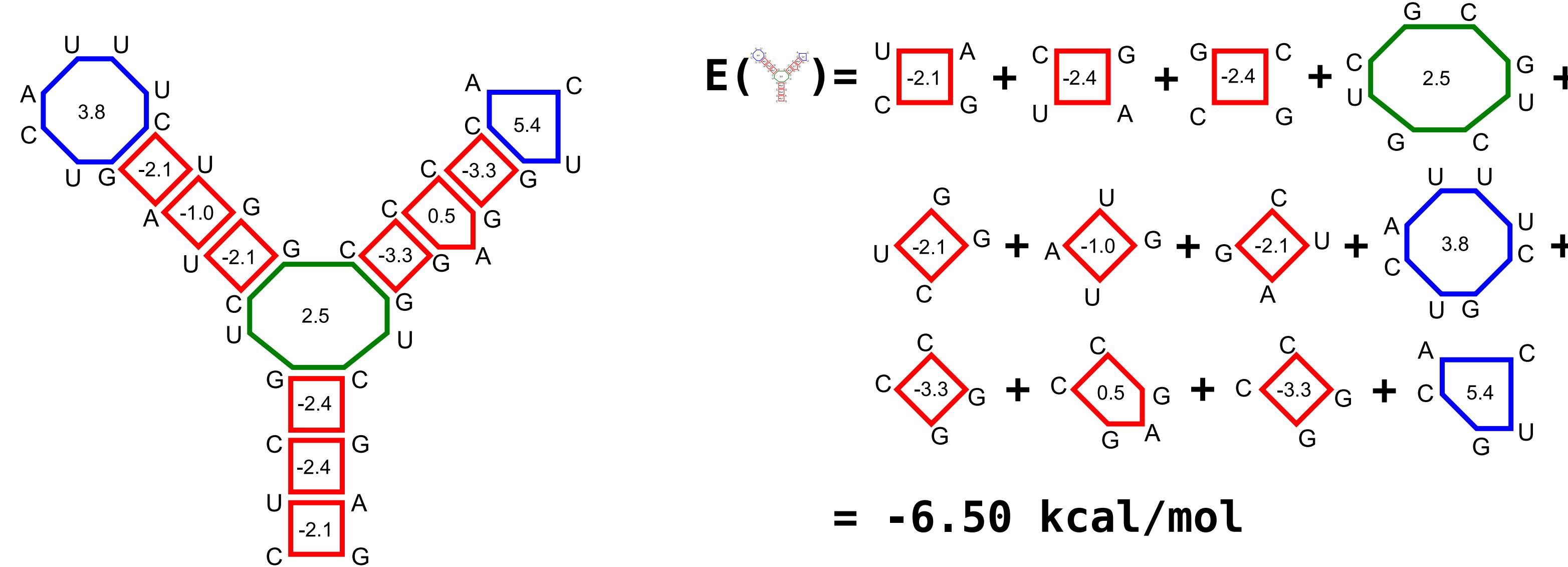


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Nearest neighbor energy model

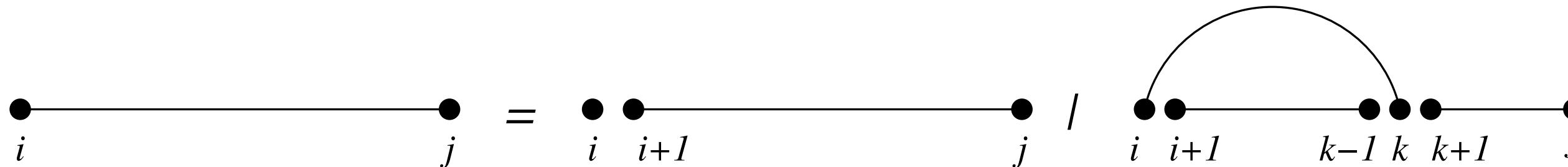


- Secondary structure s is uniquely decomposed into loops L
- Contributions of a base pair only depends on neighbouring pairs
- Each loop L is assigned a free energy contribution E_L^1

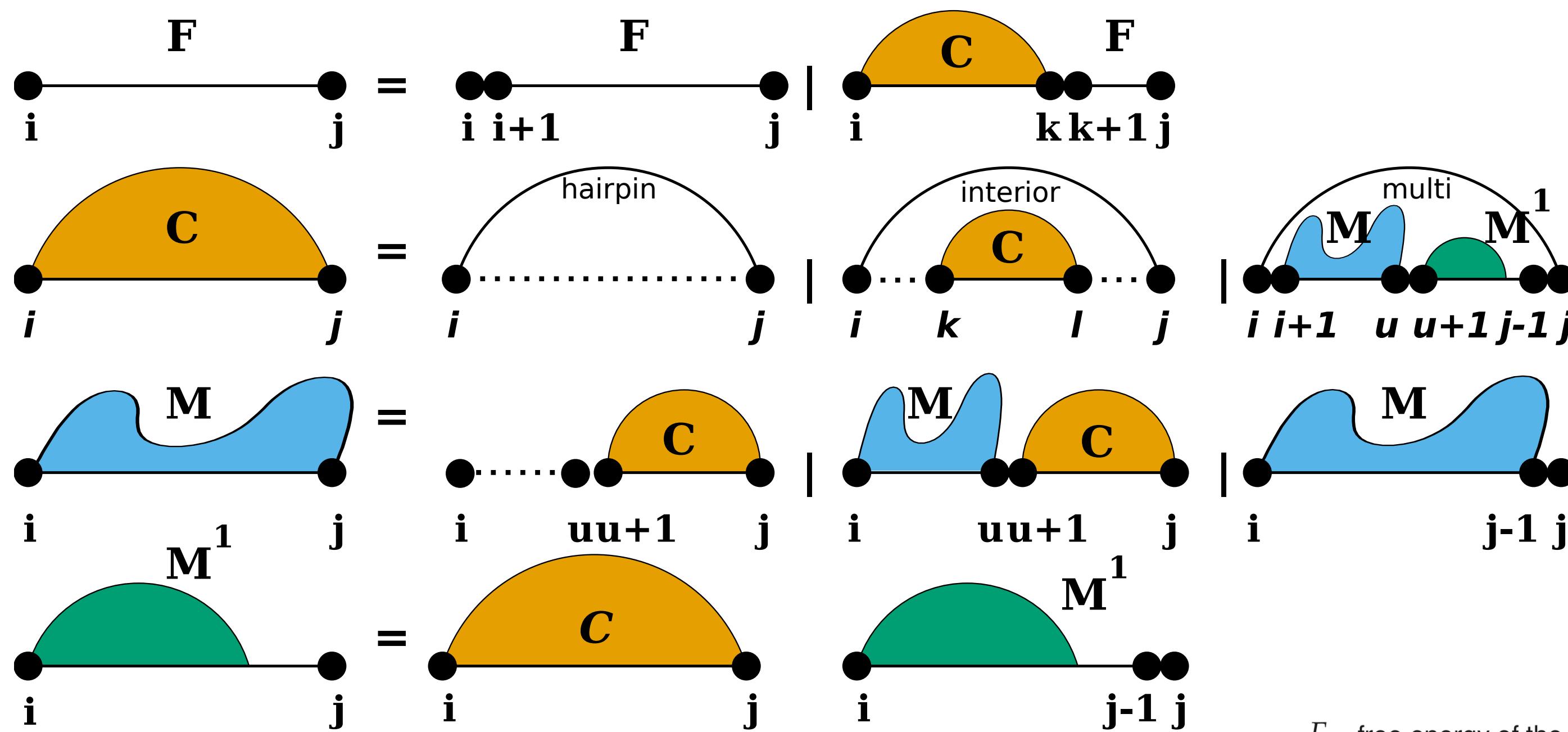
$$E(s) \approx \sum_{L \in s} E_L$$

RNA secondary structure prediction

Nussinov decomposition scheme:



Full decomposition scheme:



F_{ij} free energy of the optimal substructure on the subsequence $x[i..j]$.

C_{ij} optimal free energy on $x[i..j]$, where (i, j) pair.

M_{ij} $x[i..j]$ is part of a multiloop and contains at least one pair.

M_{ij}^1 same as M_{ij} but contains exactly one component closed by (i, h) .

RNA secondary structure prediction

- Minimum free energy (MFE)
- Suboptimal secondary structures

- Partition function Z

$$p(s) = e^{-\beta E(s)} \quad \text{with} \quad \beta = \frac{1}{kT} \longrightarrow Z = \sum_{s \in \Omega} e^{-\beta E(s)}$$

- Probability of feature \mathcal{F}

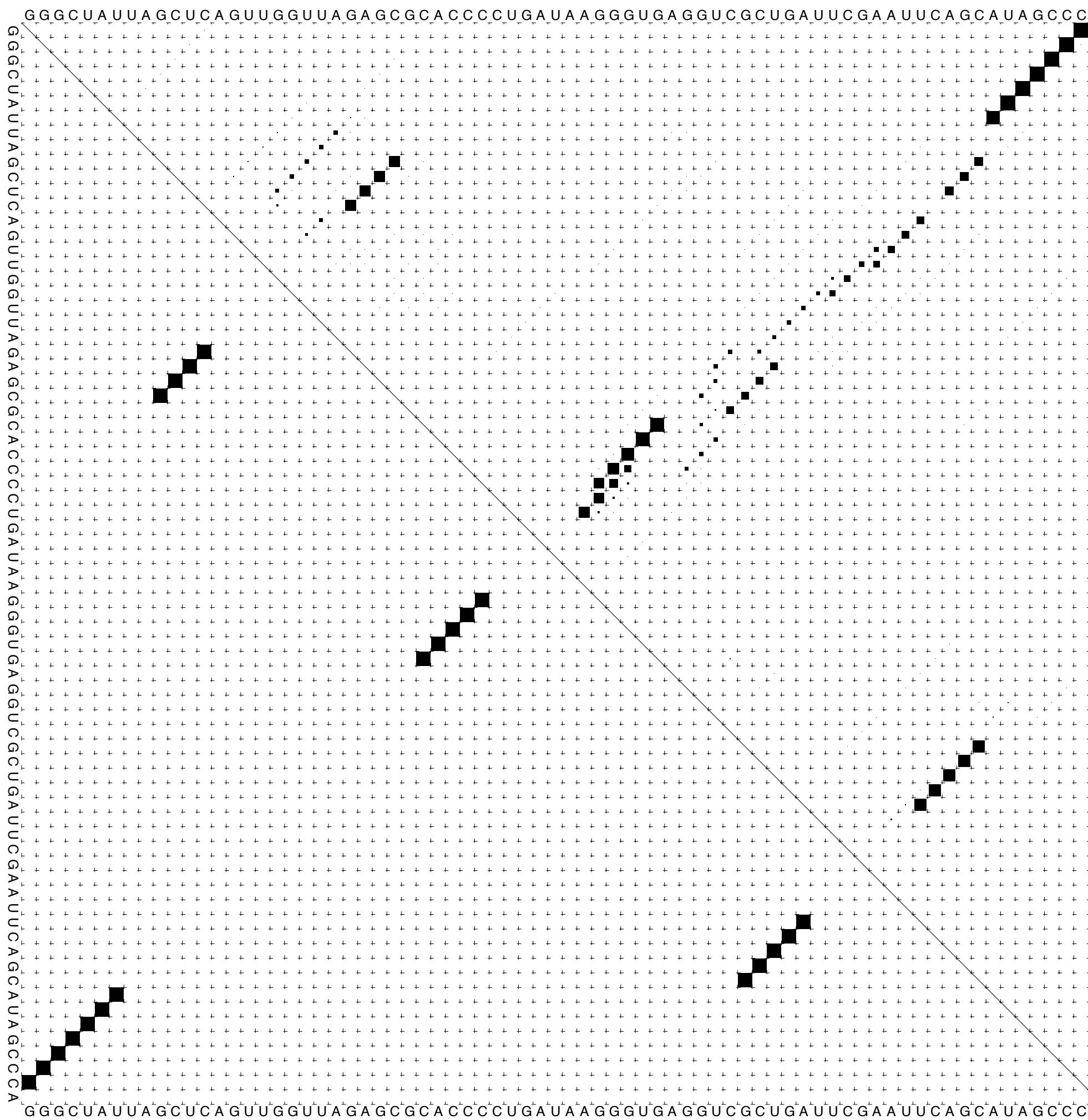
$$p(\mathcal{F}) = \frac{Z_{\mathcal{F}}}{Z} \quad \text{with} \quad Z_{\mathcal{F}} = \sum_{s | F \in s} e^{-\beta E(s)}$$

- Base pair probabilities

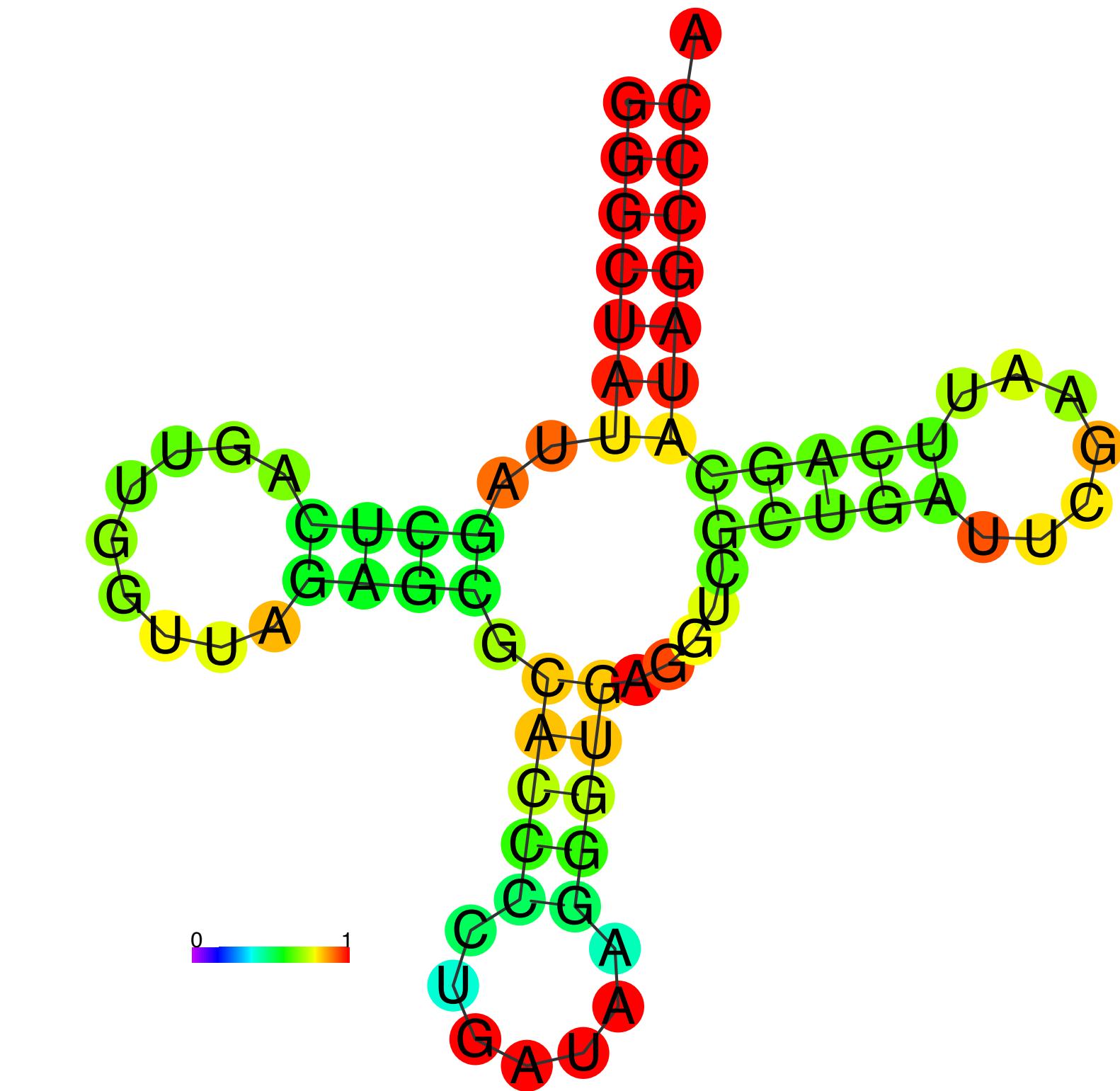
- Stochastic backtracking (Boltzmann sampling)

- Global/local reliability measures

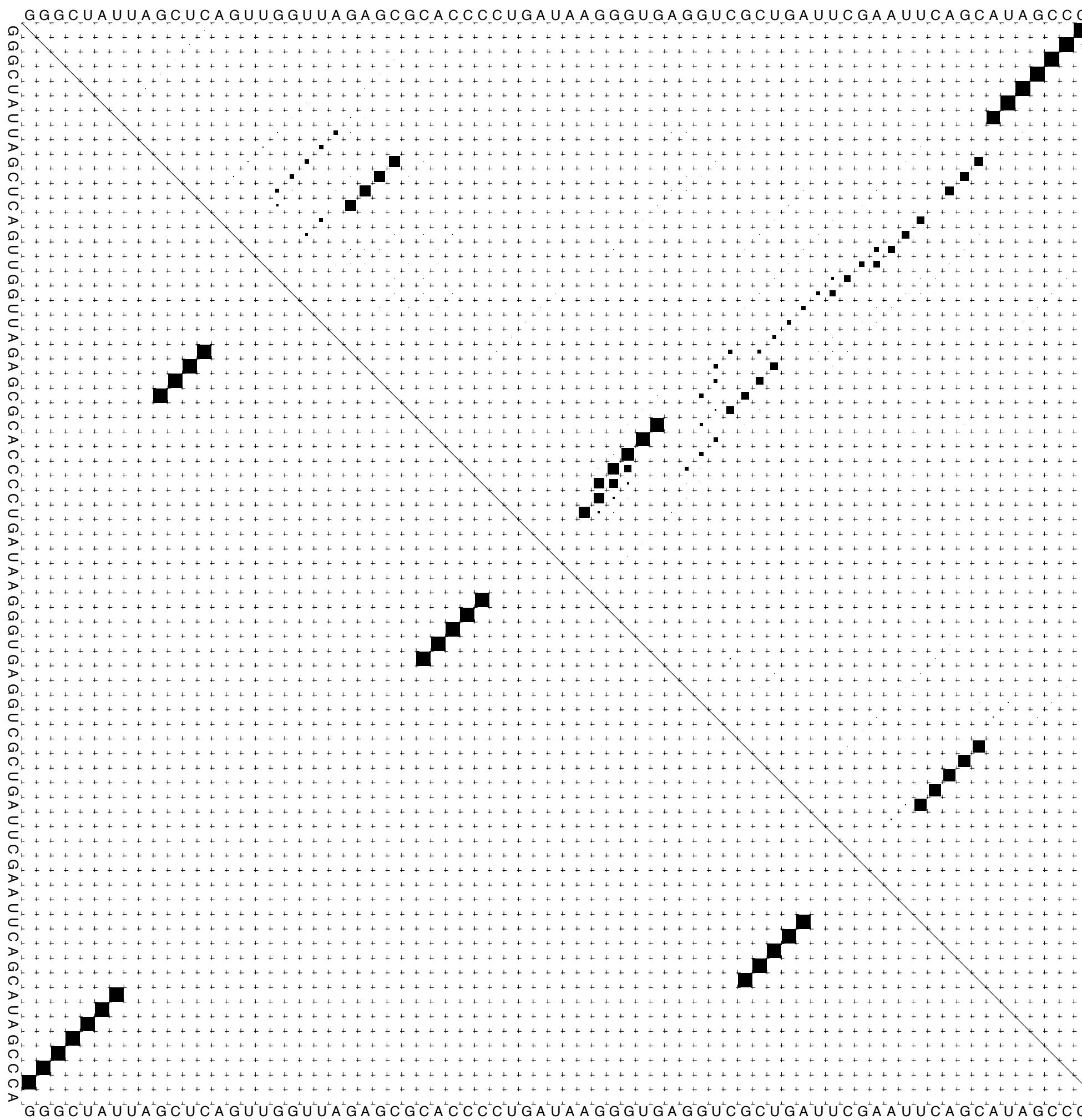
Base pair probabilities



Base pair probability dot plot

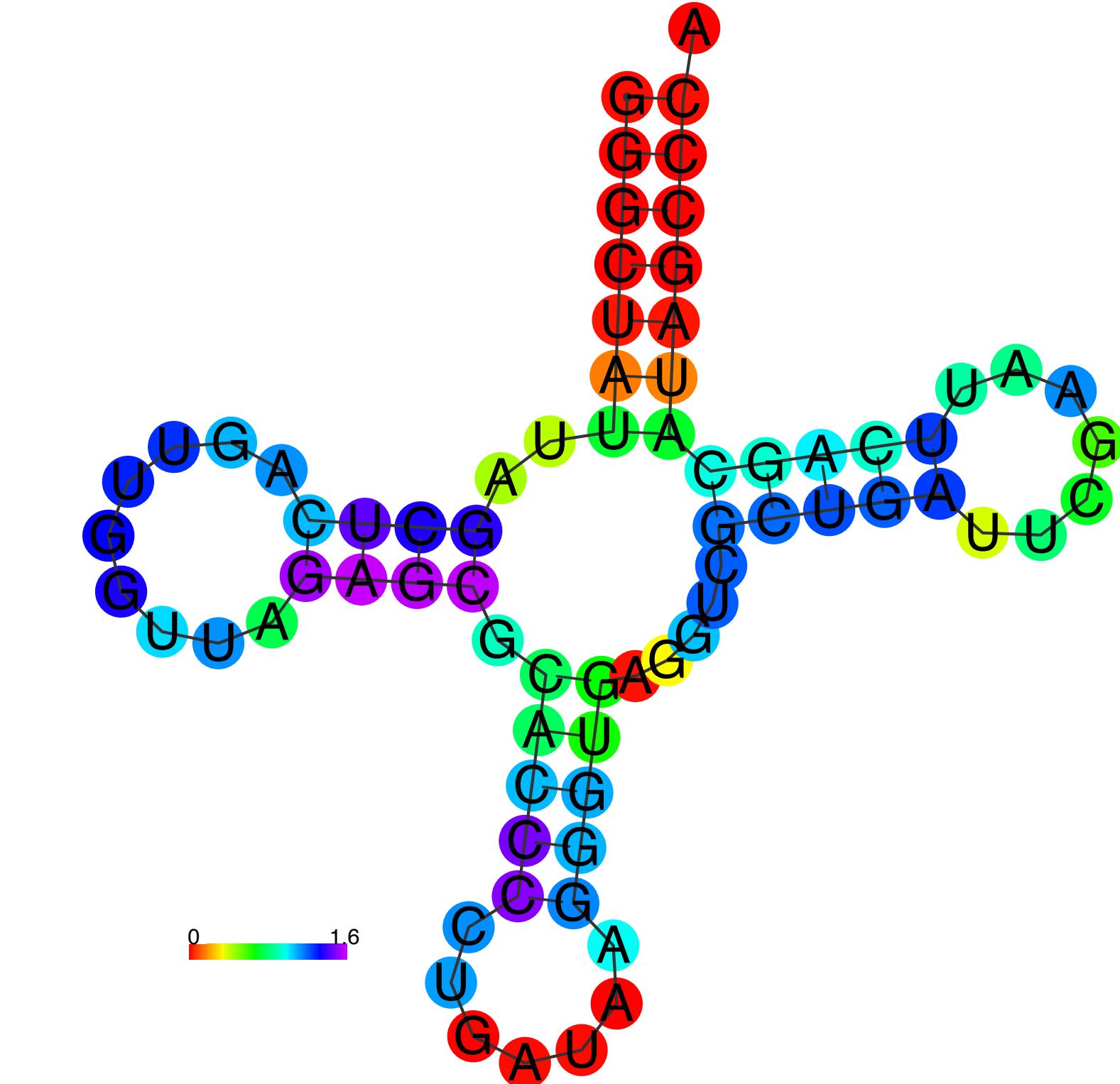


Well-definedness: Positional entropy



Local reliability:

Which parts of the prediction can we trust?



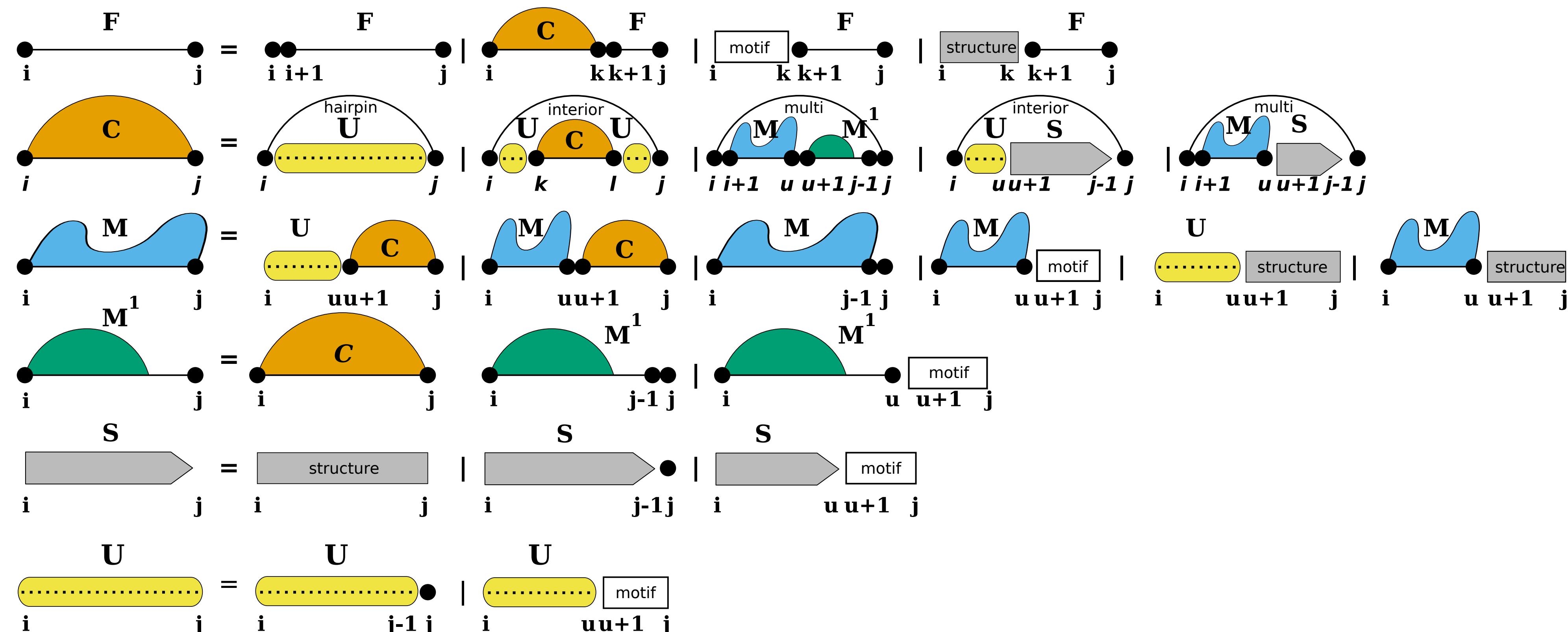
Positional ('Shannon') entropy is computed from pair probabilities

$$PE(i) = - \sum_k p_{ik} \ln p_{ik}$$

RNA secondary structure prediction

The ViennaRNA Package enables the decomposition schema (folding grammar) to be:

- Constrained in terms of candidate space (hard constraints)
- Constrained in terms of candidate evaluation (soft constraints)
- Extended by self-enclosed structured/unstructured domains



Applications to constraint folding

Candidate space (hard constraints):

- Force | prohibit nucleotides to pair, e.g. within a pore
- Force | prohibit base pair formation, e.g. cross-linked pairs

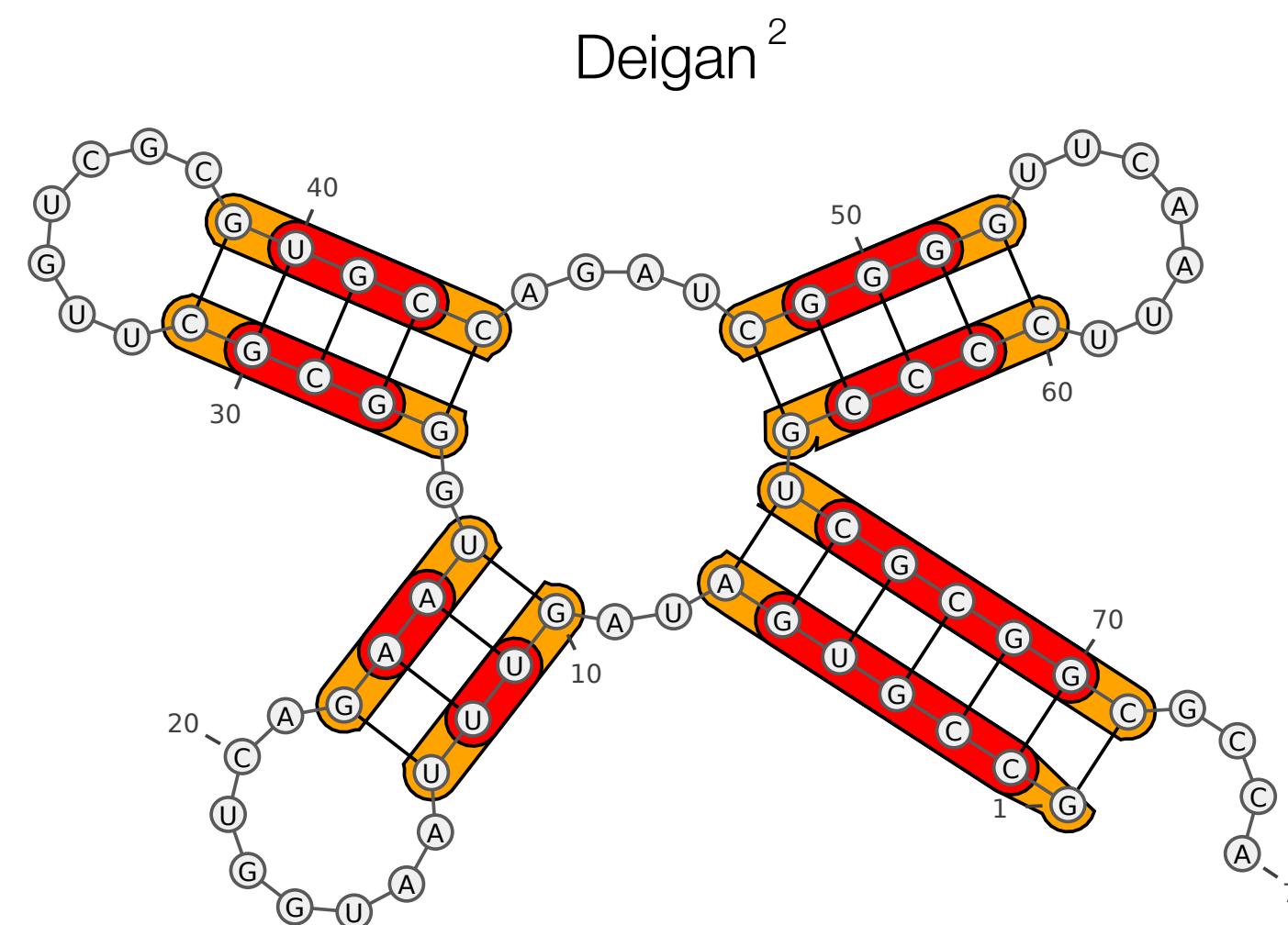
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Candidate evaluation (soft constraints):

- Include chemical probing data to guide structure prediction, e.g. SHAPE reactivity data



- Reactivity probes backbone flexibility (unpairedness)
- No nucleobase bias
- Convert reactivity to pseudo-energy for structure prediction

$$\Delta G(i) = m * \ln(\text{reactivity}[i] + 1) + b$$

²Deigan et.al. (2009) PNAS 106, 97-102

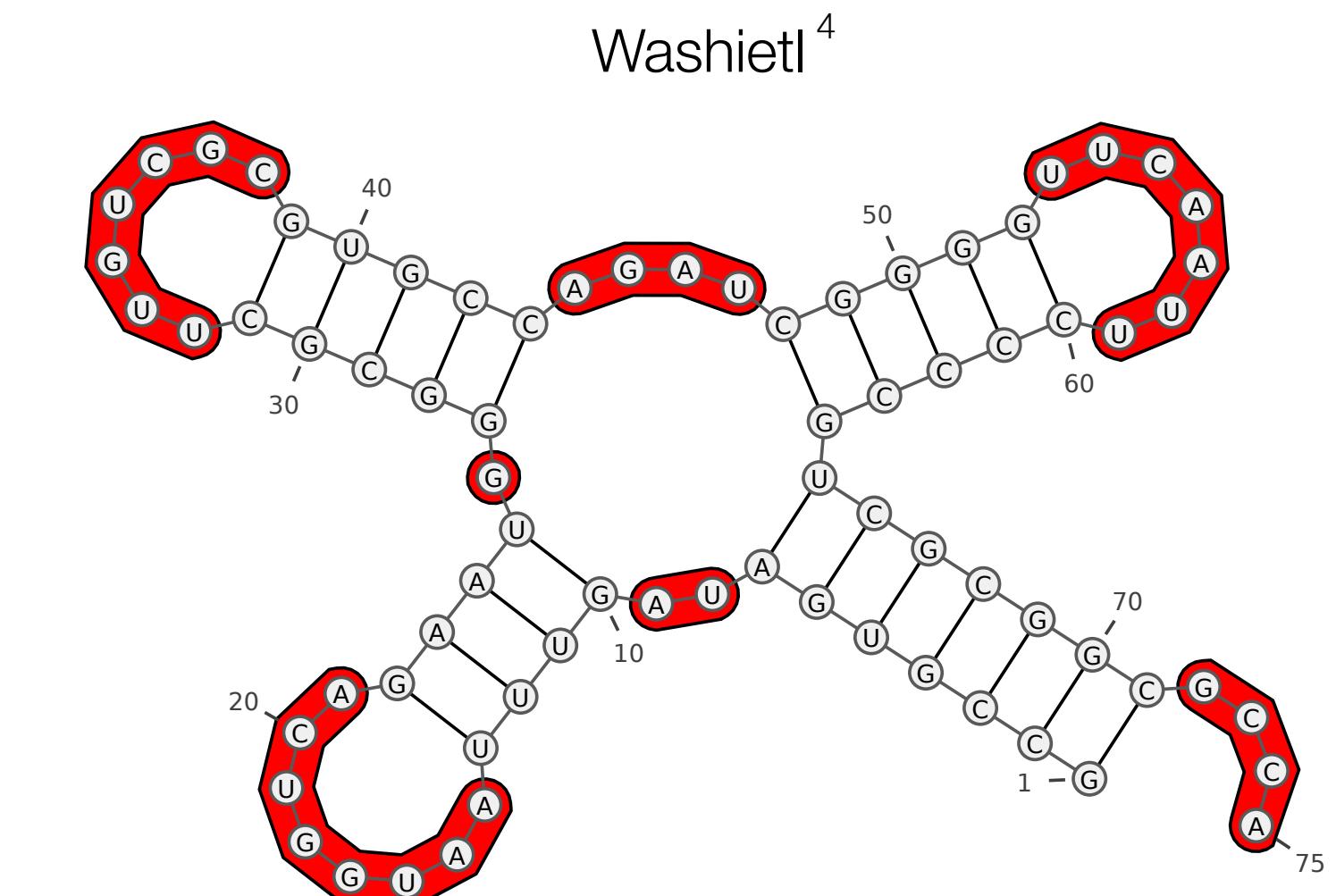
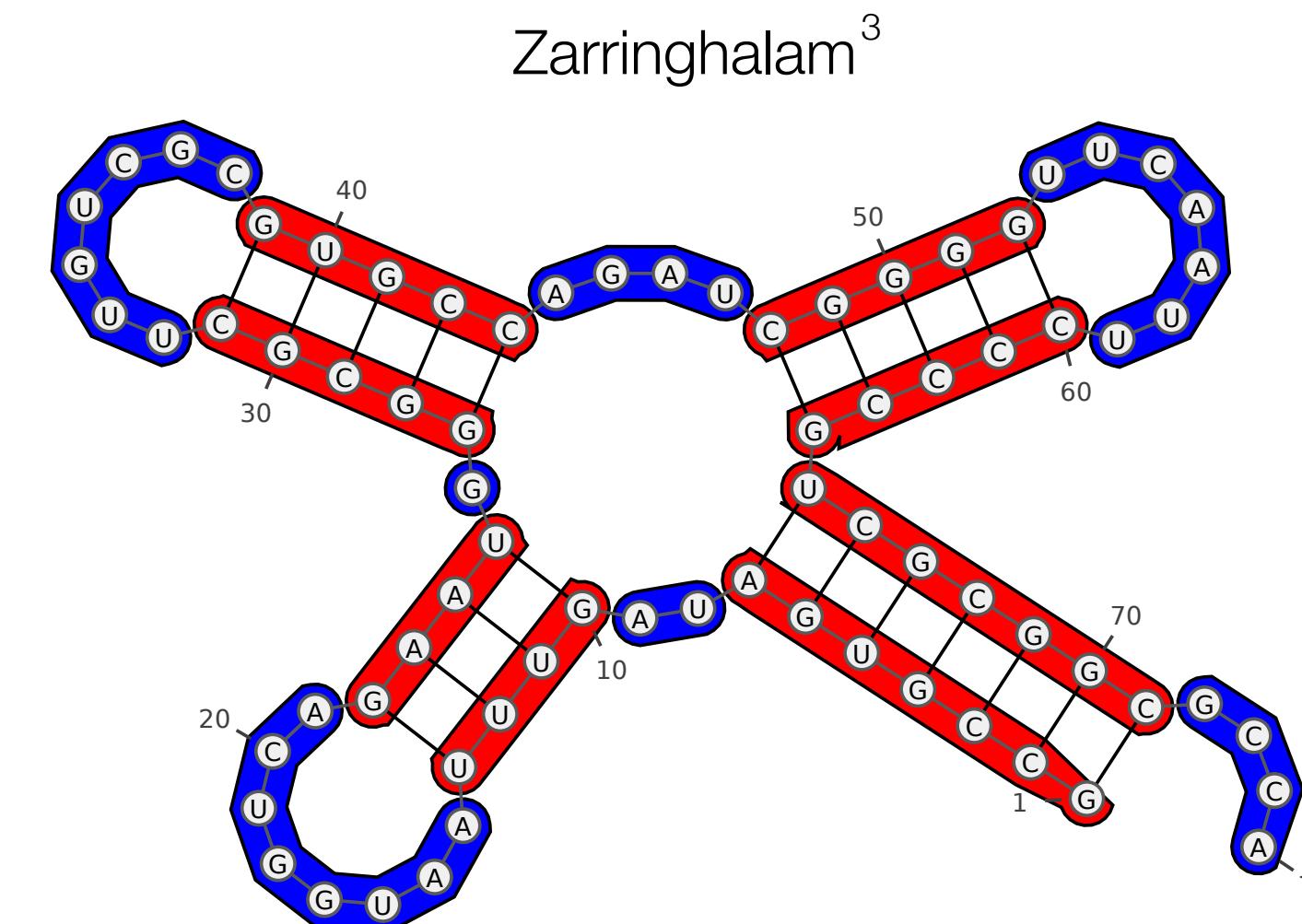
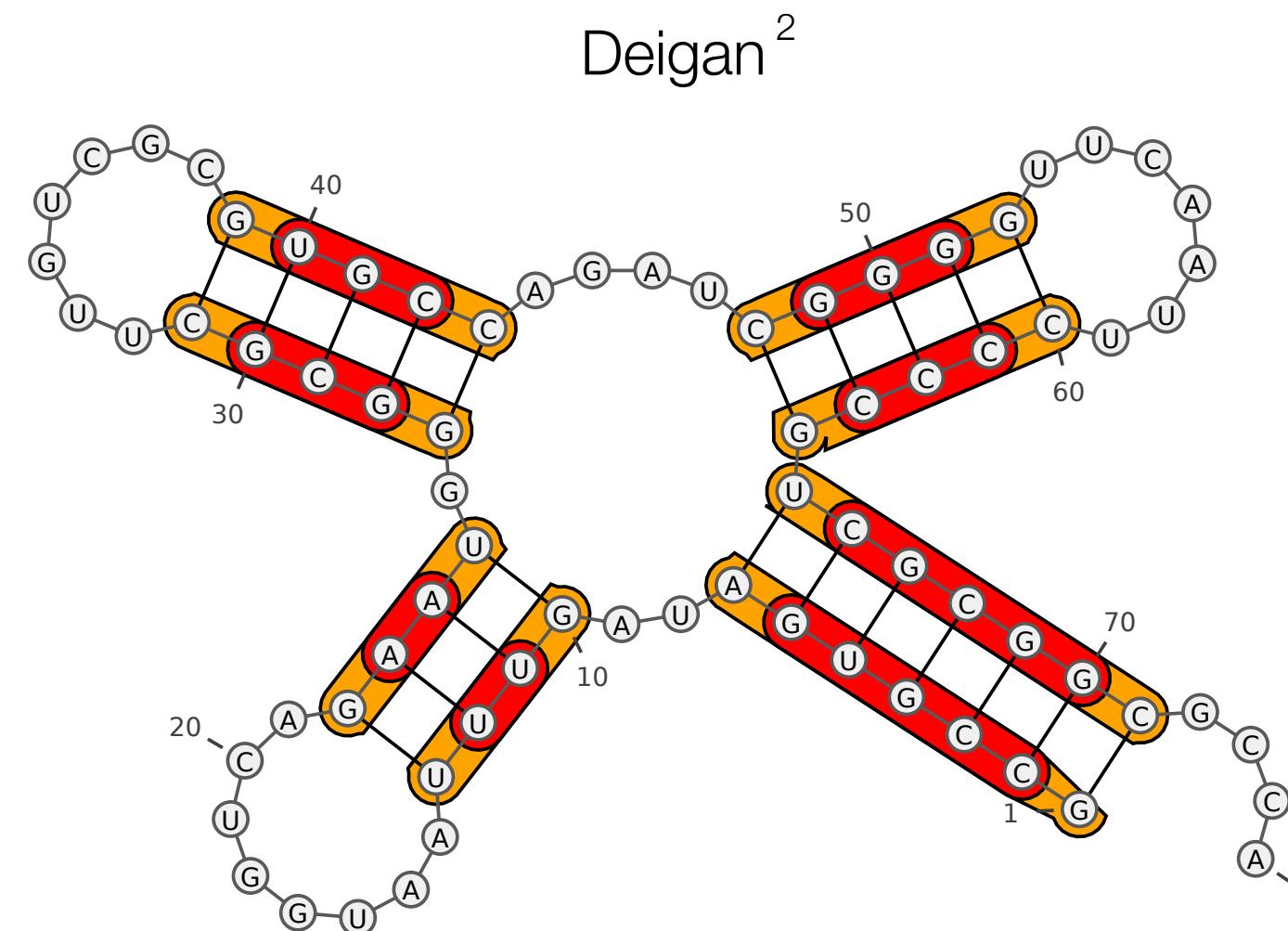
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$$\Delta G(i) = m * \ln(\text{reactivity}[i] + 1) + b$$

$$\Delta G(x, i) = \beta * |x - q_i|$$

$x \in [0(\text{unpaired}), 1(\text{paired})]$

$$F(\vec{\epsilon}) = \sum_{i=1}^n \frac{\epsilon_i^2}{\tau^2} + \sum_{i=1}^n \frac{(p_i(\vec{\epsilon}) - q_i)^2}{\sigma^2} \rightarrow \min$$

²Deigan et.al. (2009) PNAS 106, 97-102

³Zaringhalam et.al. (2012) PLoS One 7, e45160

⁴Washietl et.al. (2012) NAR 40, 4261-72

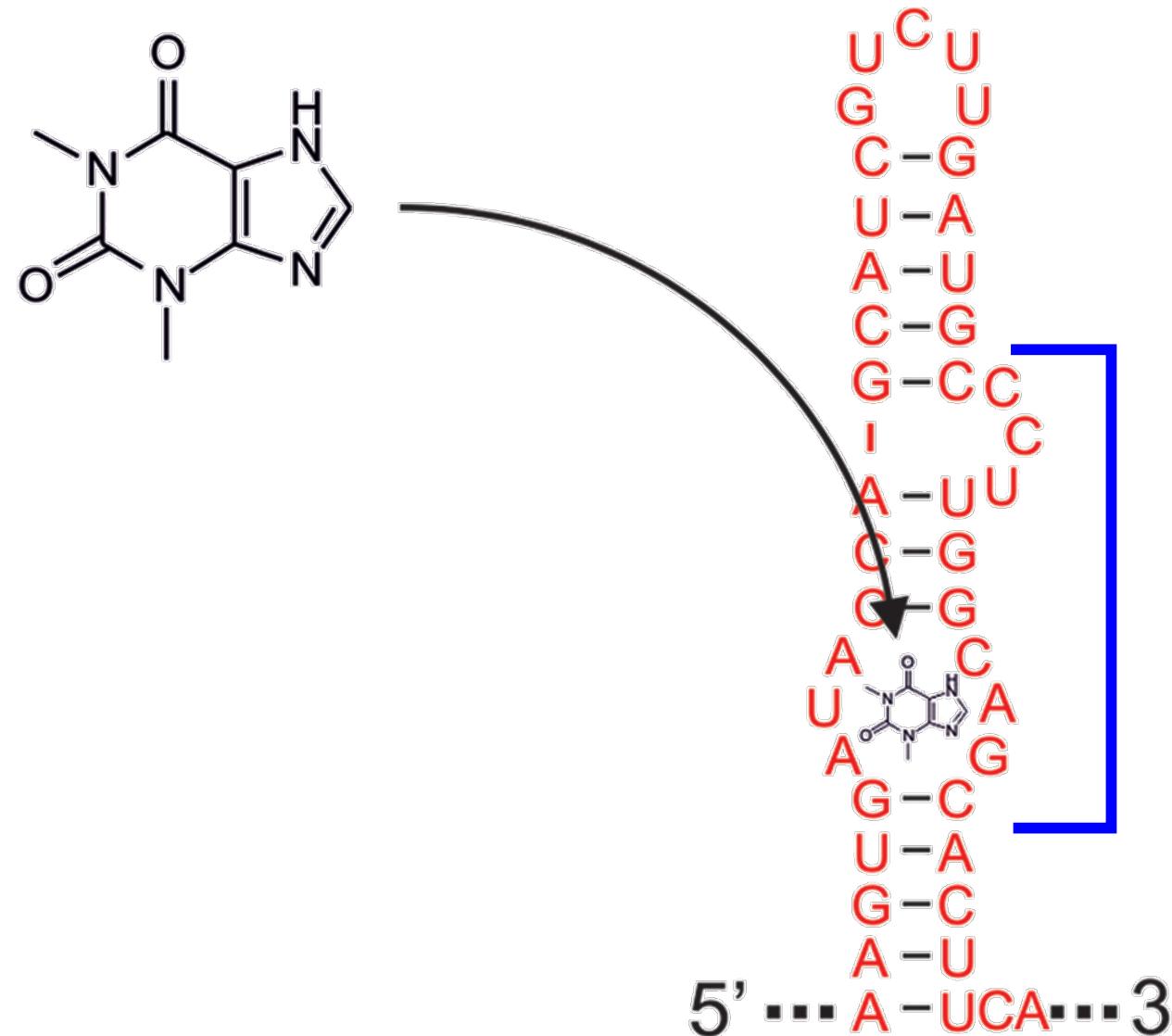
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 - Model (more or less) complex RNA-ligand interactions for interior loops and hairpin loops



```
$ RNAfold -p --motif="GAUACCAG&CCCUUGGCAGC, (...(((&)...))...)...,-9.22" --verbose
>theo-P-IS10
read ligand motif: GAUACCAG&CCCUUGGCAGC, (...(((&)...))...)..., -9.220000
GGUGAUACCAGAUUUUCGCGAAAAAUCCUUGGCAGCACCUUCGACAUUCUUGUCUGAUUAUUGAUUUUUCGCGAAACCAUUUGAUCAUAUGACAAGAUUGAG
((((....((((((.....))))...))))...((.(((((((.((((.(((.....))))...))))...))))...))).. (-33.82)
specified motif detected in MFE structure: (4,36) (11,26)
((((....((((((.....))))...))))..., .(((((((.((((.(((.....))))...))))...))))...))).. [-35.14]
((((....((((((.....))))...))))....((((((((.((((.(((.....))))...))))...))))...))).... {-24.20 d=4.35}
specified motif detected in centroid structure: (4,36) (11,26)
frequency of mfe structure in ensemble 0.116952; ensemble diversity 6.71
```

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Structured domains:

- G-Quadruplexes

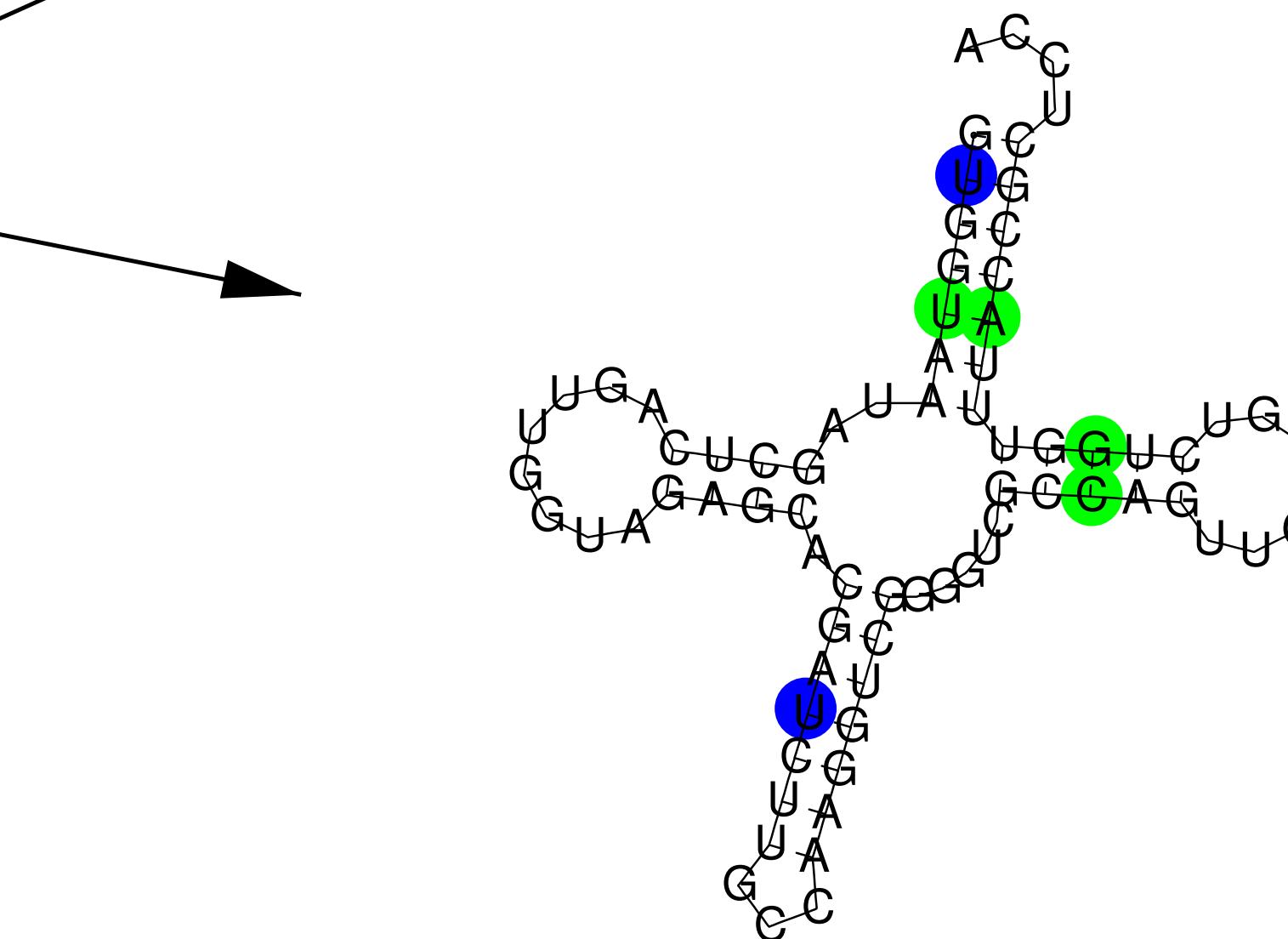
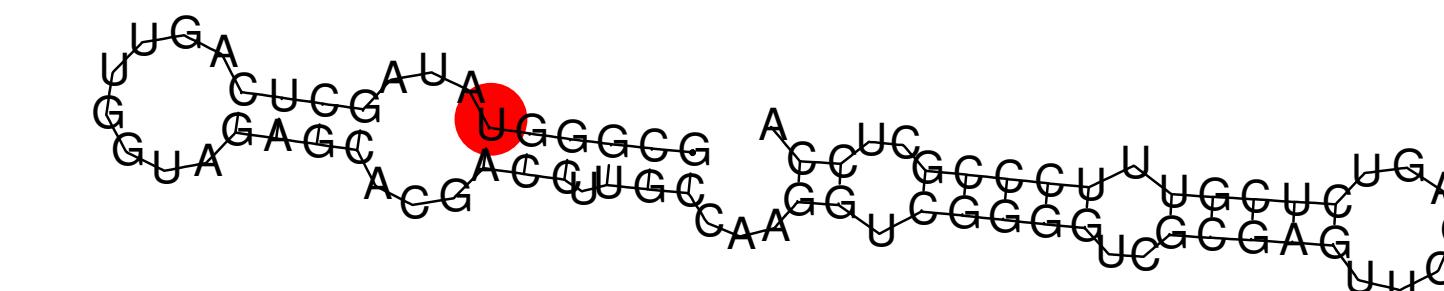
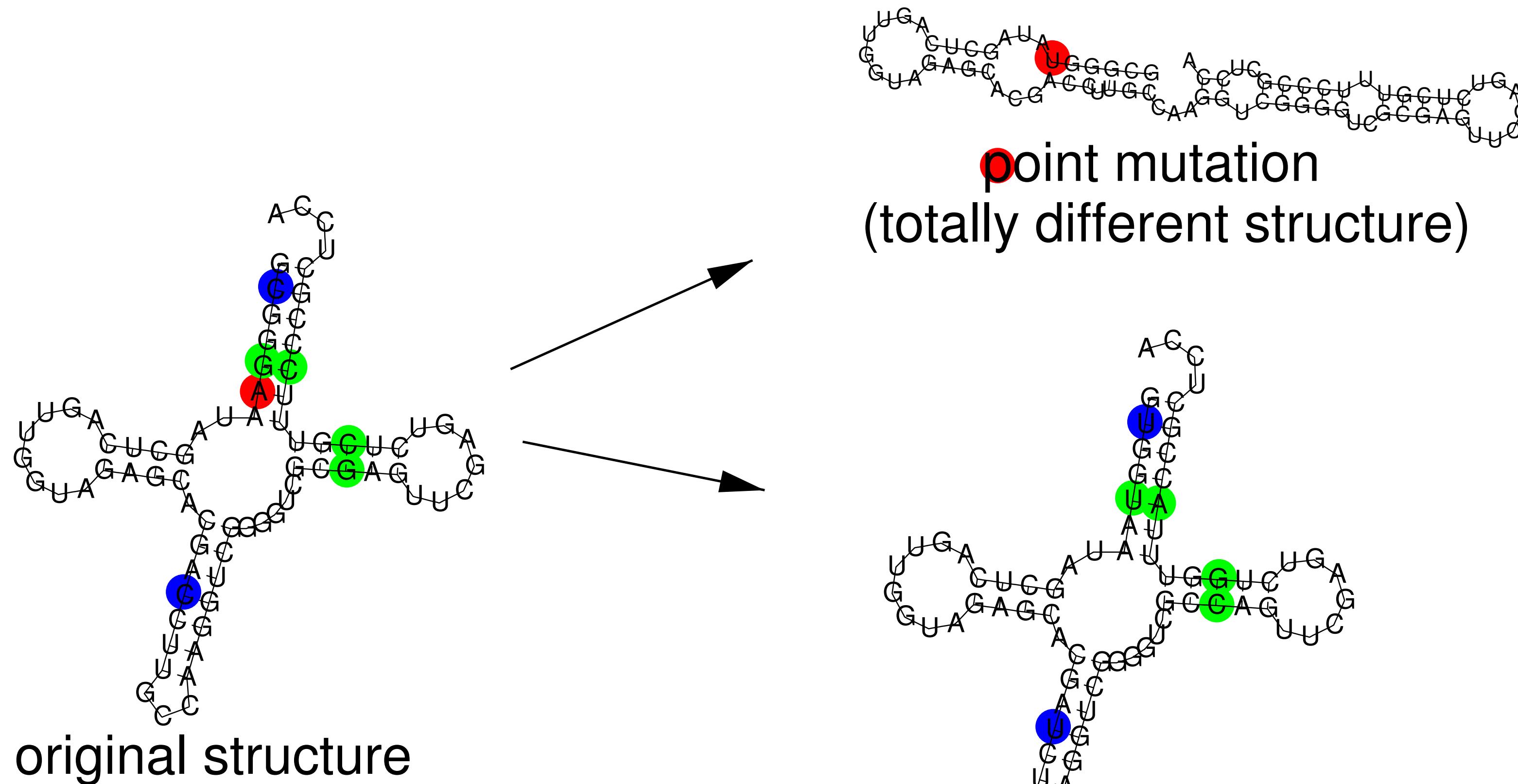
Unstructured domains:

- (IUPAC) motif based default ligand binding for MFE/partition function of single RNA sequences
- Model (more or less) complex RNA-ligand interactions for interior loops and hairpin loops

RNA-RNA interaction

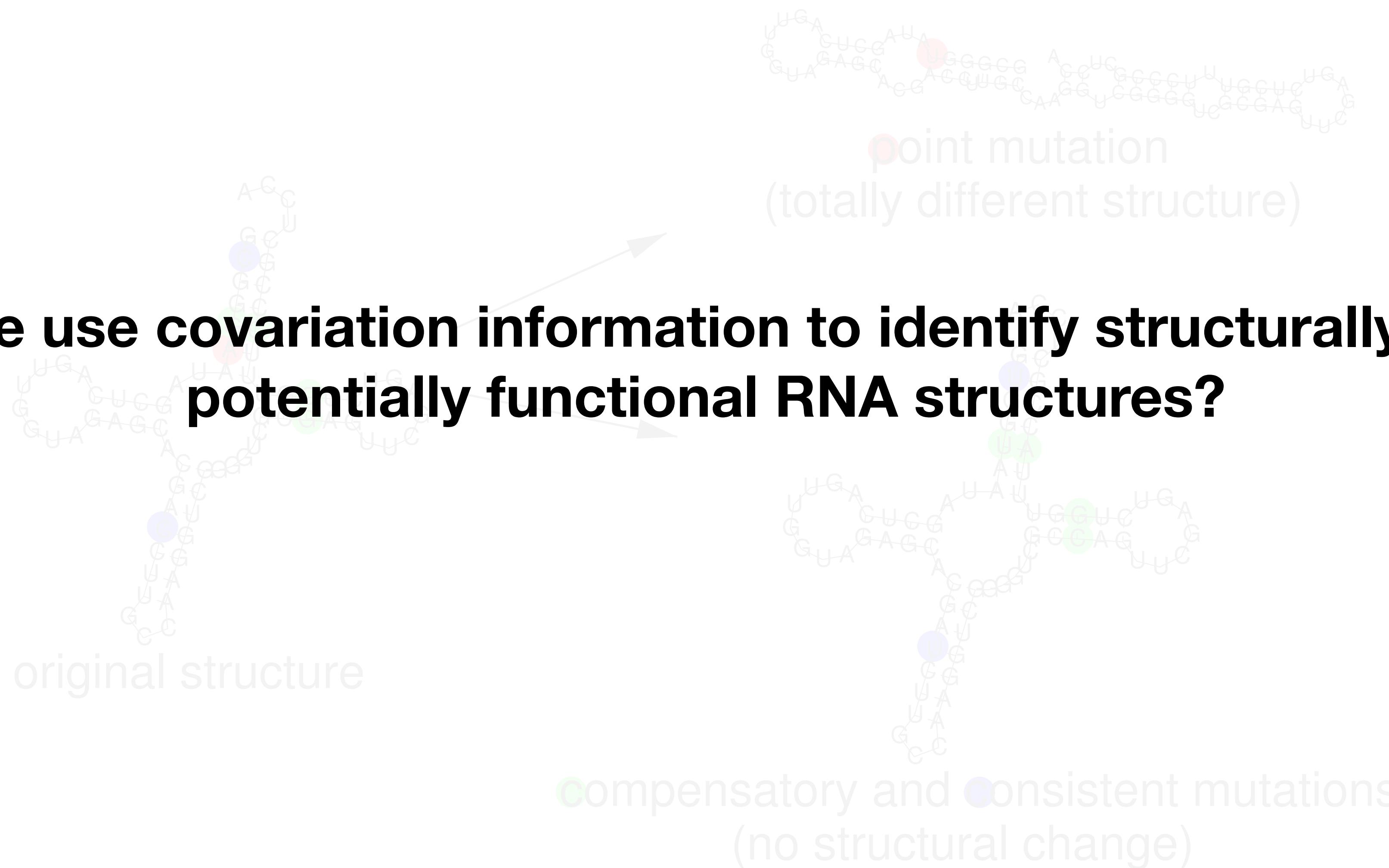
- **RNAduplex**
Simplified duplex interaction (intermolecular bp): MFE, suboptimal structures
- **RNAcofold**
Sequence concatenation (inter/intramol. bp): MFE, suboptimal, partition function, concentration dependency
- **RNAup**
Two-step process (inter/intramolecular bp; kissing hairpins): MFE, suboptimal structures
- **RNAplex**
Fast heuristic for genome-wide interaction prediction: MFE, suboptimal structures
- **RNAmultifold**
Concatenation approach for multiple strands: MFE, suboptimal, partition function, concentration dependency

Mutations affect RNA structure



Mutations affect RNA structure

How can we use covariation information to identify structurally conserved, potentially functional RNA structures?



Consensus structures: Alignment folding

Combine covariance analysis and folding into one DP algorithm

- Apply conventional folding algorithm to alignment
- Use a modified energy function that includes covariance score

$$E_c(A, \Psi) = \sum_k E(A_k, \Psi) + cv \cdot \sum_{(i,j) \in \Psi} B_{ij}$$

- Can be used for all variants: MFE, partition function, ...
- Efficient: $\mathcal{O}(N \cdot n^2 + n^3)$ CPU and $\mathcal{O}(n^2)$ memory for alignment length n and N sequences
- Same results as RNAfold for single sequences



Consensus structures: Alignment folding

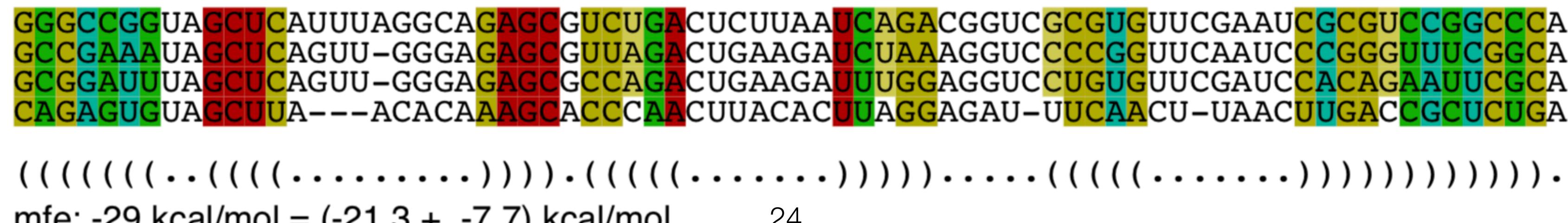
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RNAalifold

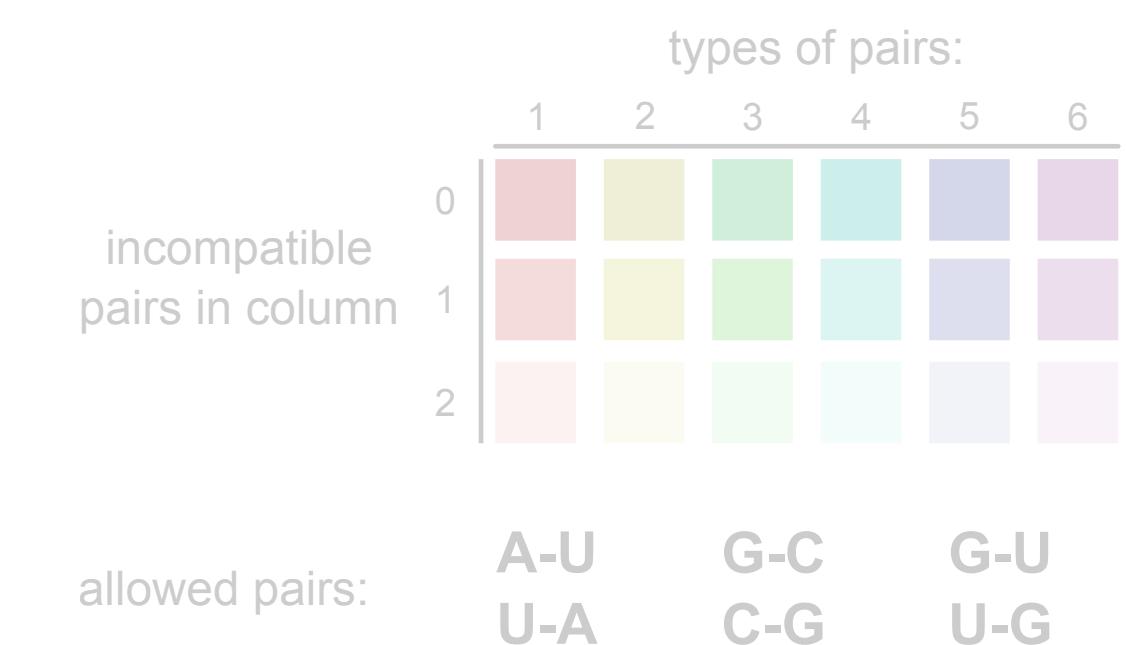
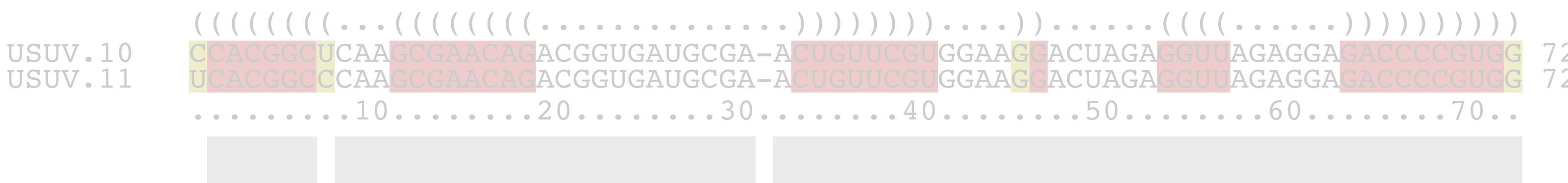
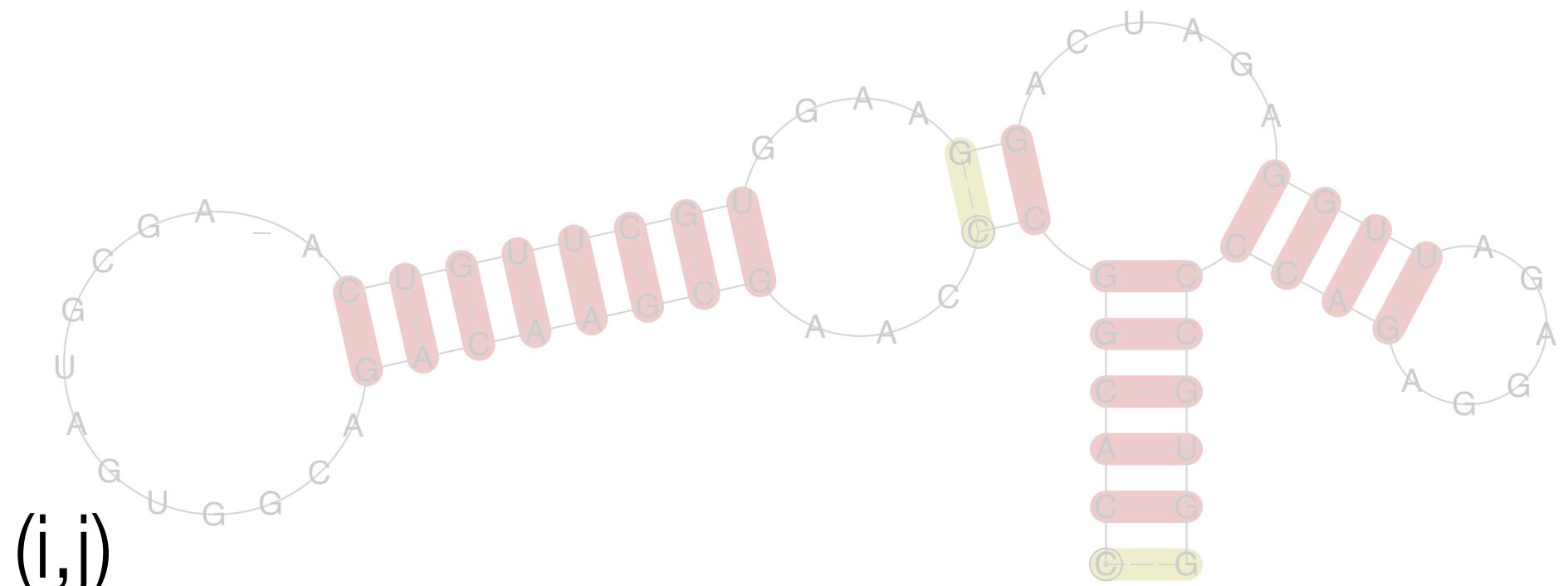
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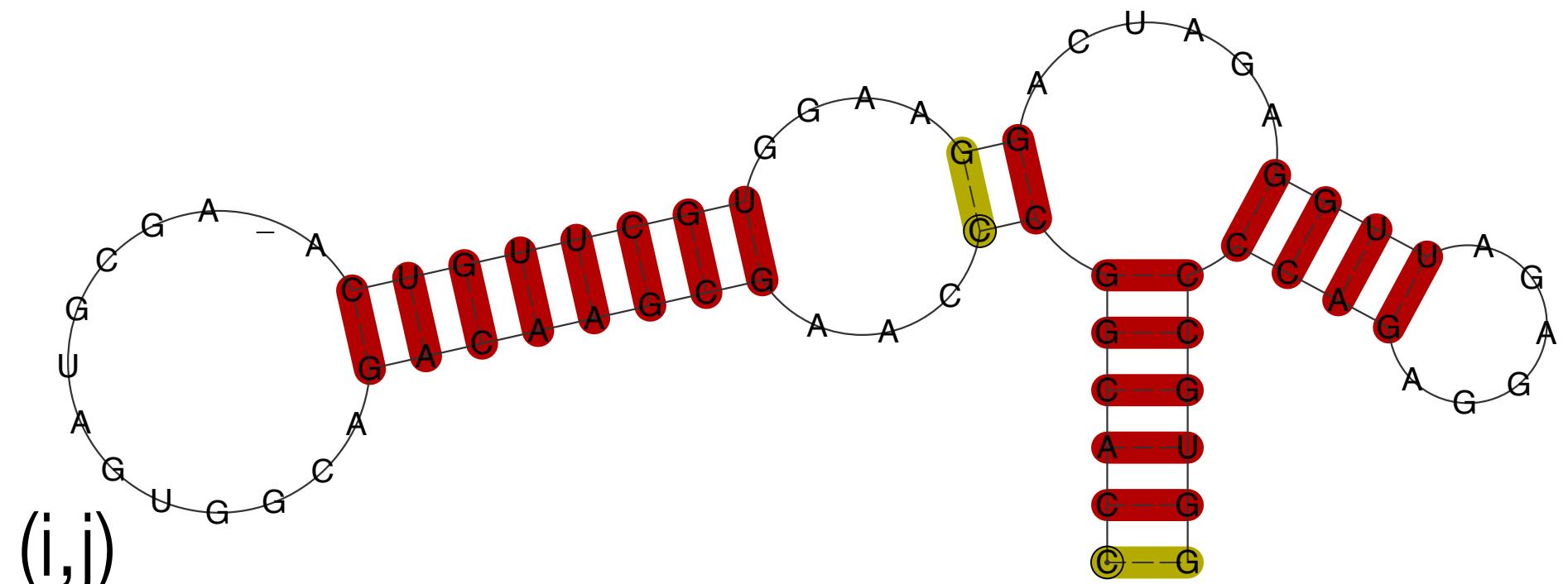
RNA covariation as evolutionary trait

- High mutation rate in RNA viruses due to error-prone RdRP
- For base pair (i,j): GC/CG/AU/UA/GU/UG
- Consistent mutation: different standard combinations
- Compensatory mutation: both positions are mutated
- Presence of both strongly supports predicted base pair (i,j)

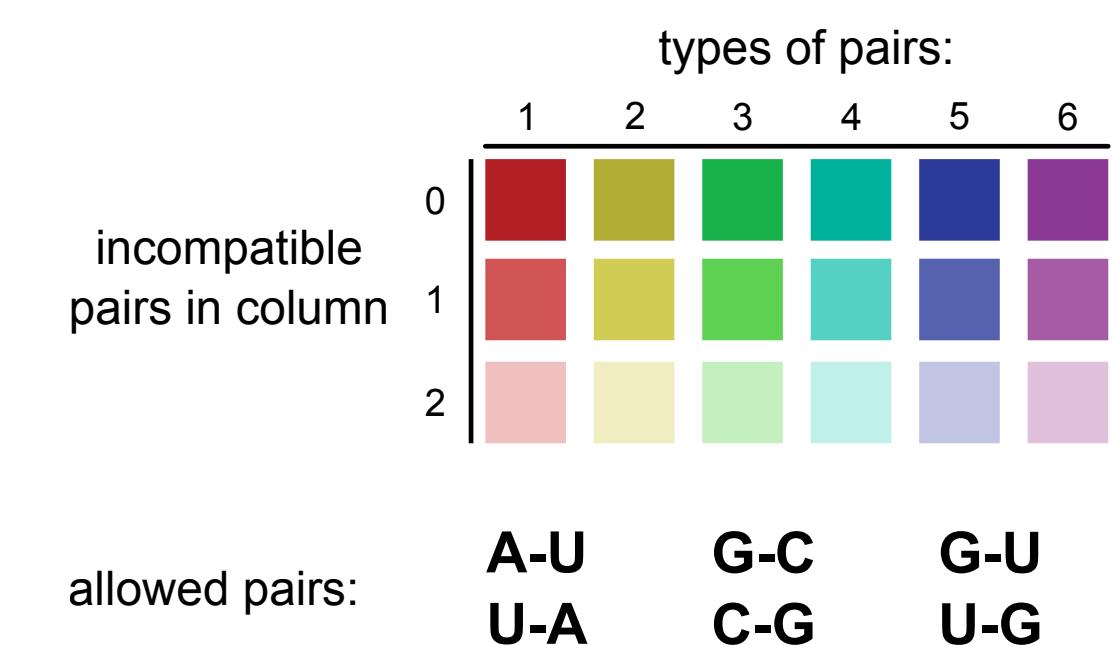


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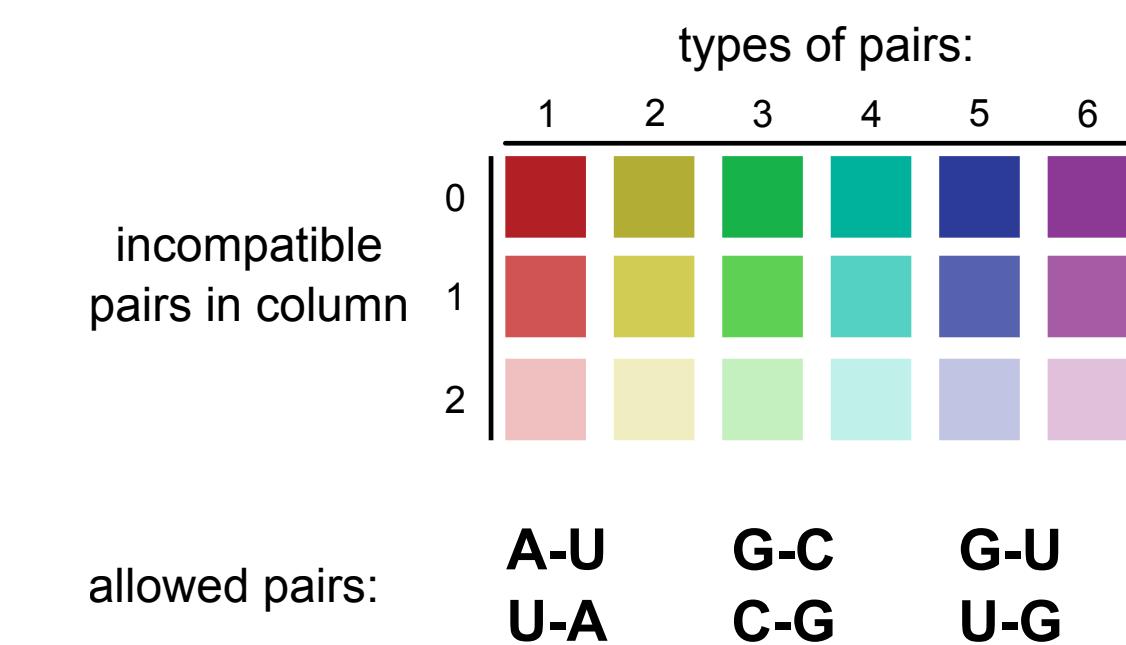
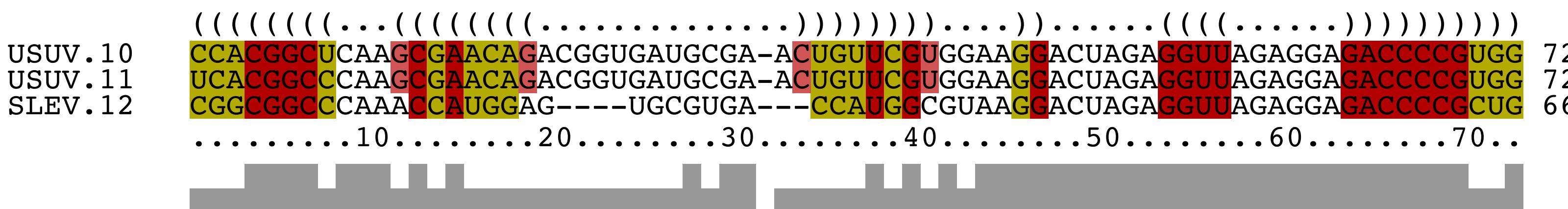
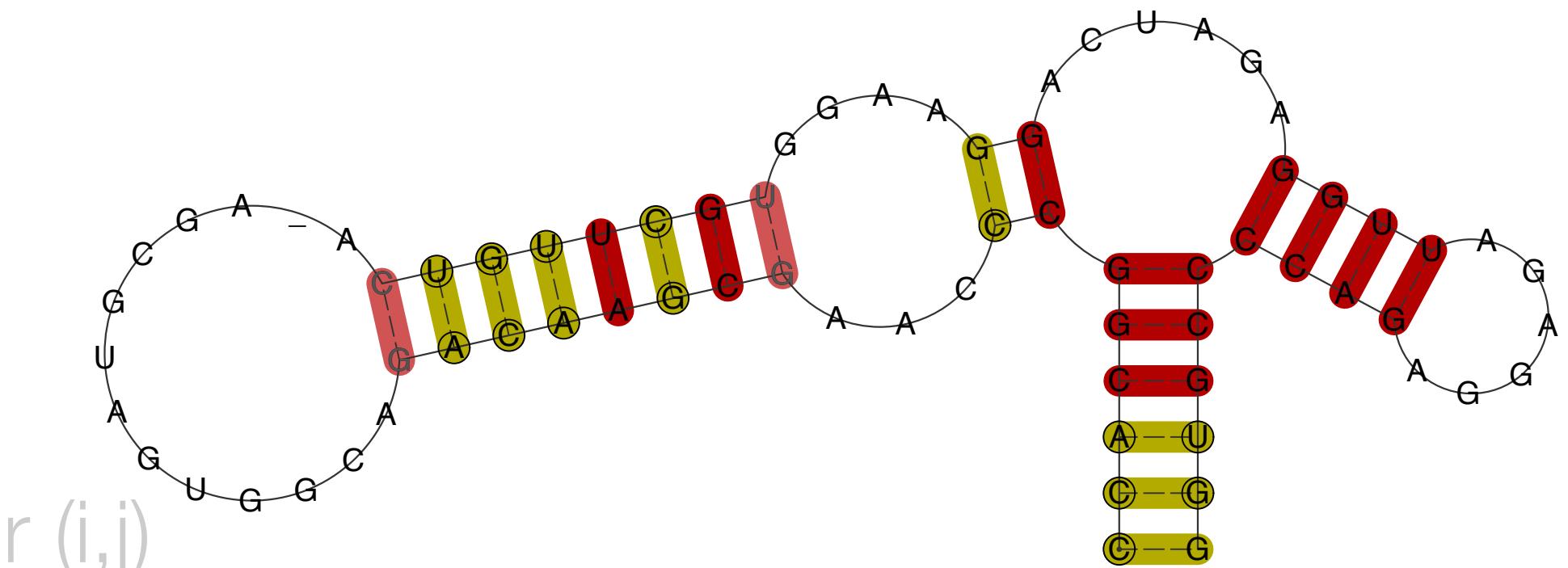


USUV.10	<code>(((((.....((((.....)))))))).....((.....))))))))</code>	
USUV.11	<code>CCACGGCUCAA<color>GC</color>GAACAGACGGUGAUGC<color>G</color>A-A<color>C</color>UGUUCGUGGAAG<color>G</color>CACUAGA<color>GG</color>GUAGAGGA<color>G</color>ACCCC<color>G</color>UGG</code>	72
	<code>UCACGGCCCAAG<color>G</color>C<color>A</color>ACAGACGGUGAUGC<color>G</color>A-A<color>C</color>UGUUCGUGGAAG<color>G</color>GACUAGA<color>GG</color>GUAGAGGA<color>G</color>ACCCC<color>G</color>UGG</code>	72
10.....20.....30.....40.....50.....60.....70..	



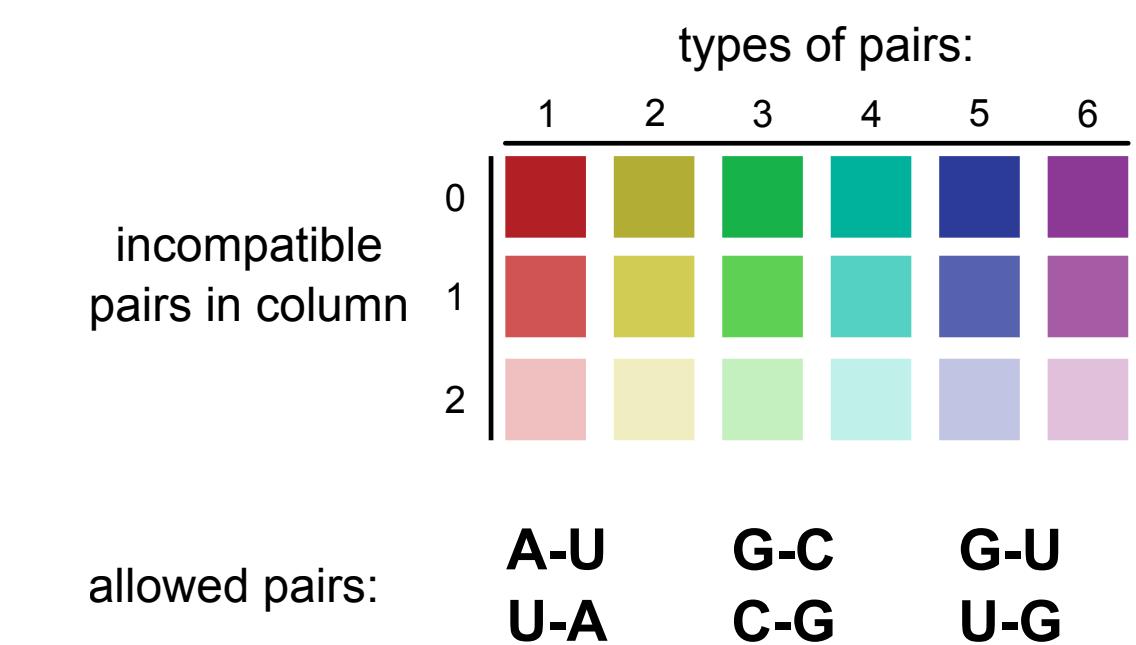
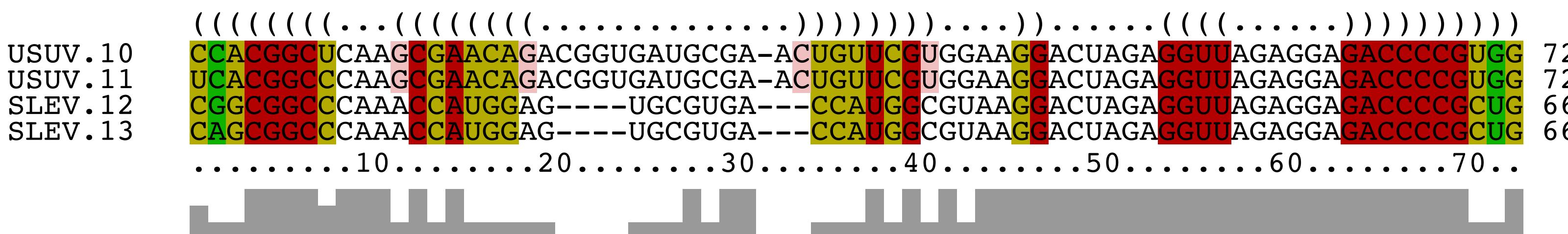
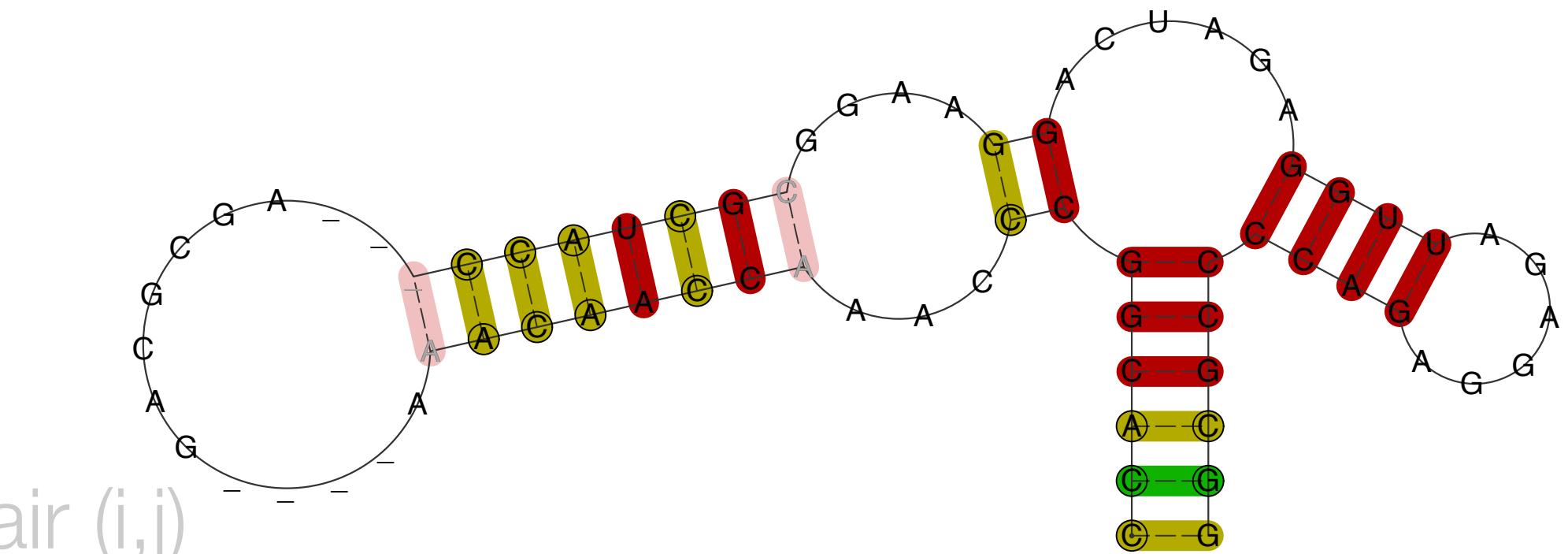
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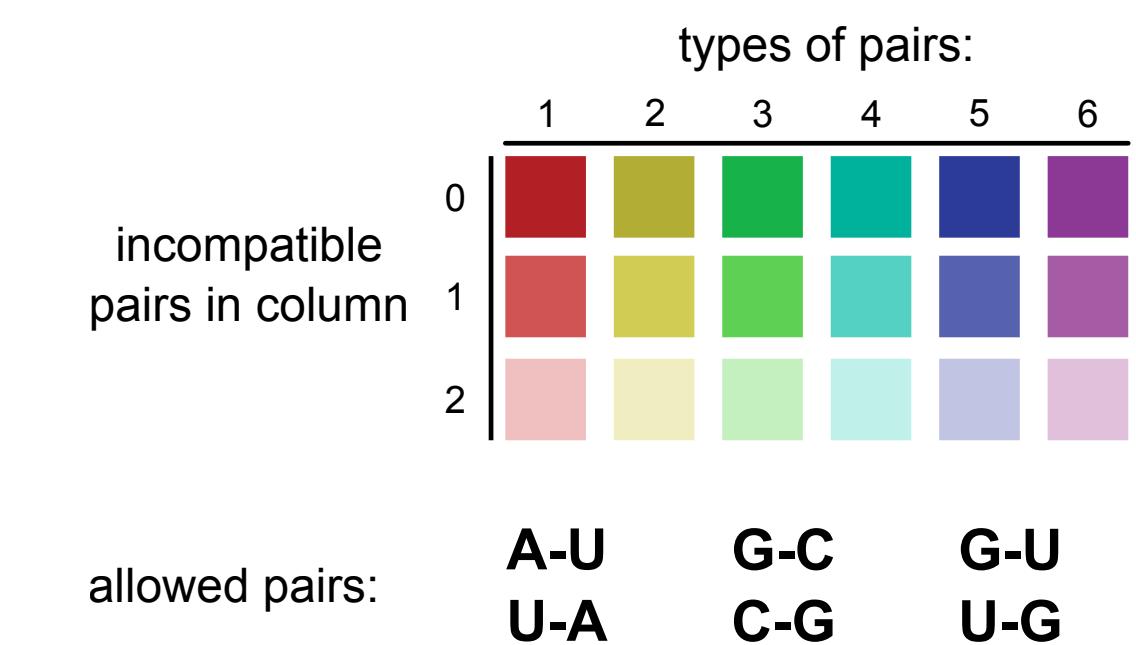
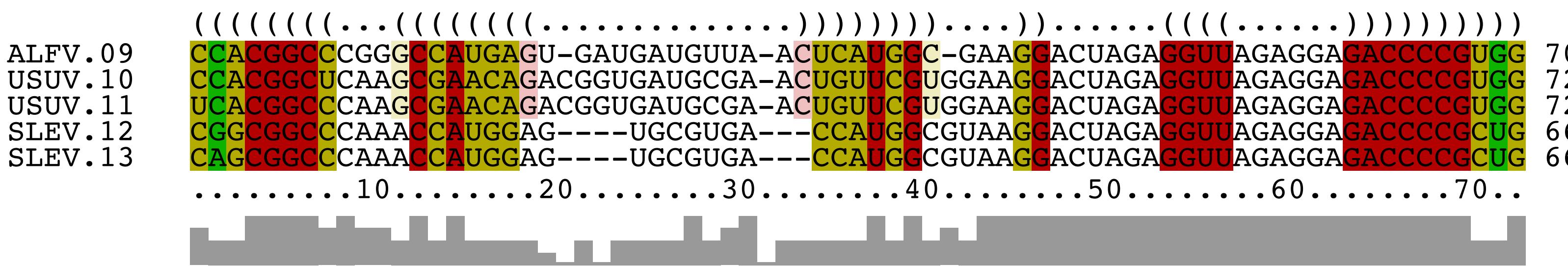
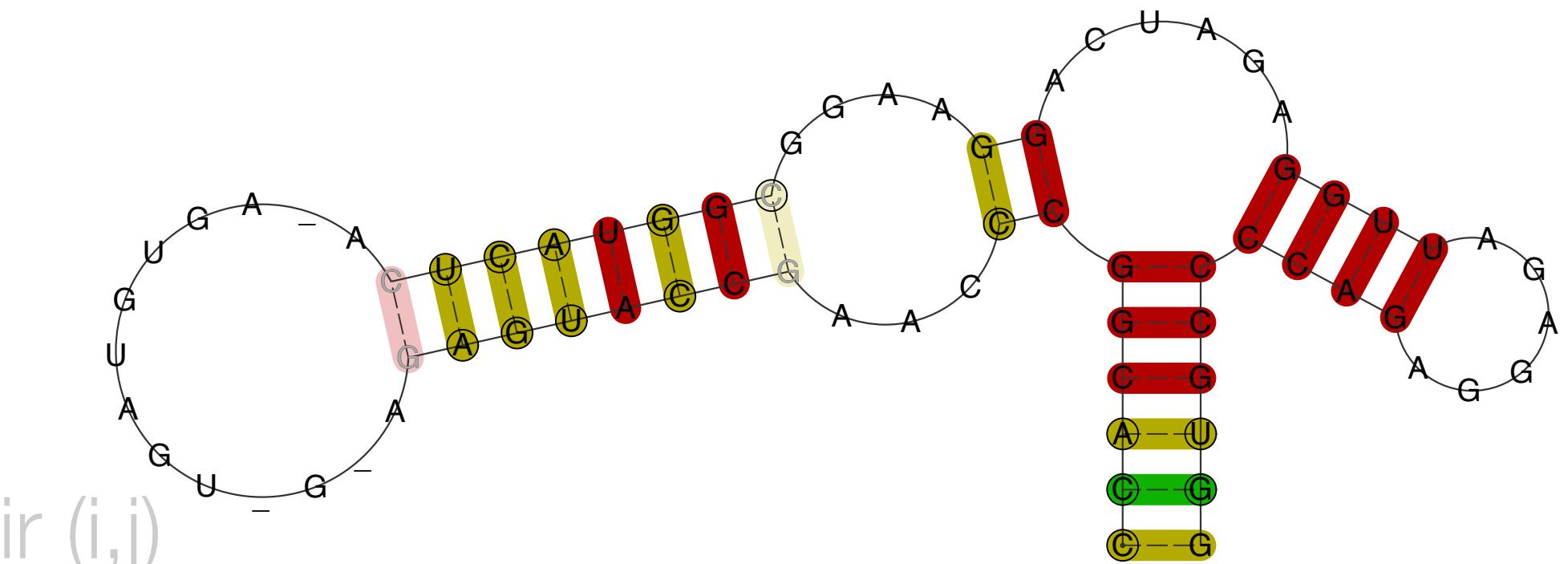
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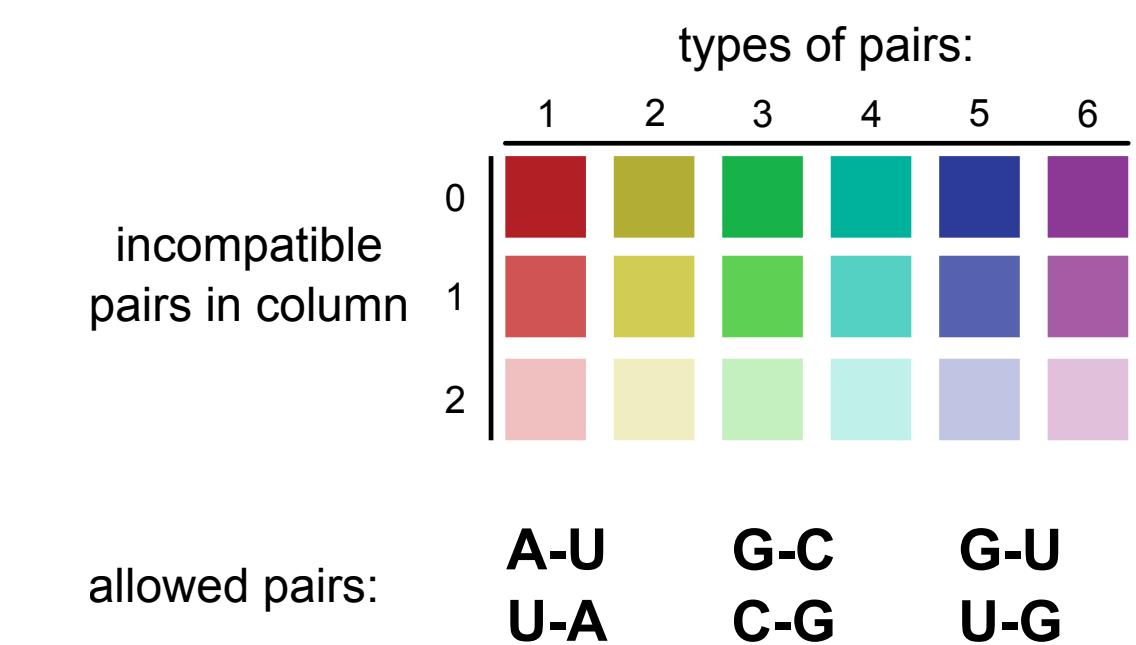
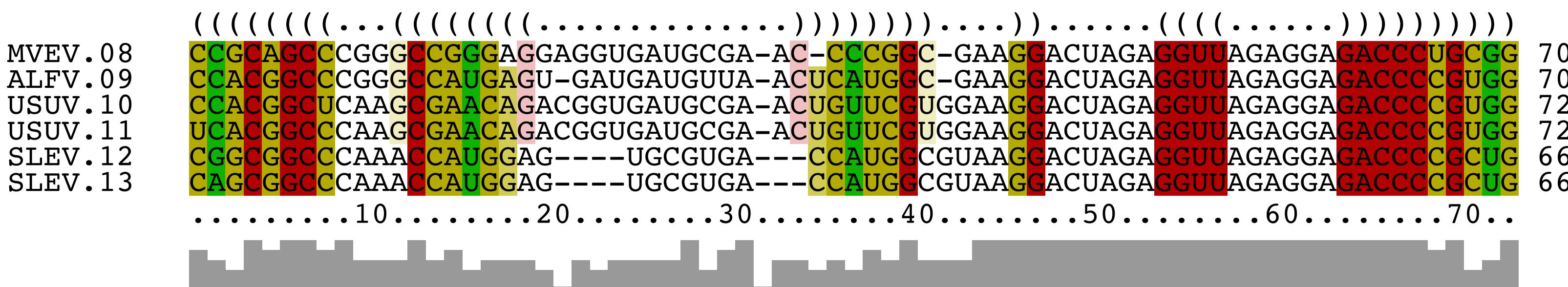
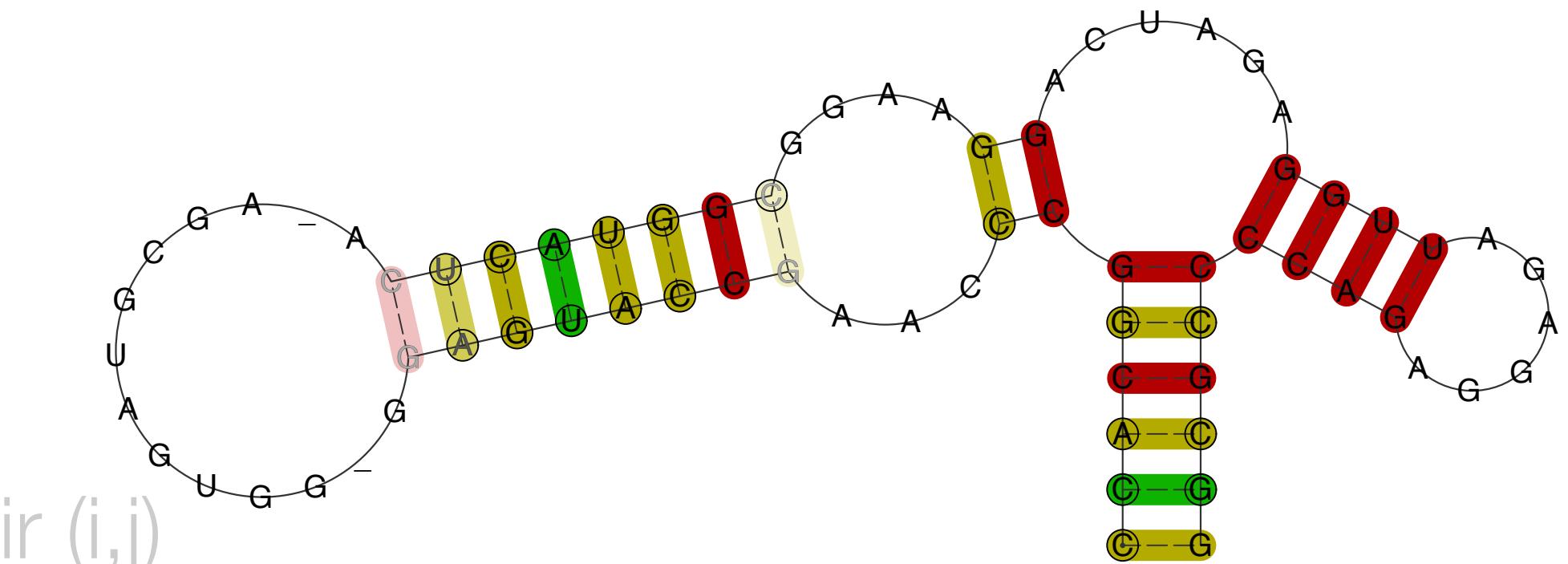
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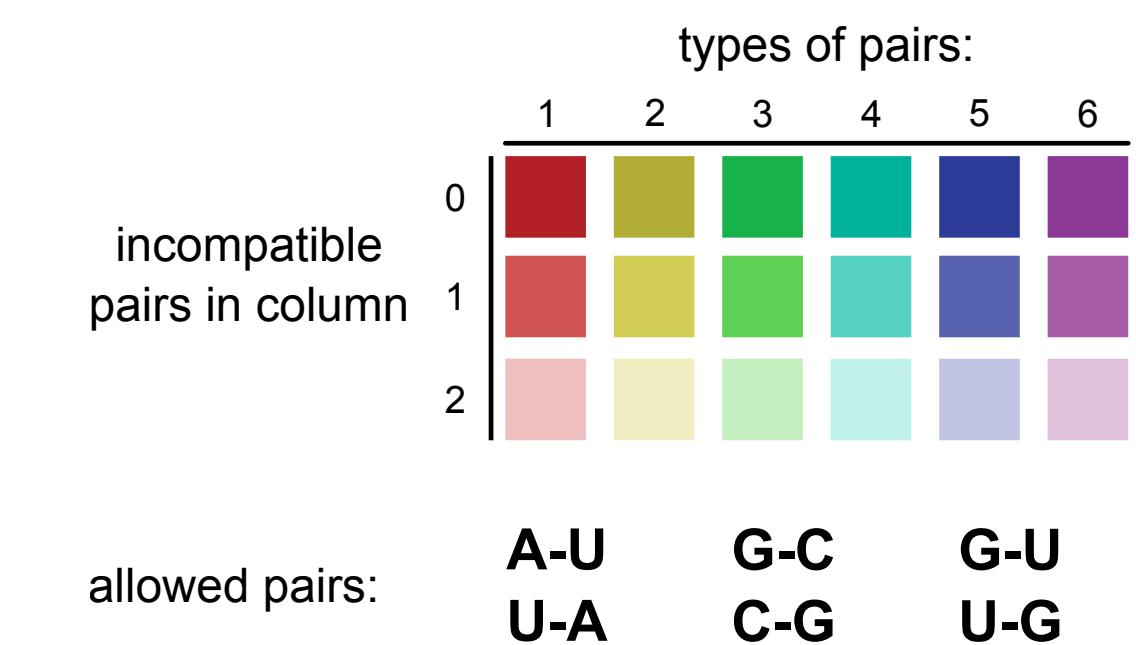
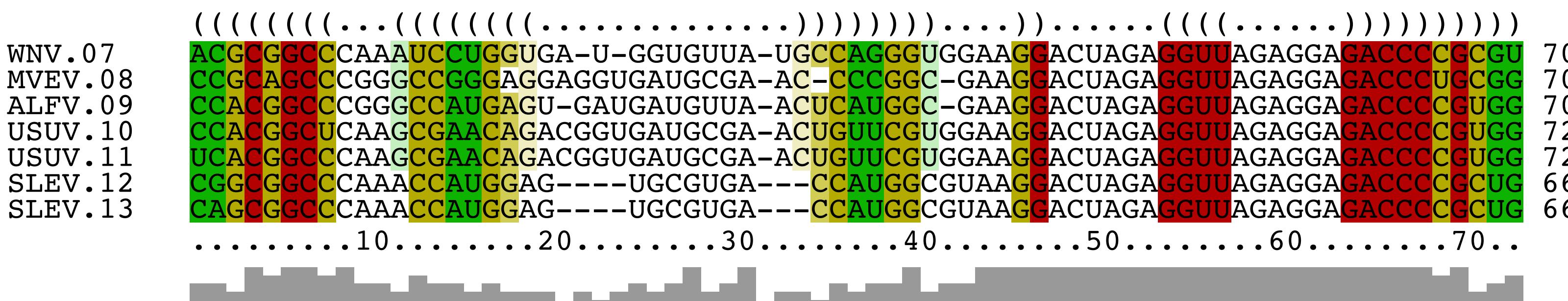
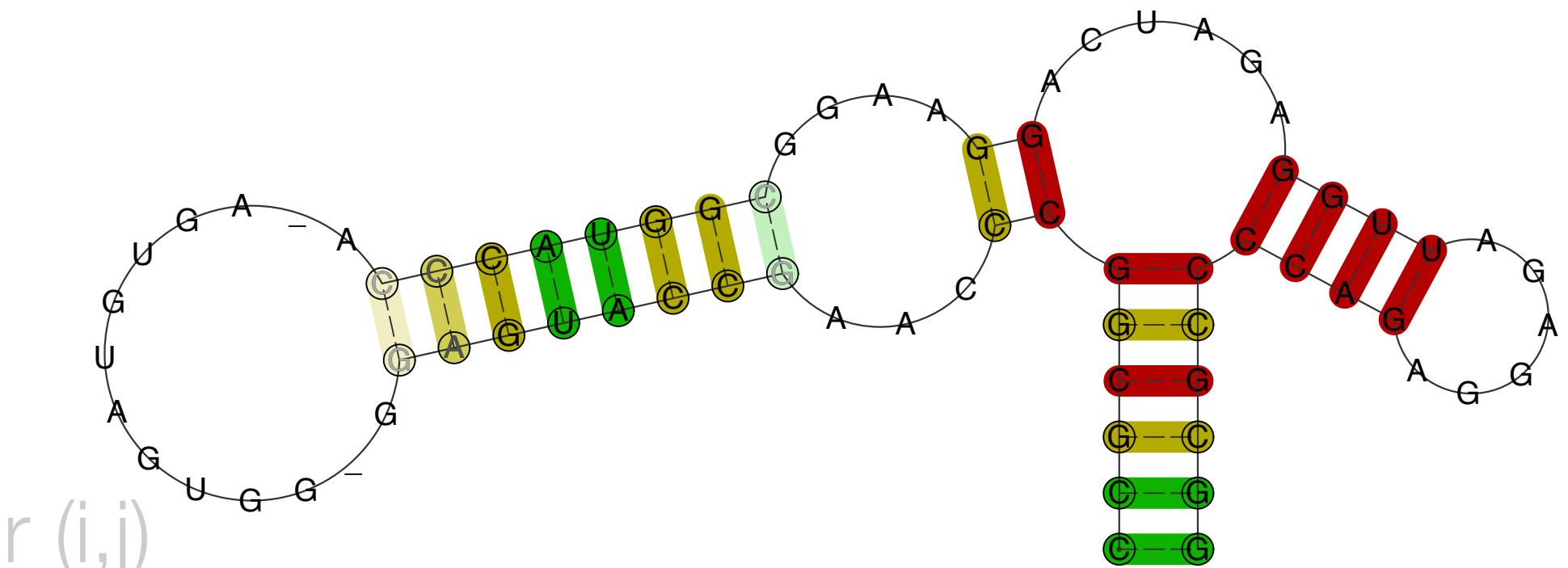
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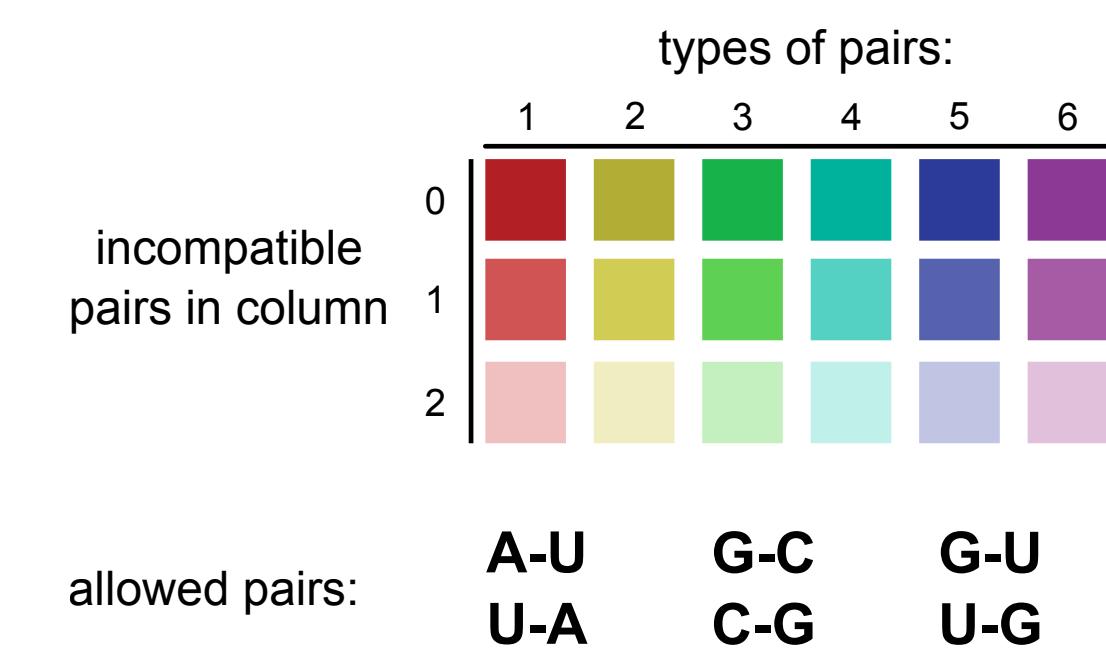
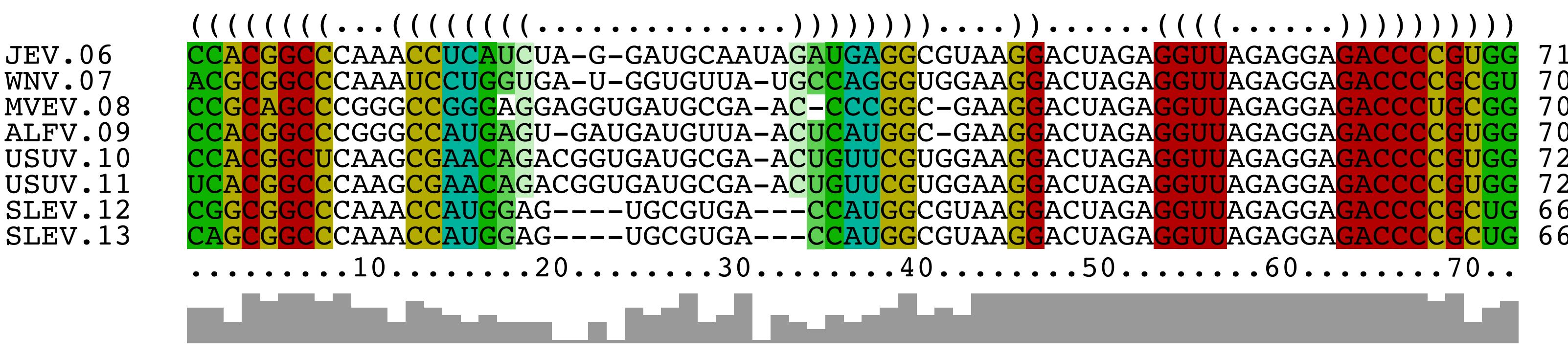
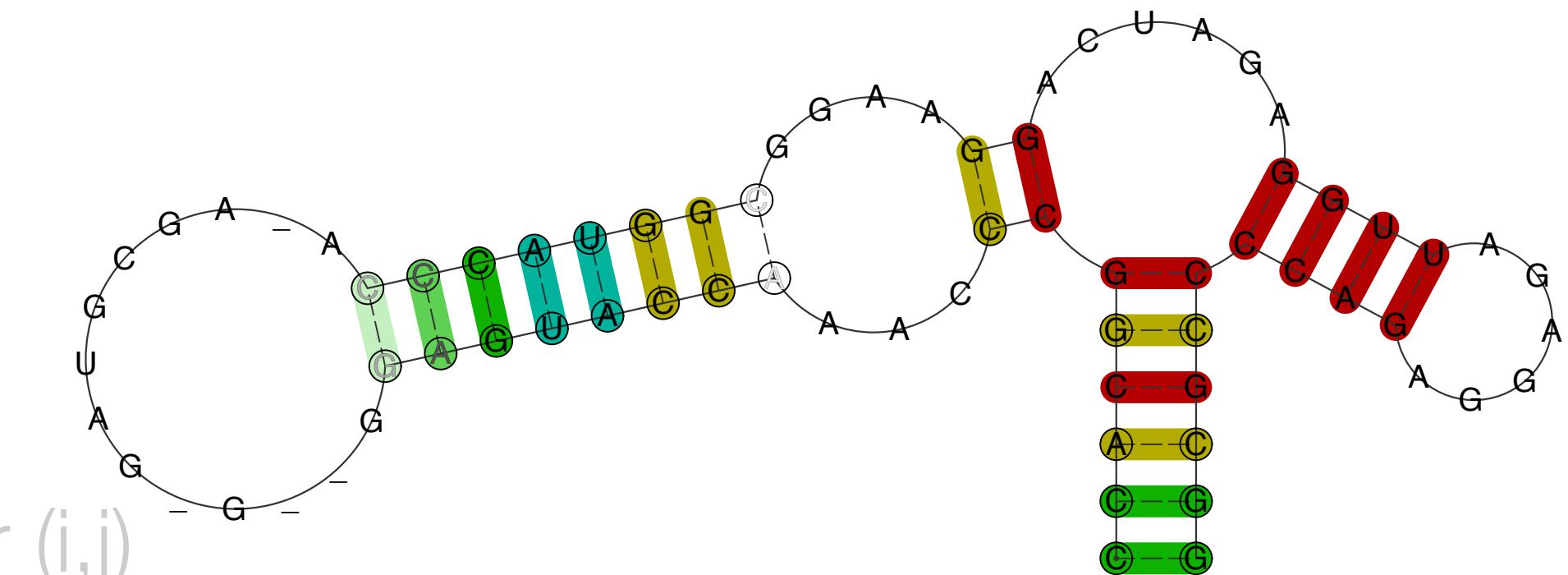


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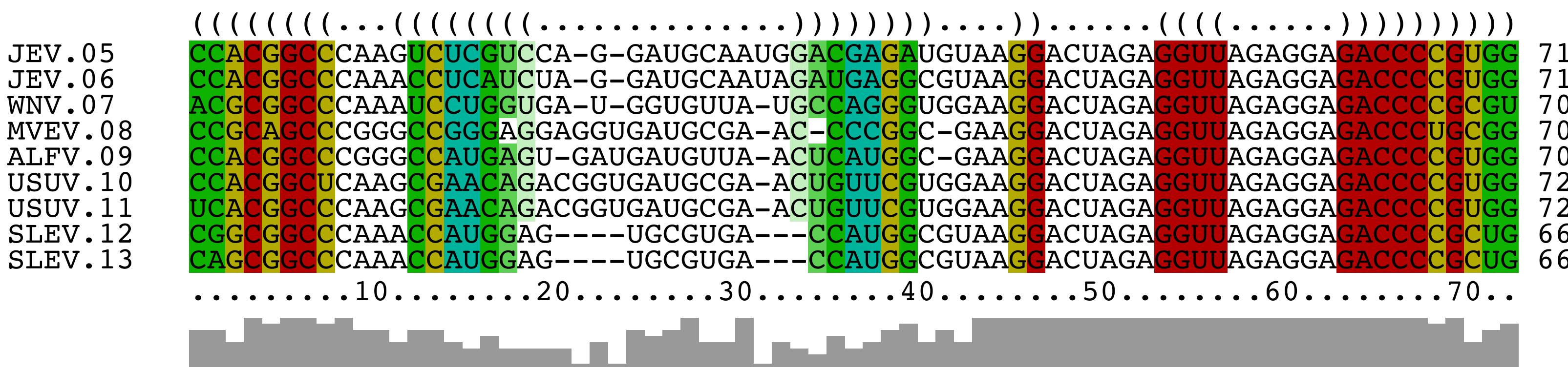
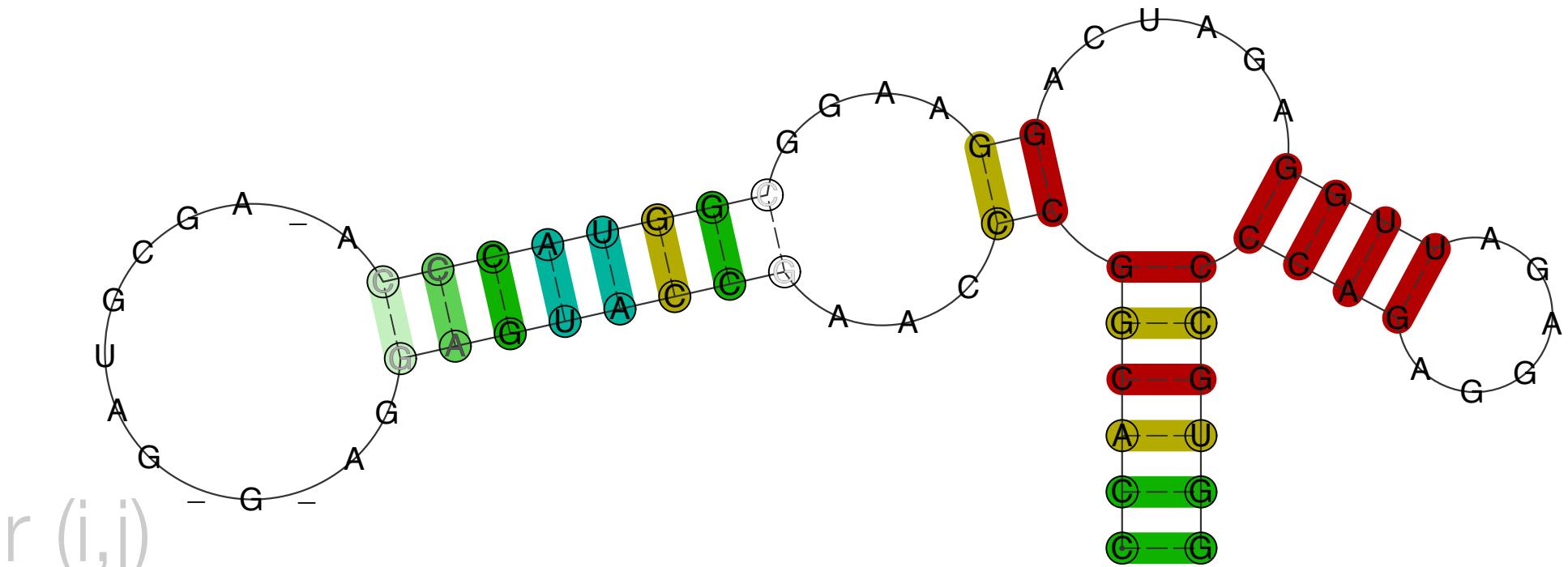


RNA covariation as evolutionary trait



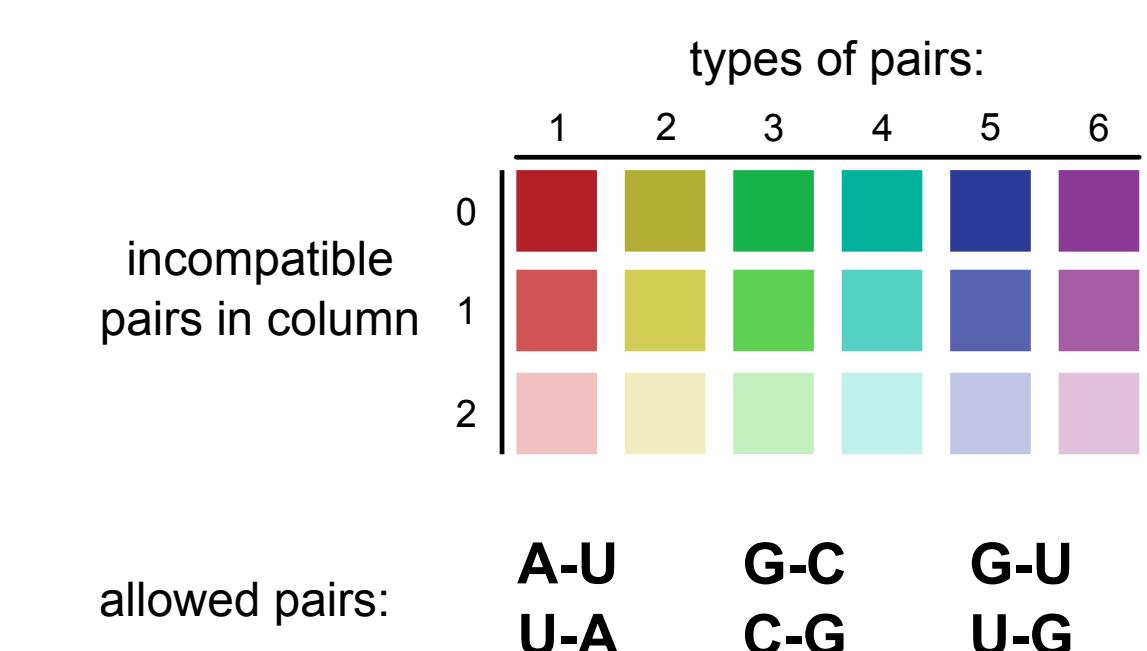
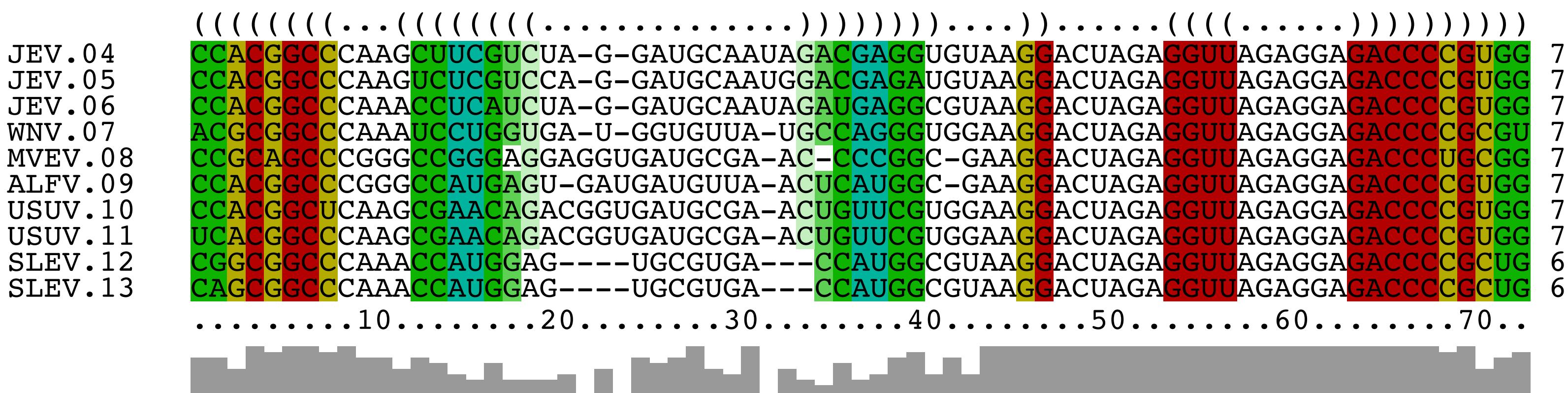
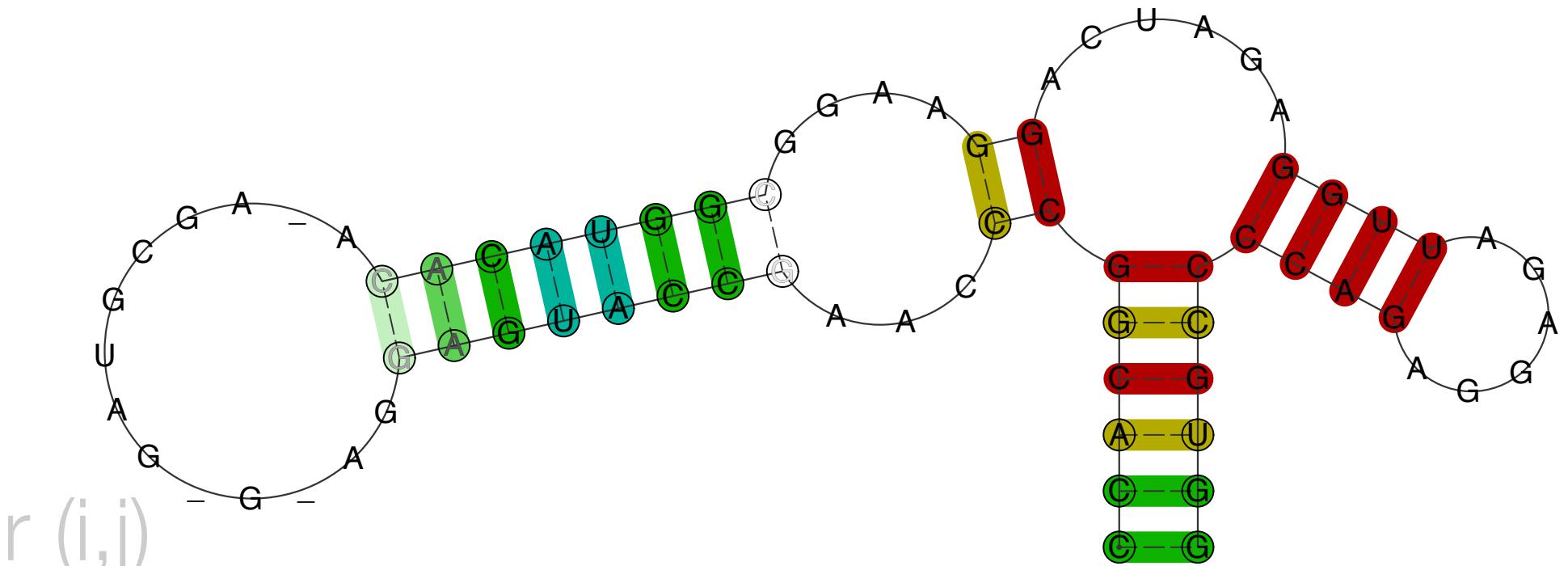
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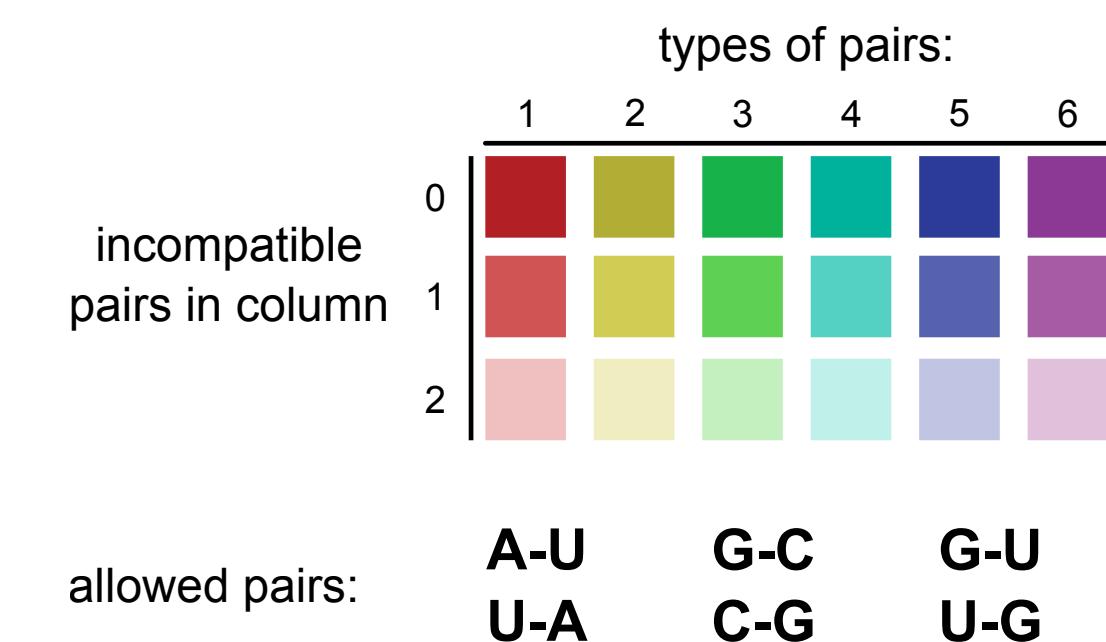
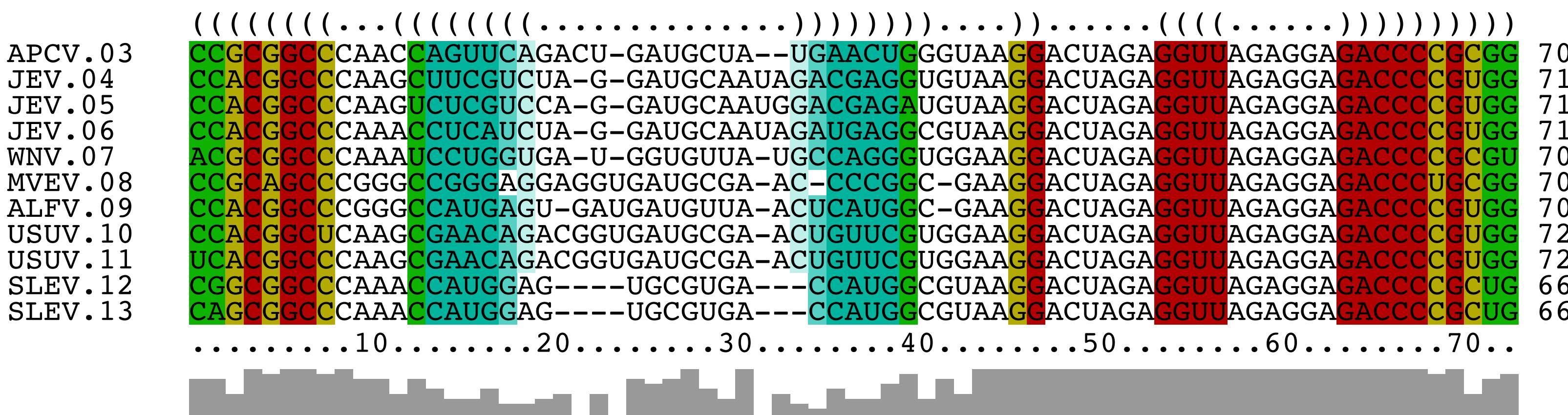
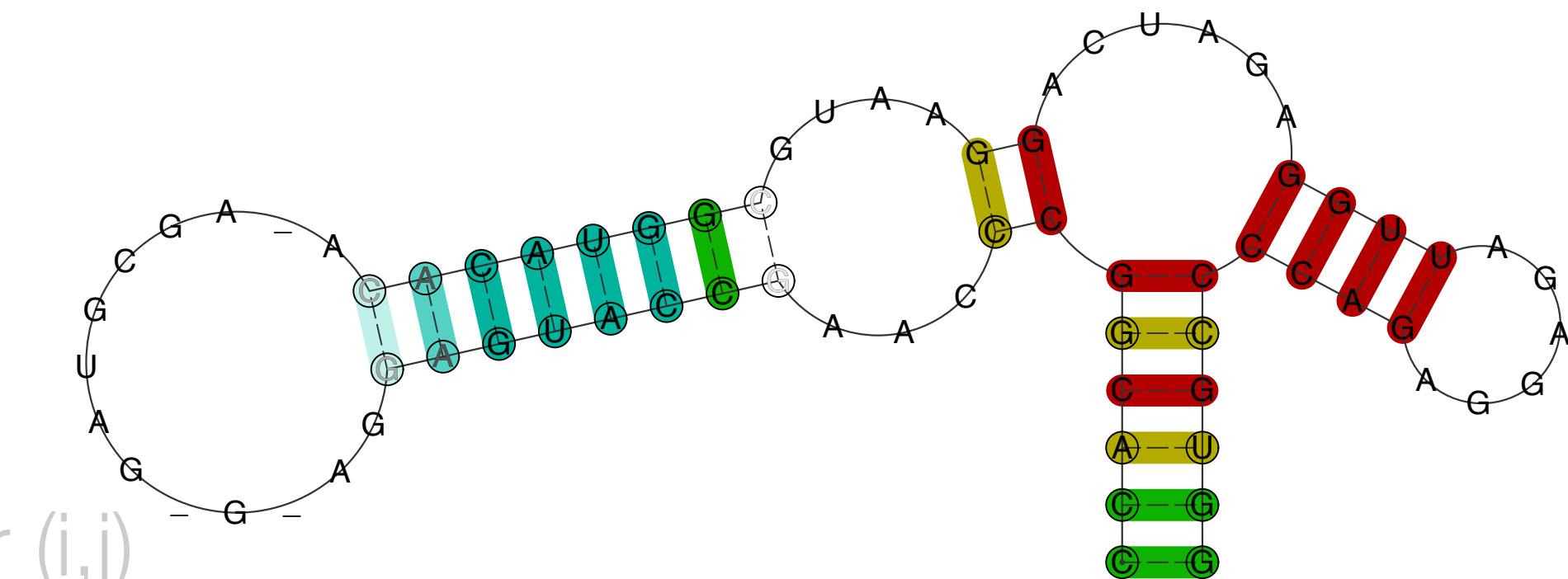


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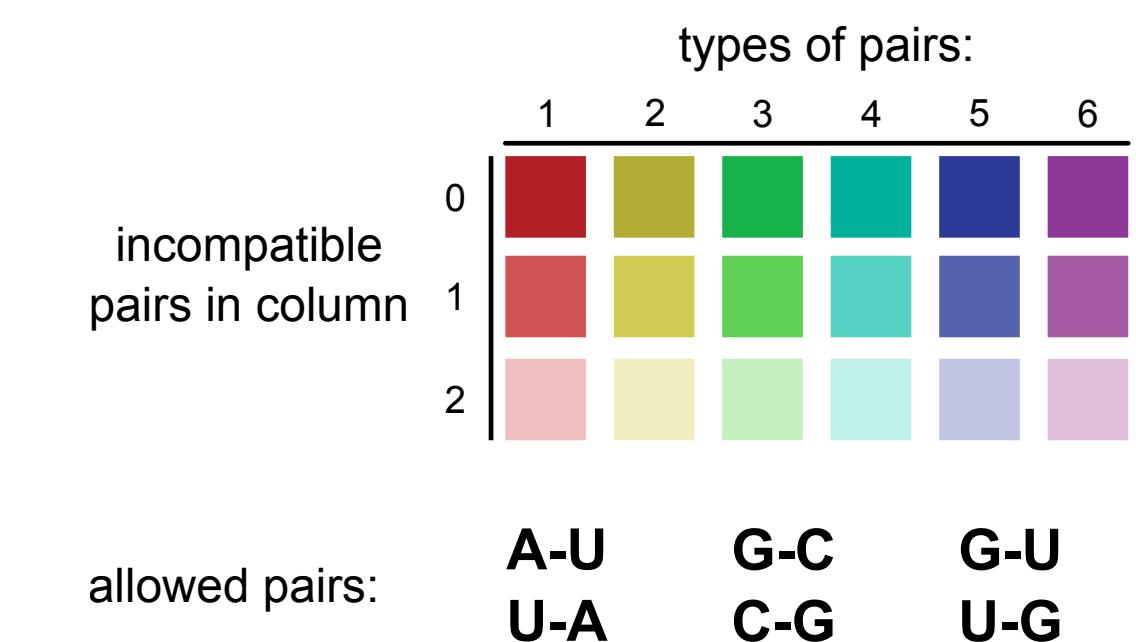
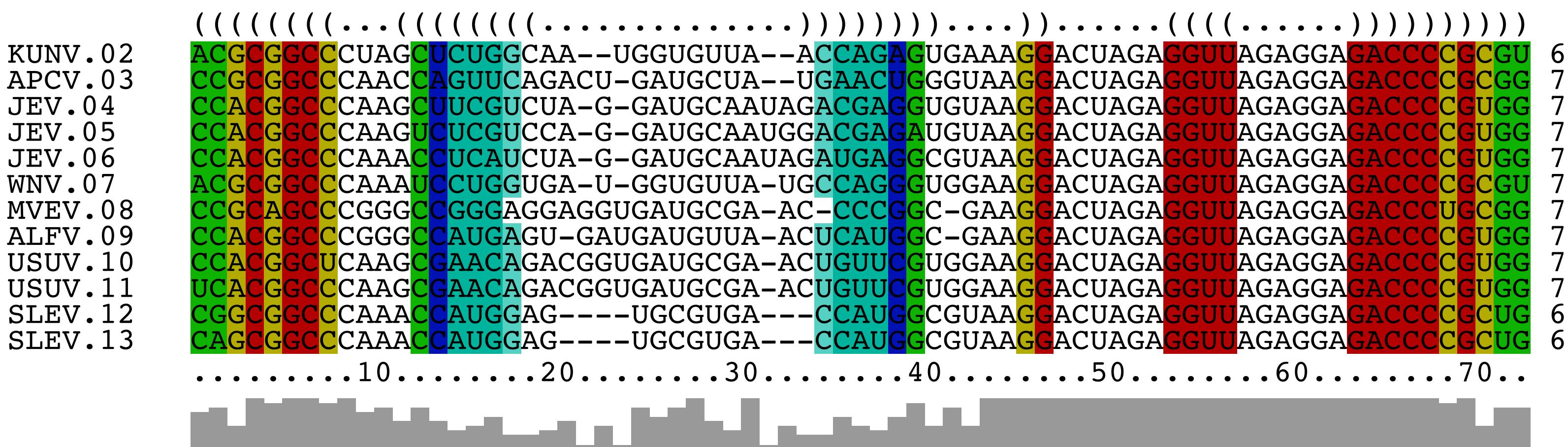
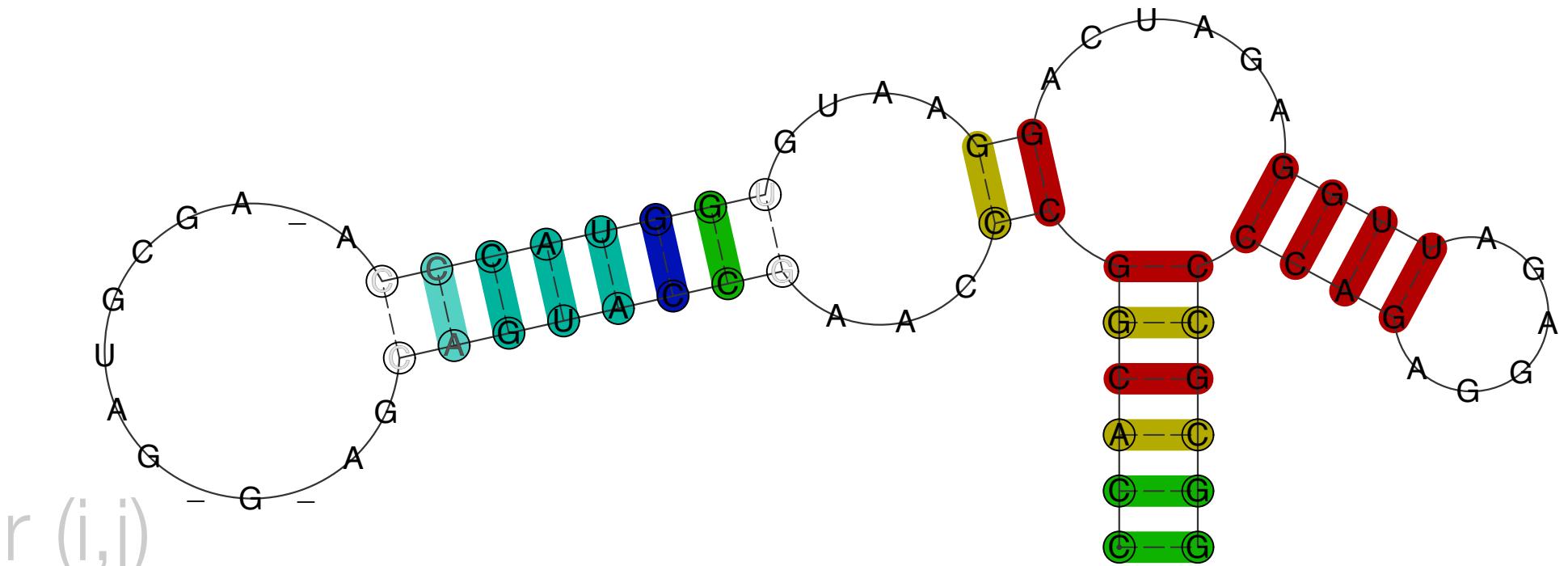


RNA covariation as evolutionary trait



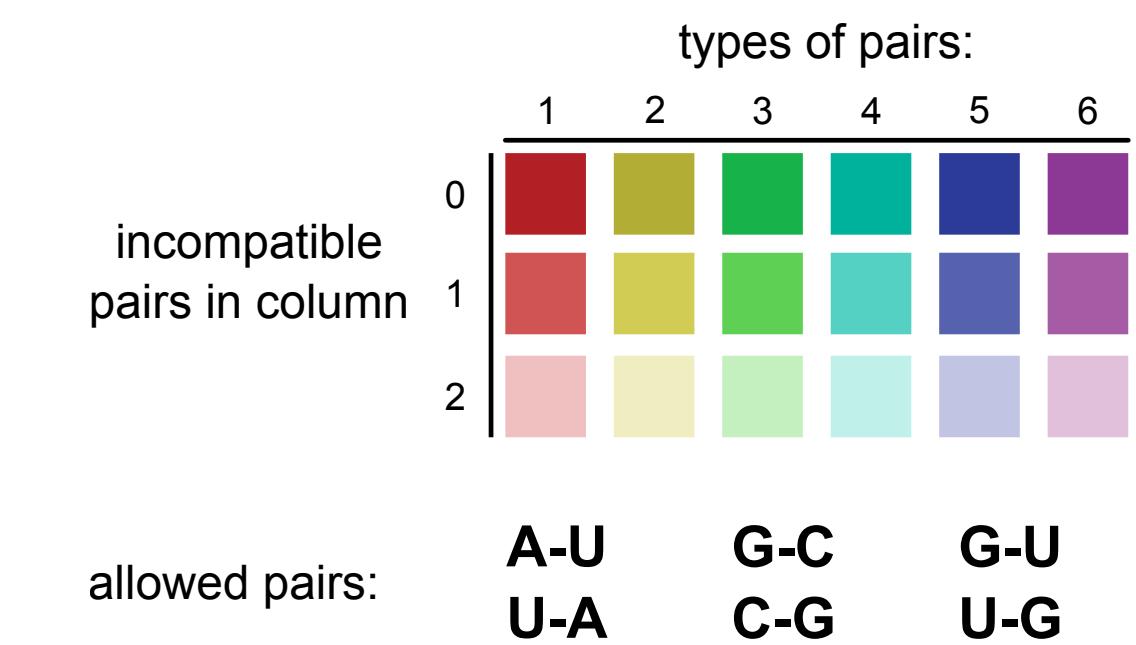
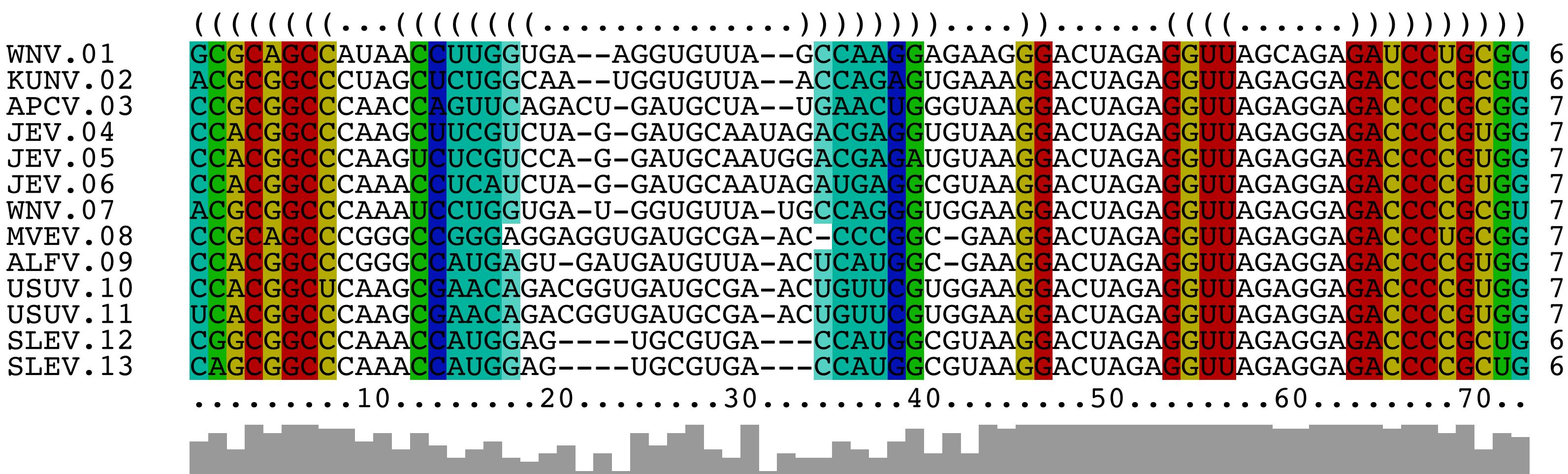
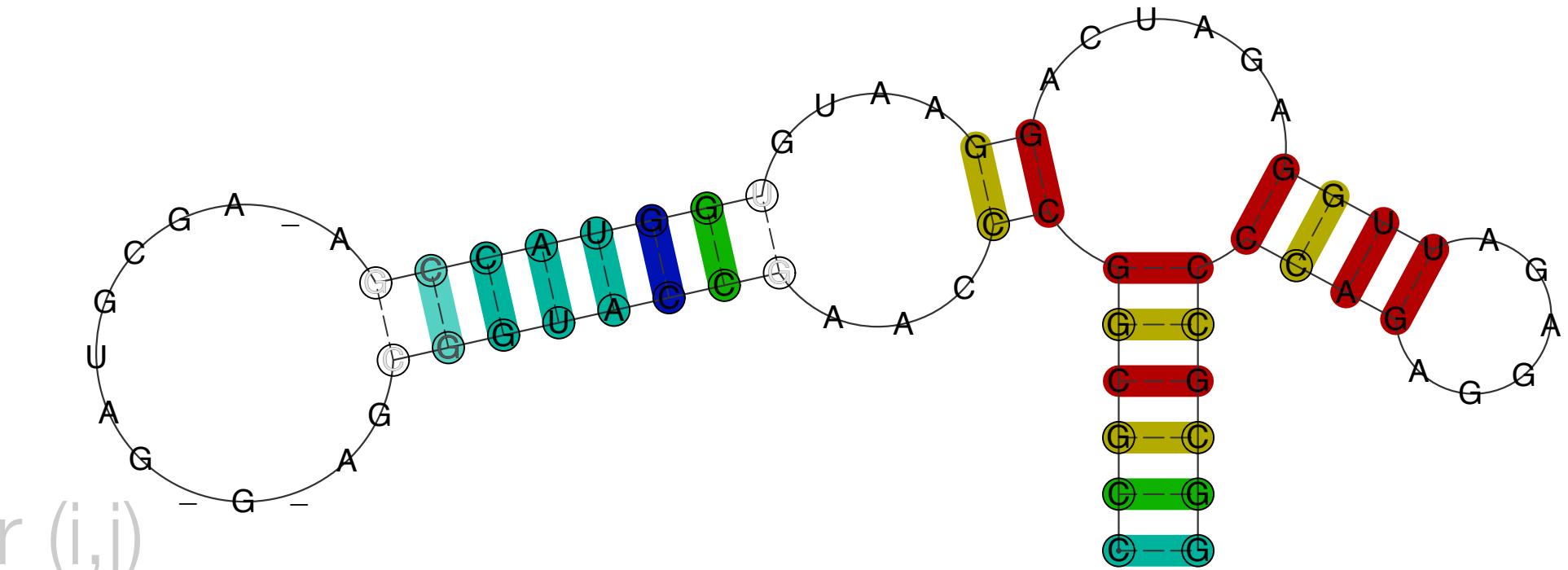
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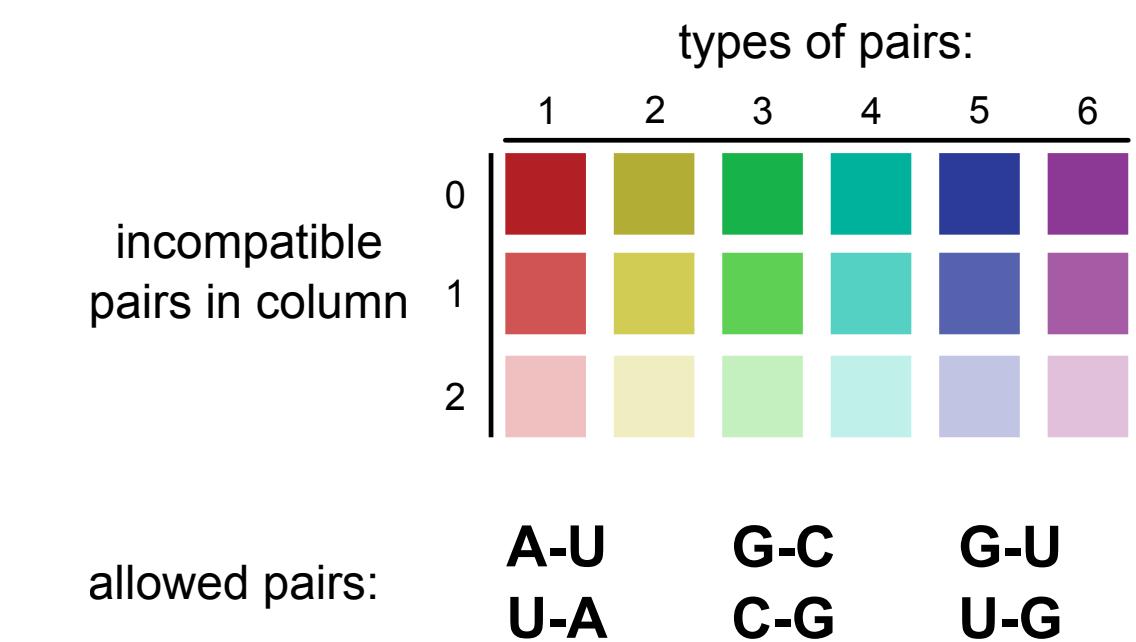
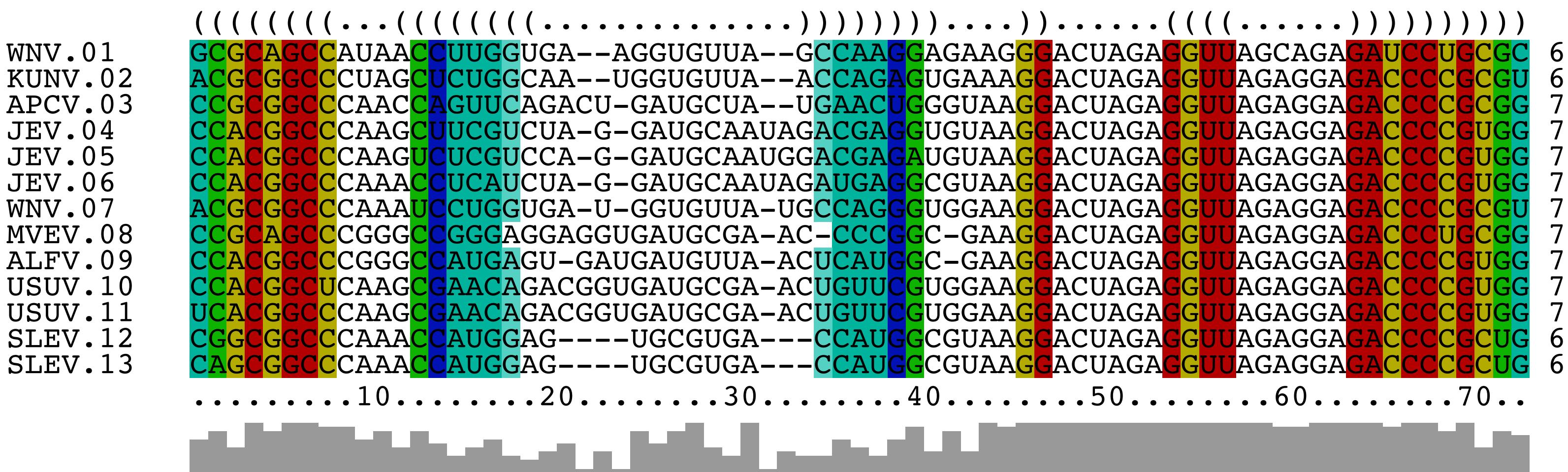
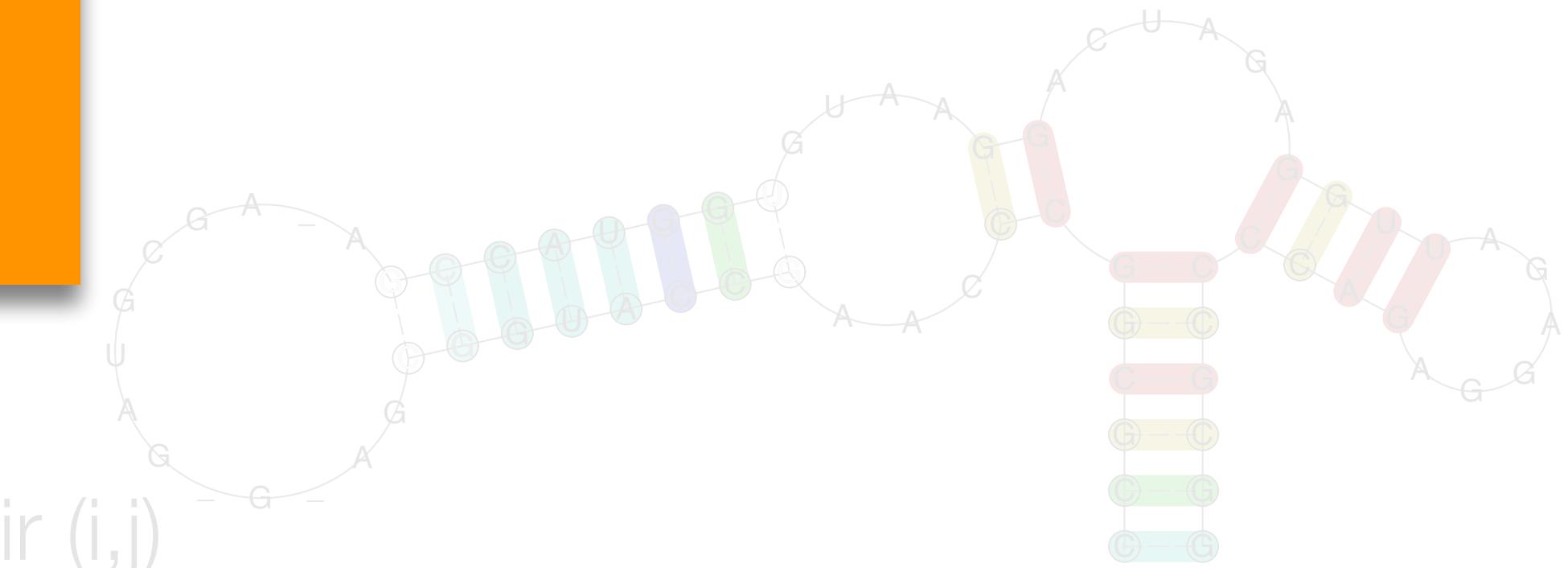
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RNA covariation as evolutionary trait

- High mutation rate in RNA viruses due to error-prone RdRP
- We use structural RNA alignments and Covariance Models to find conserved elements
- Compensatory mutation: both positions are mutated
- Presence of both strongly supports predicted base pair (i,j)



The Vienna RNA Package

- Efficient implementations for single, multiple sequence and MSA folding
- Global and local structure prediction
- Prediction of consensus structures
- Hard and soft constraints
- Complete suboptimal folding and energy landscape analysis
- Analysis of folding kinetics / co-transcriptional folding
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- Comparison of secondary structures
- Utilities for comparison, annotation, and plotting of secondary structures
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For software developers

- C library to link against your programs
- Python/Perl scripting language interface

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www.tbi.univie.ac.at/RNA

Part I

RNA structure prediction

with

ViennaRNA

Part II

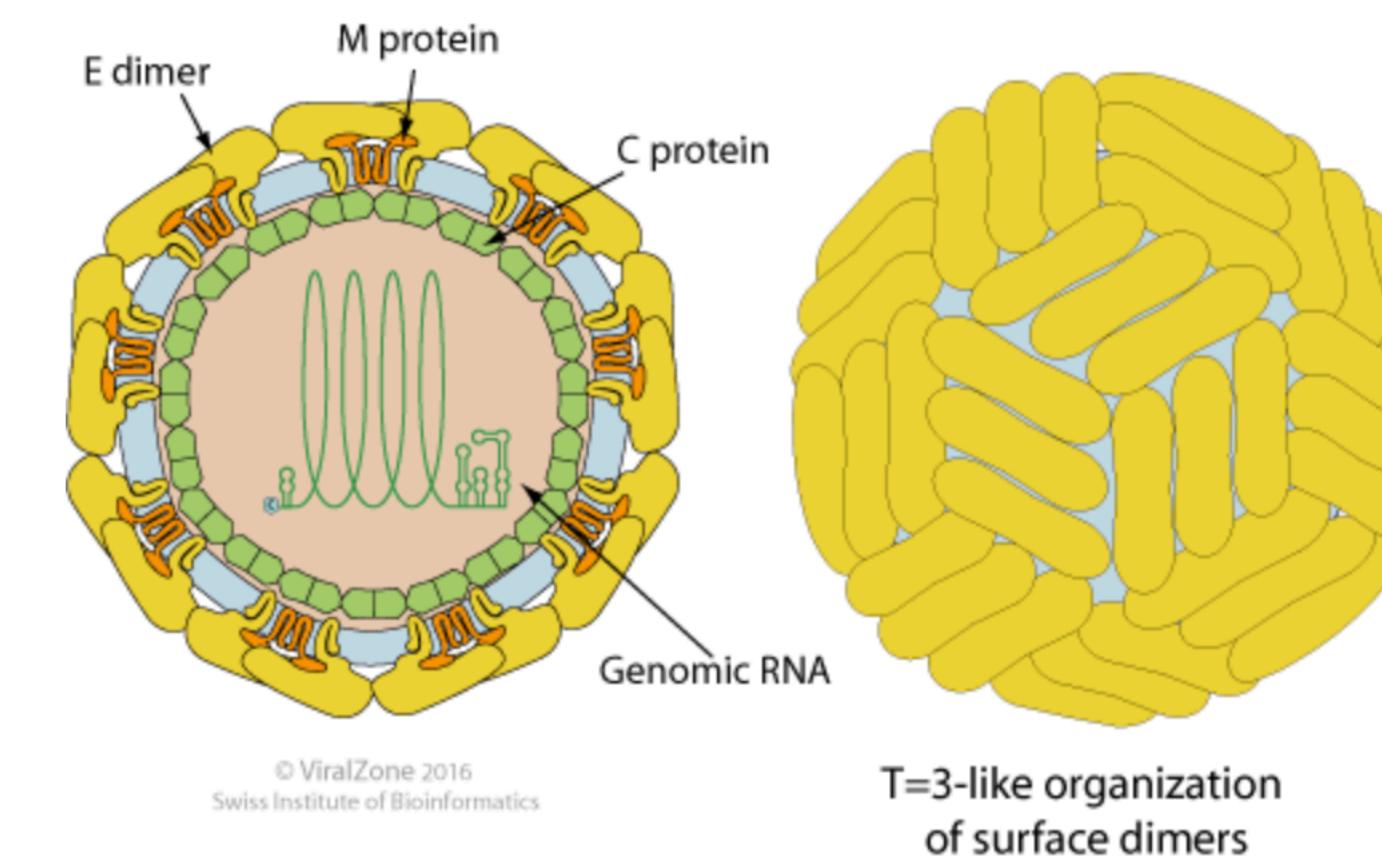
RNA structure conservation

in

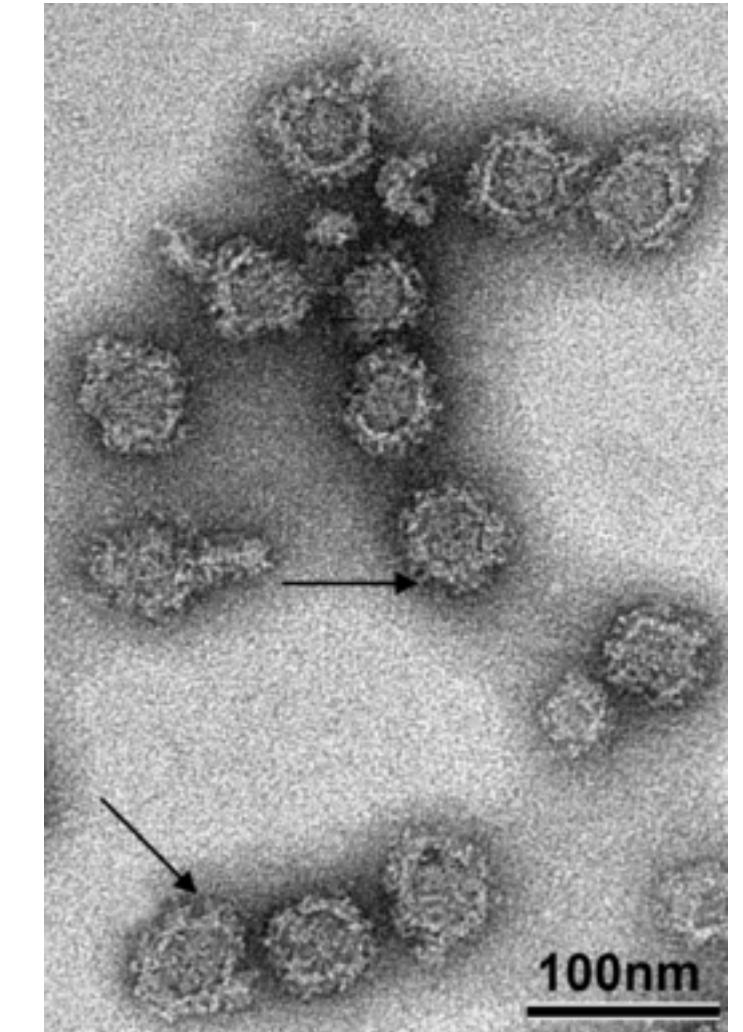
Tick-borne encephalitis virus

Tick-borne encephalitis virus (TBEV)

- Zoonotic RNA virus
(family *Flaviviridae* / genus Flavivirus)
- Endemic in forested parts of Eurasia and Japan
- Transmitted between haematophagous ticks and vertebrate hosts (reservoir hosts: small wild-living animals, rodents)
- Thousands of human infections/year. Majority is asymptomatic or subclinical, but TBEV has neurotropic potential and can cause meningitis, encephalitis or haemorrhagic syndrome
- Vaccines available

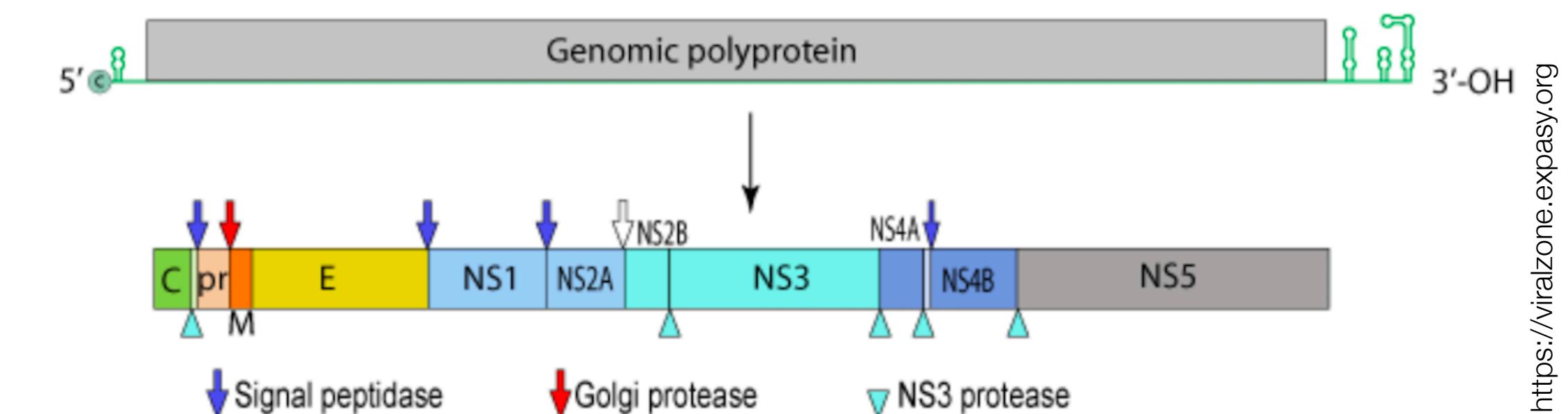


<https://viralzone.expasy.org>



100nm

<https://en.wikipedia.org>

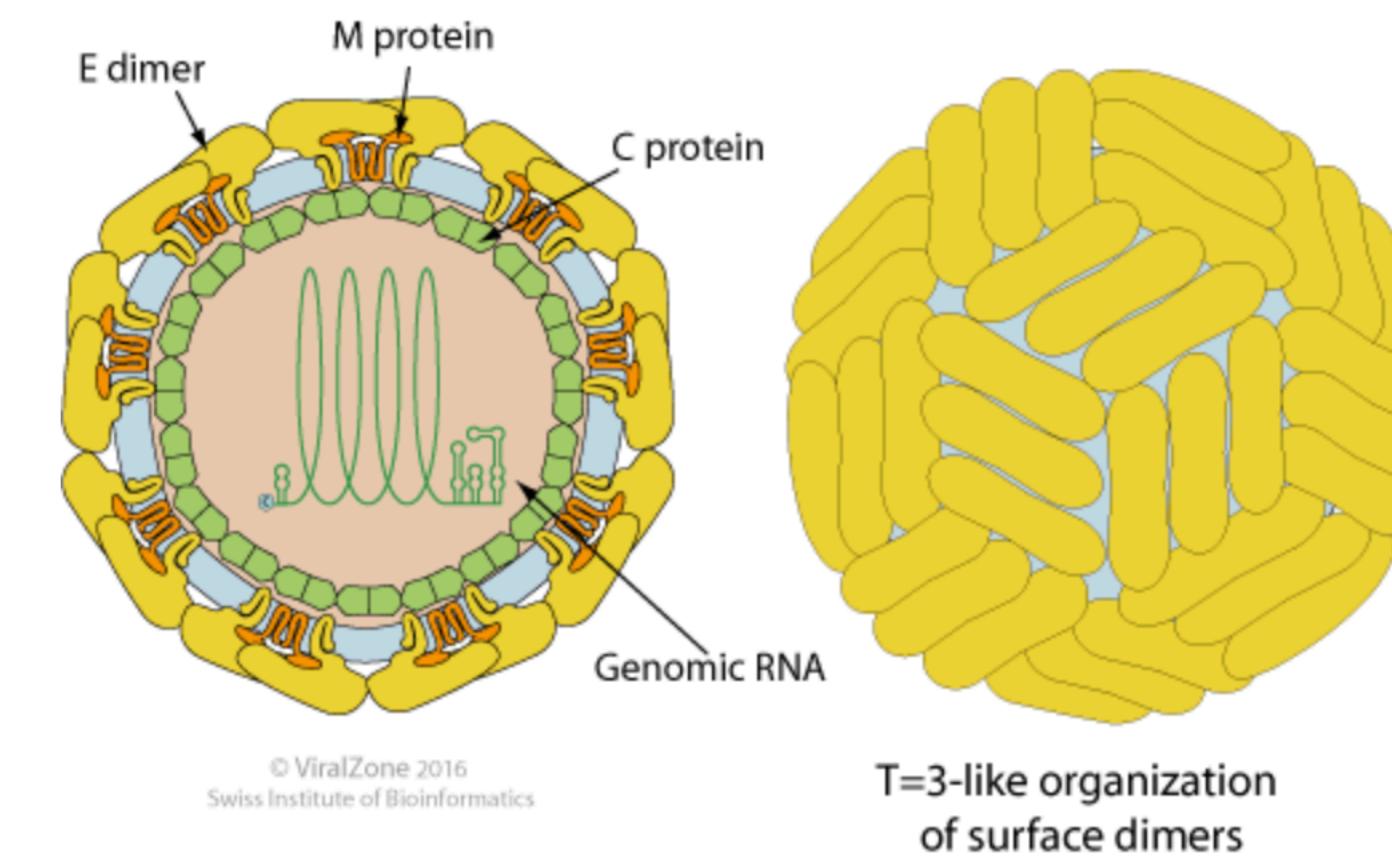


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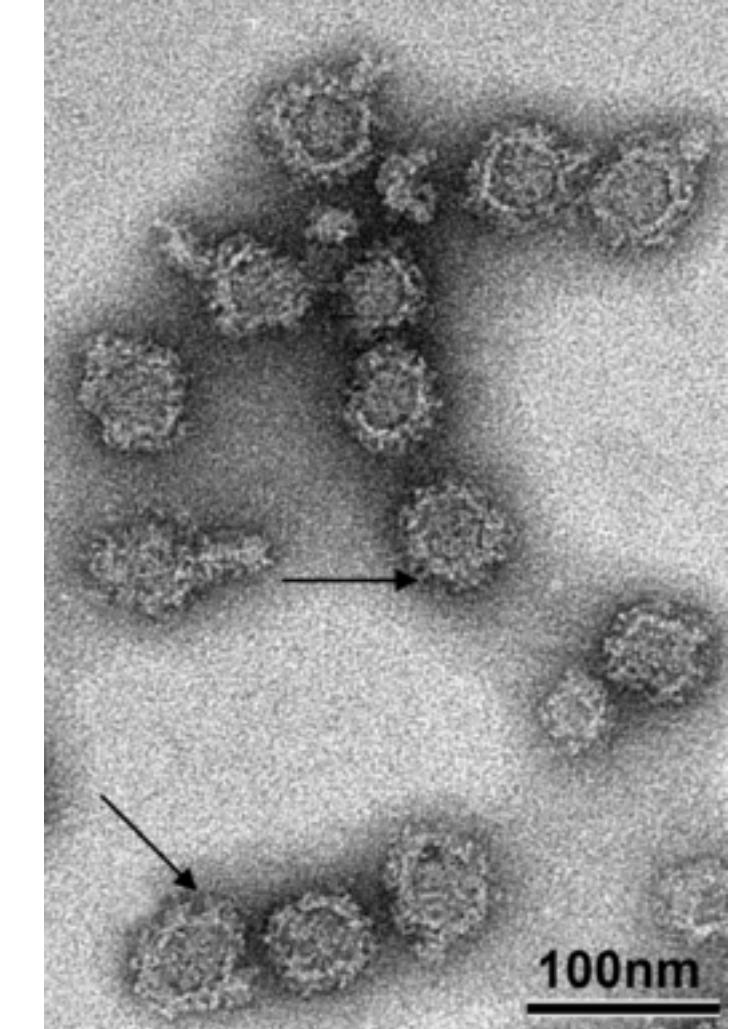
- Non-segmented, single-stranded, (+)-sense RNA genomes of ~11kB length
- Capped, non-polyadenylated
- Encodes a single ORF, flanked by highly structured 5'UTR and 3'UTR

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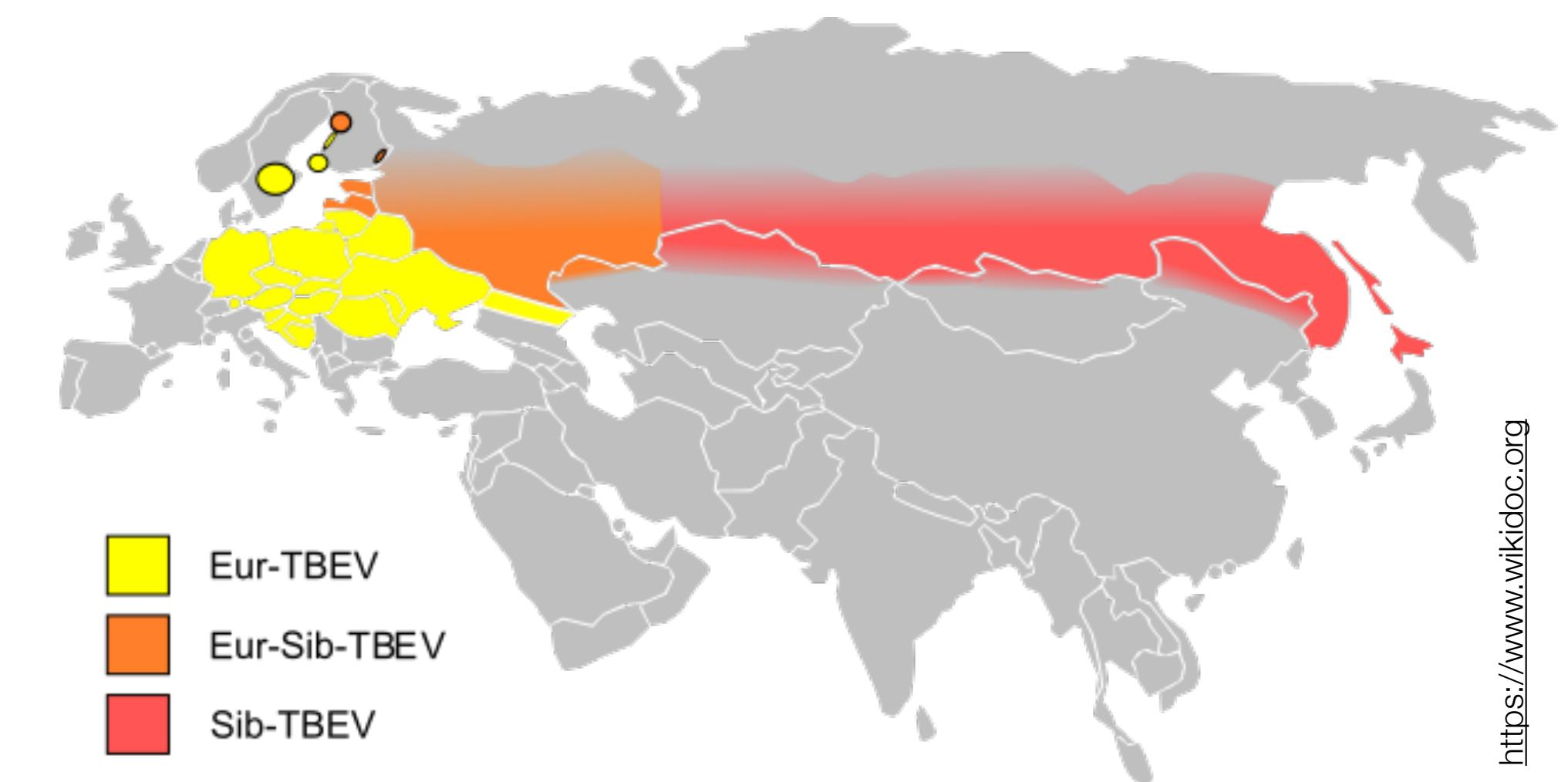


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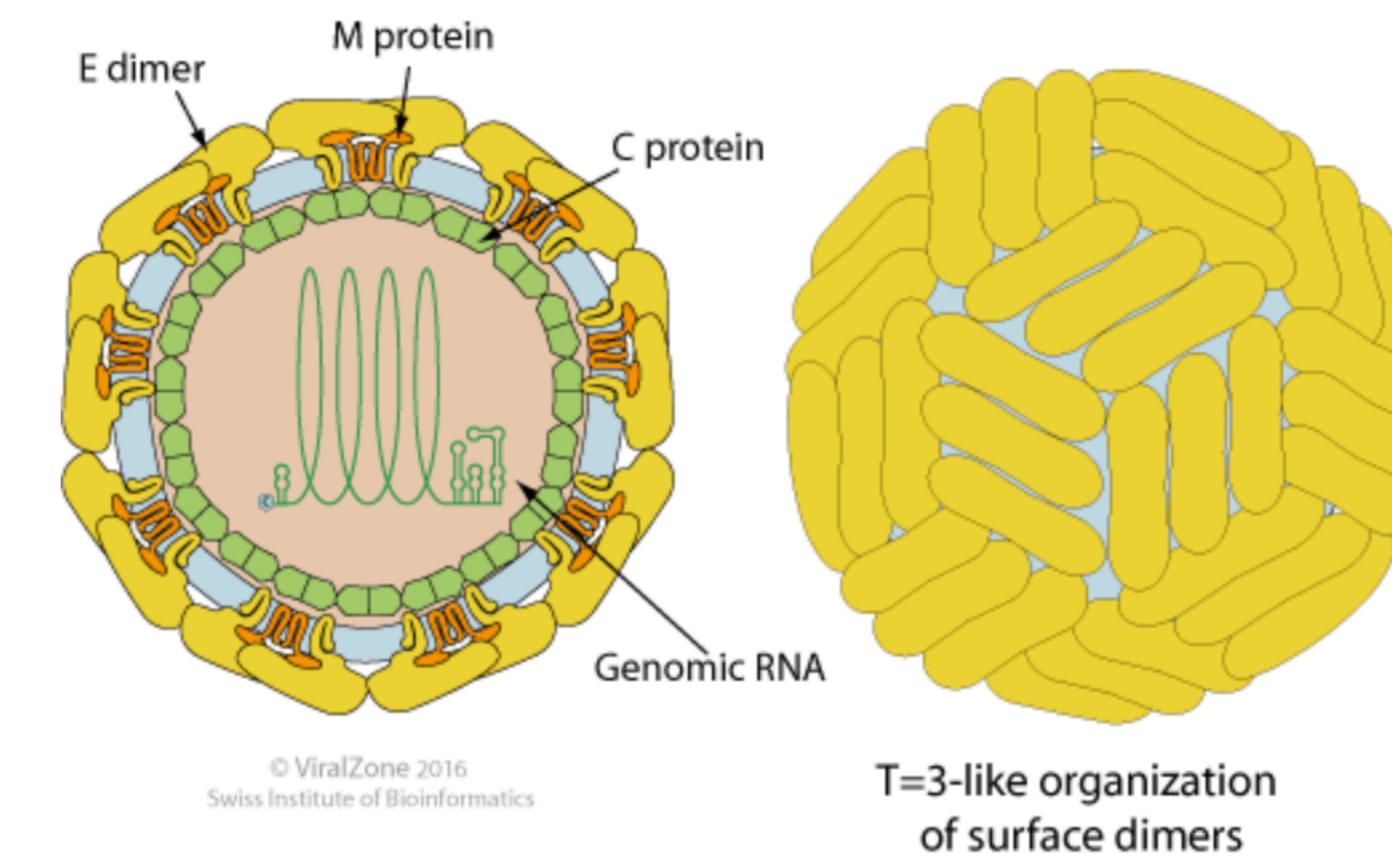
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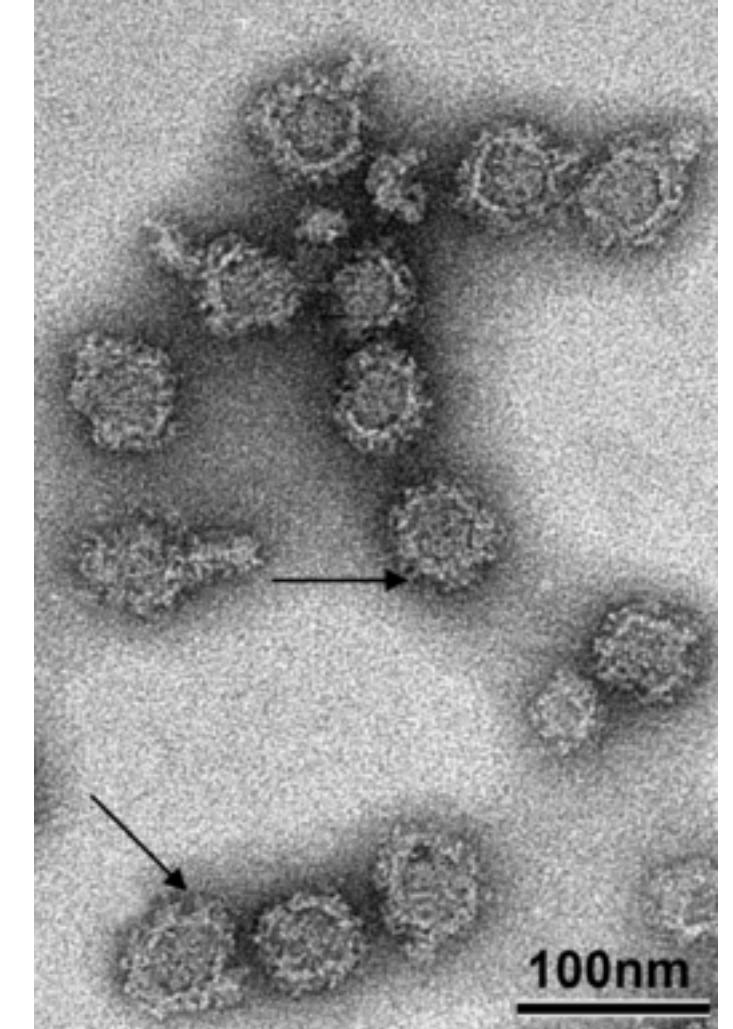
<https://www.wikidoc.org>

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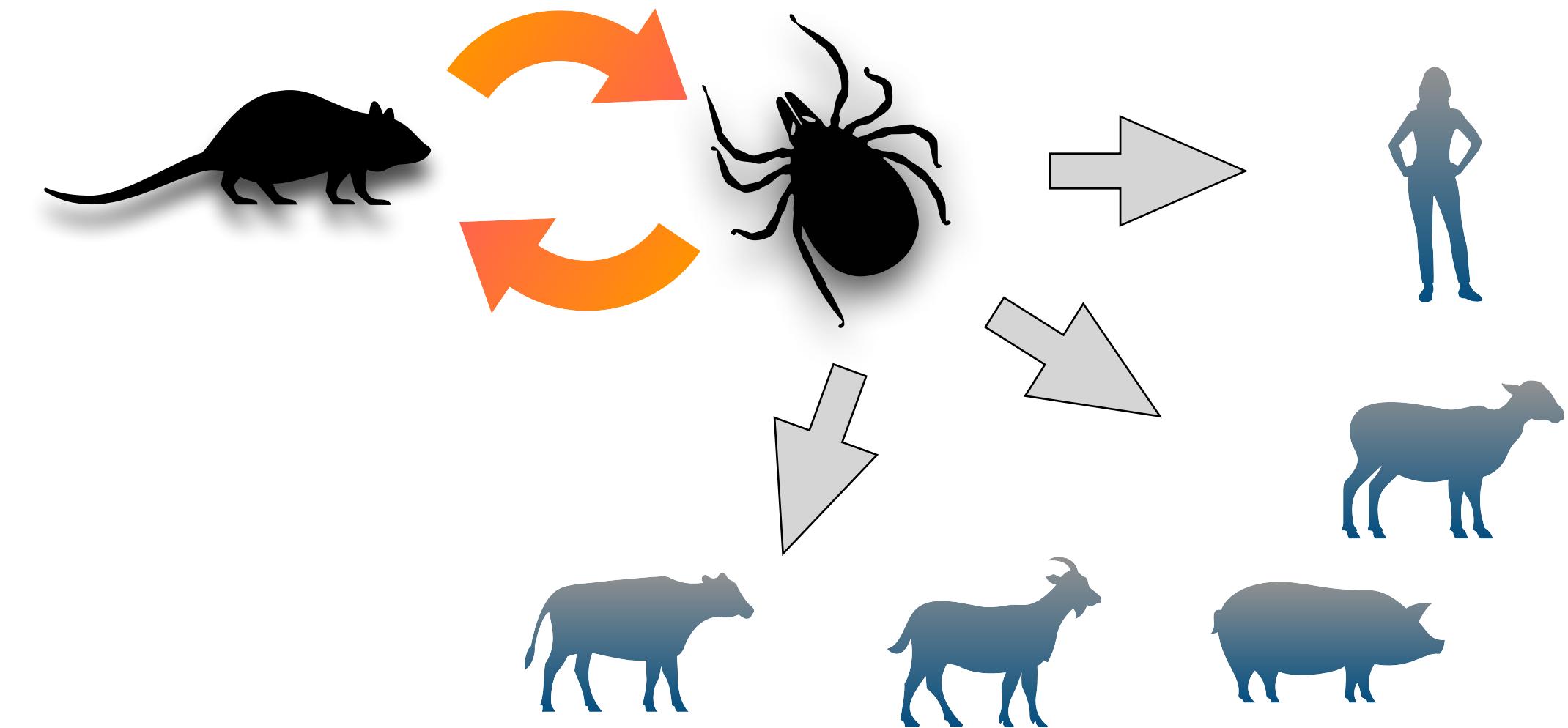
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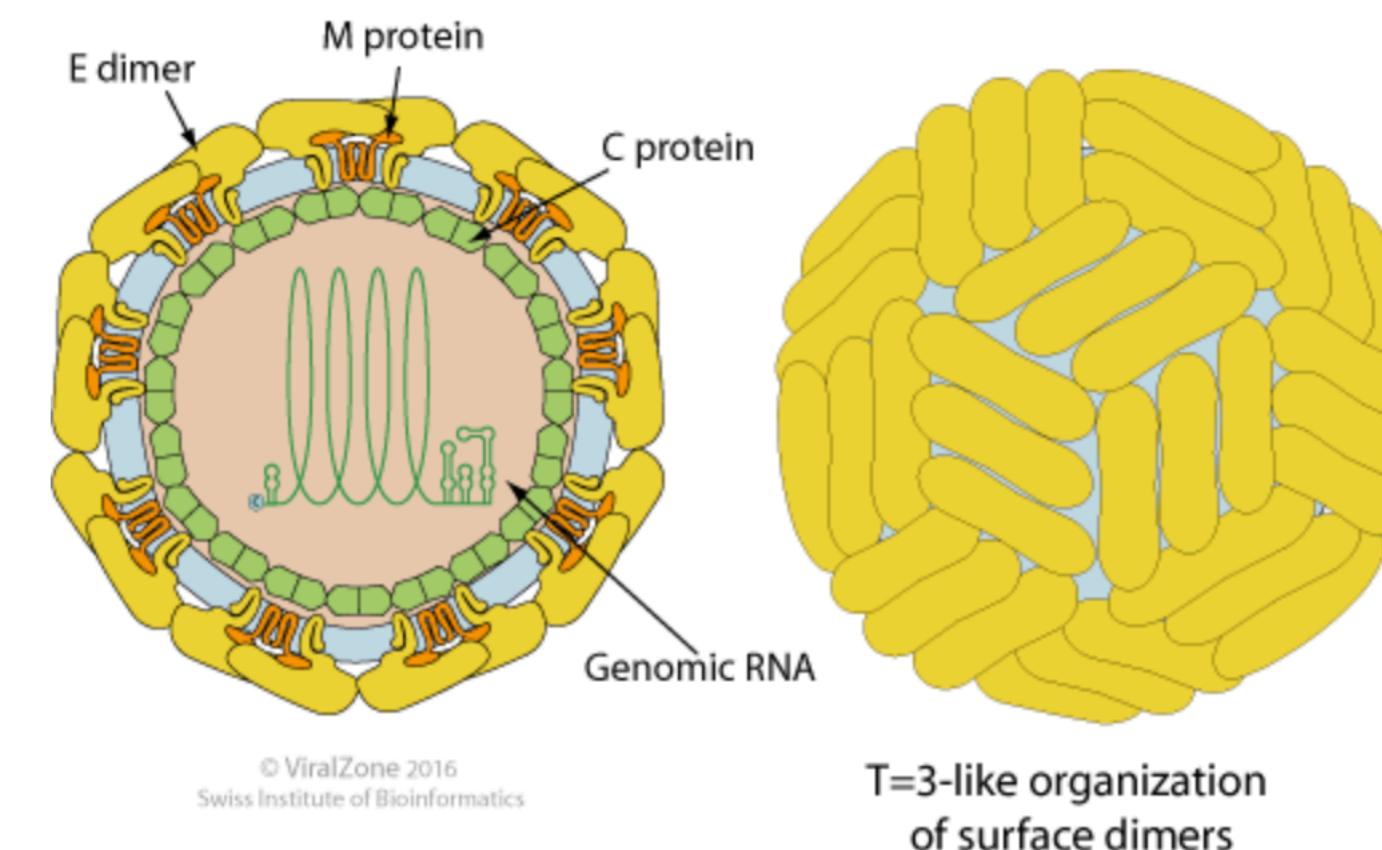


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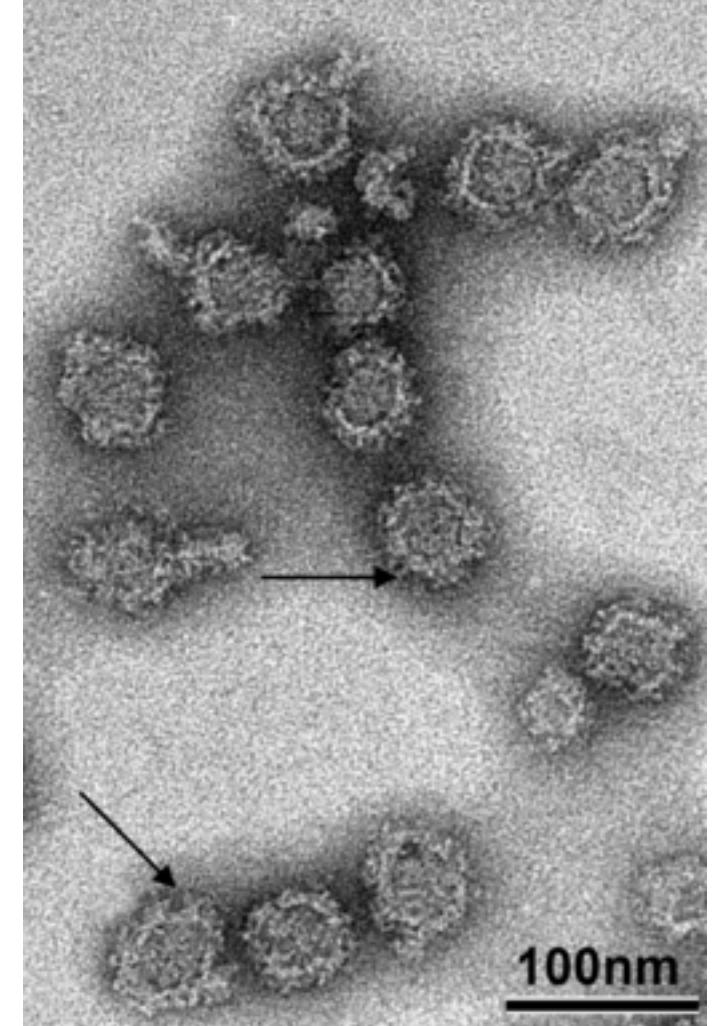


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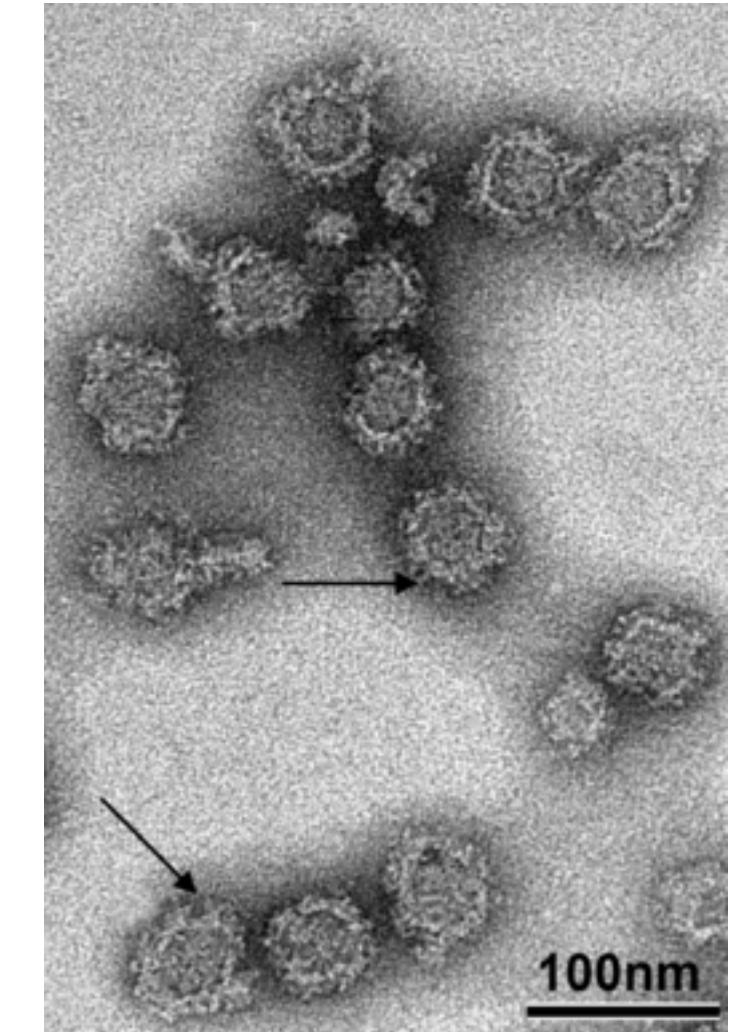
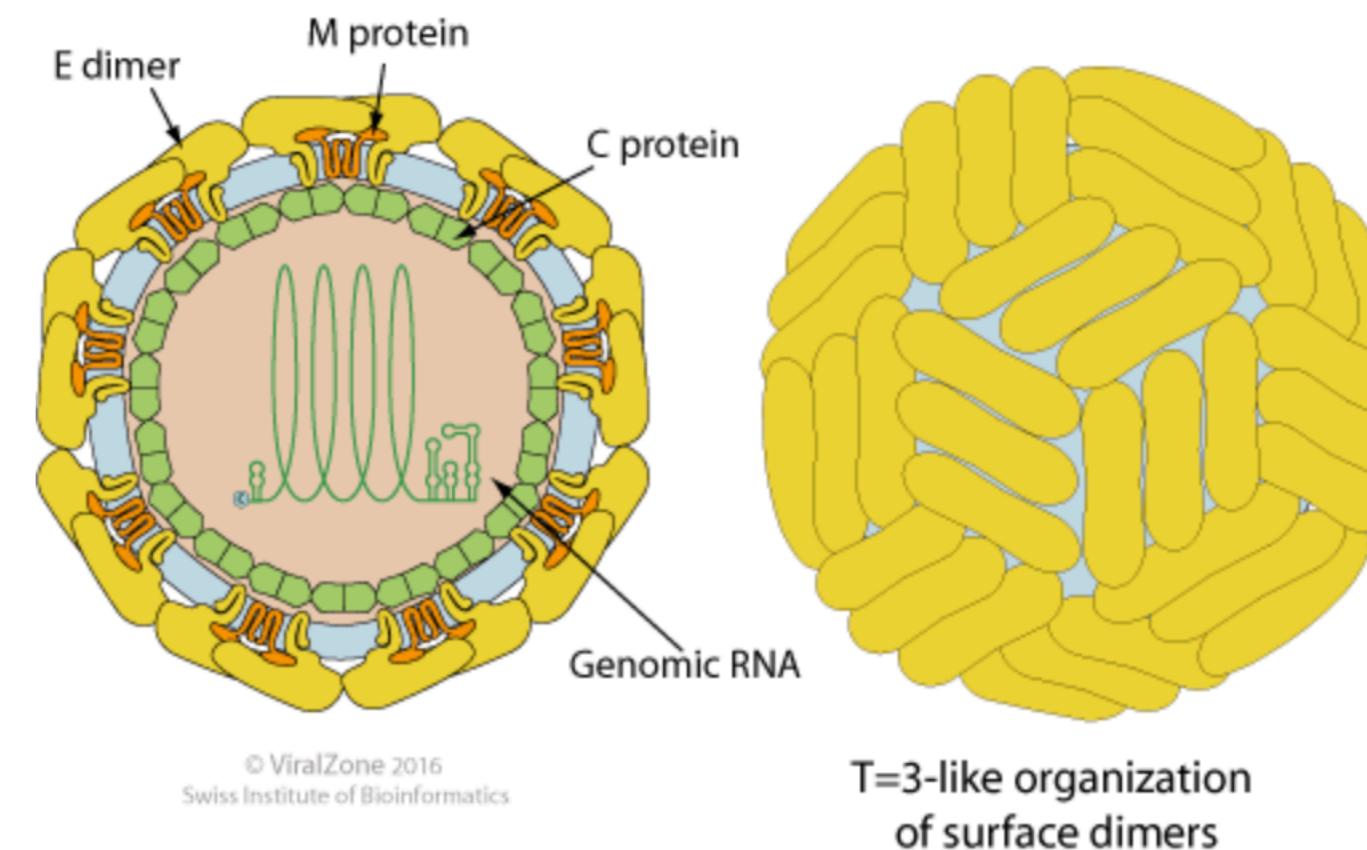
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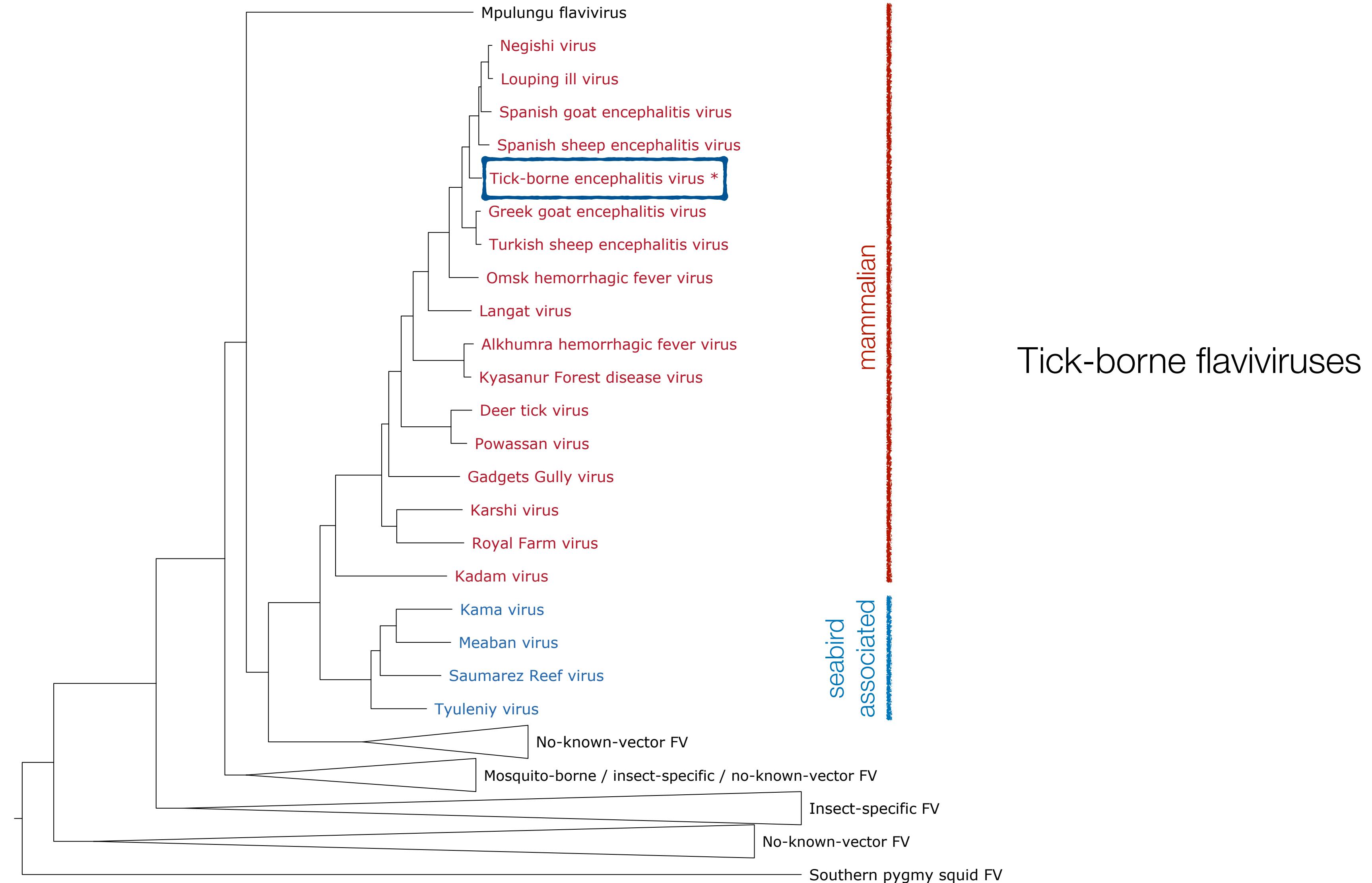
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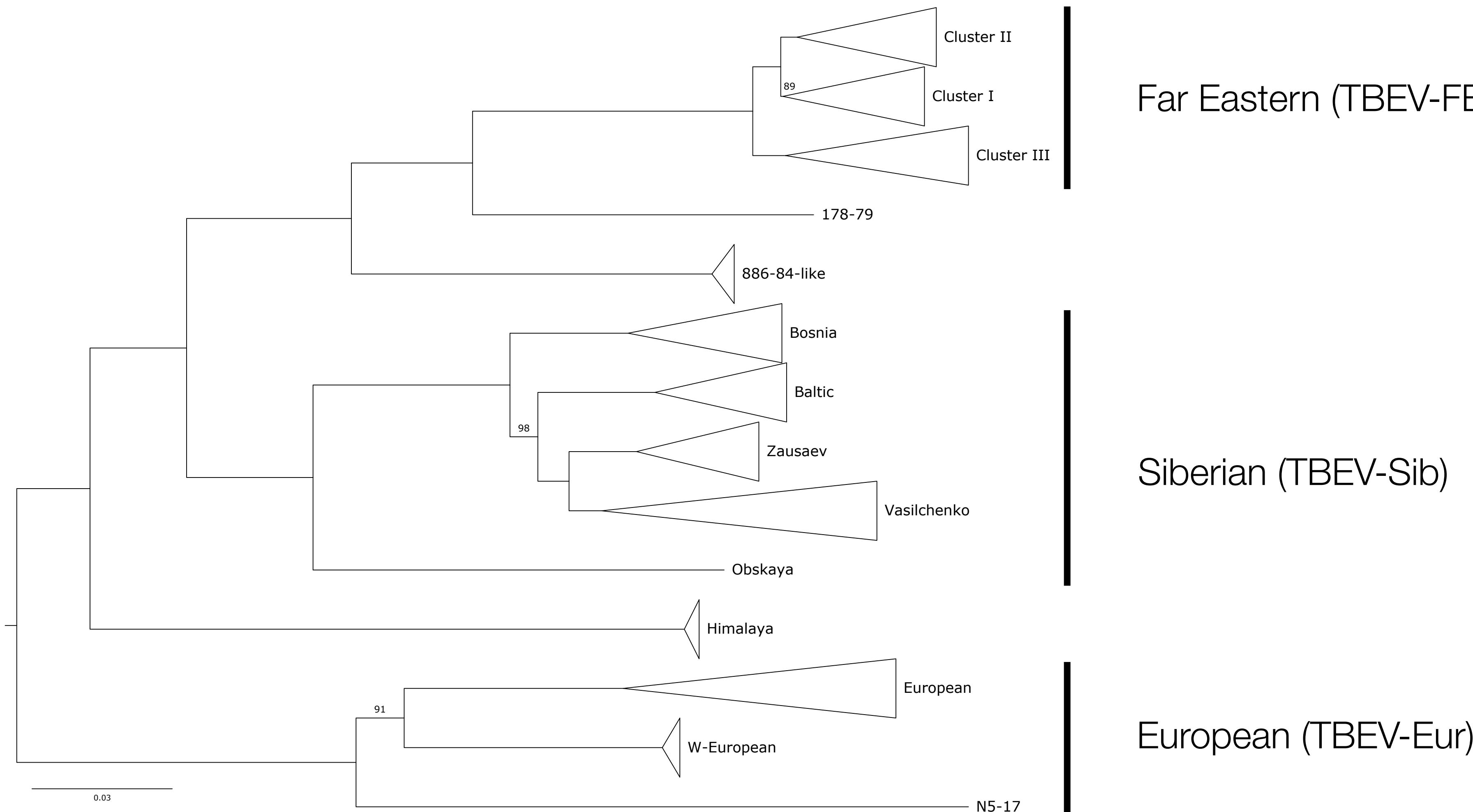


Phylogeny of tick-borne flaviviruses

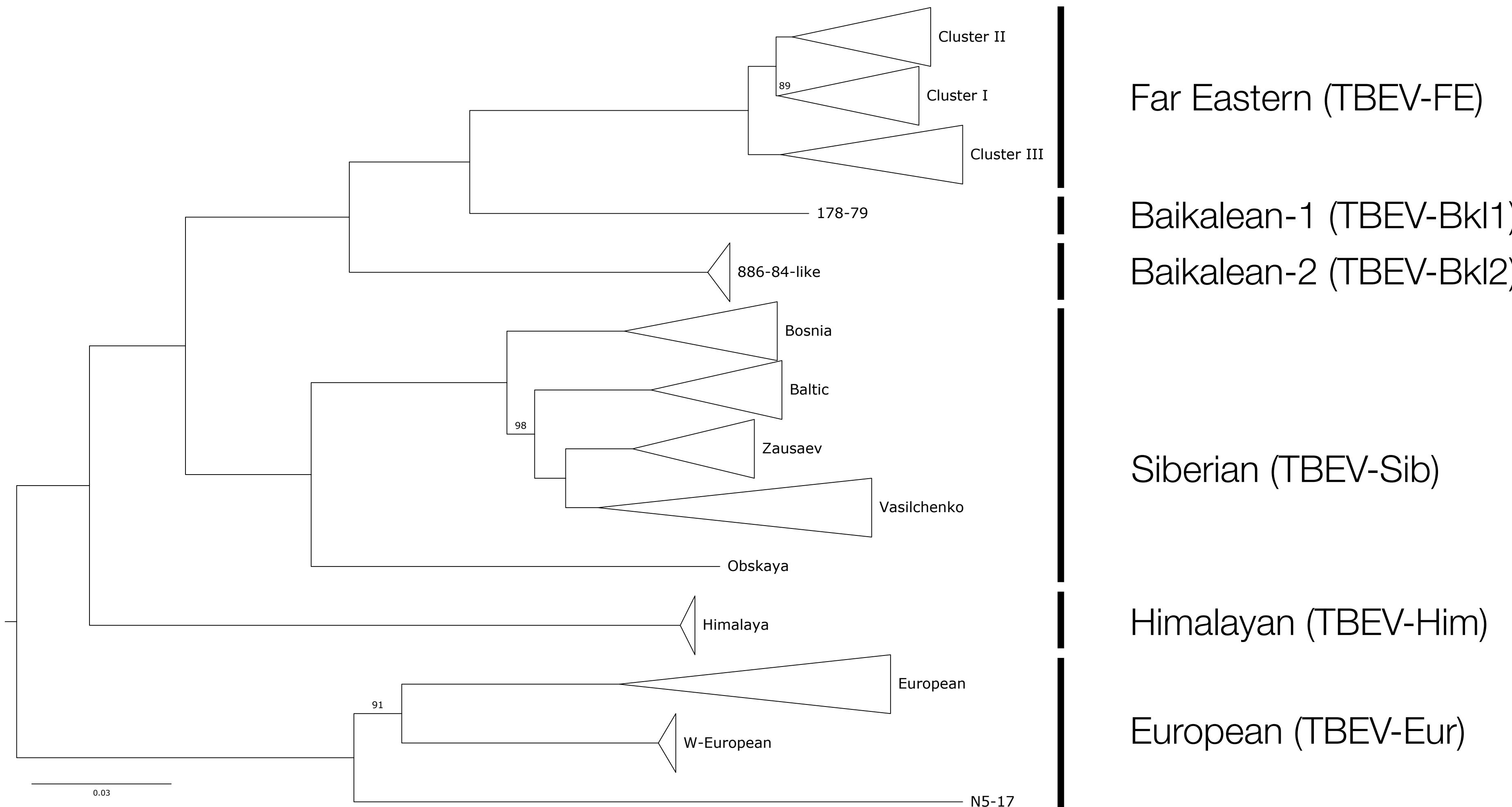


Phylogeny of tick-borne encephalitis virus

Tick-borne encephalitis virus subtypes



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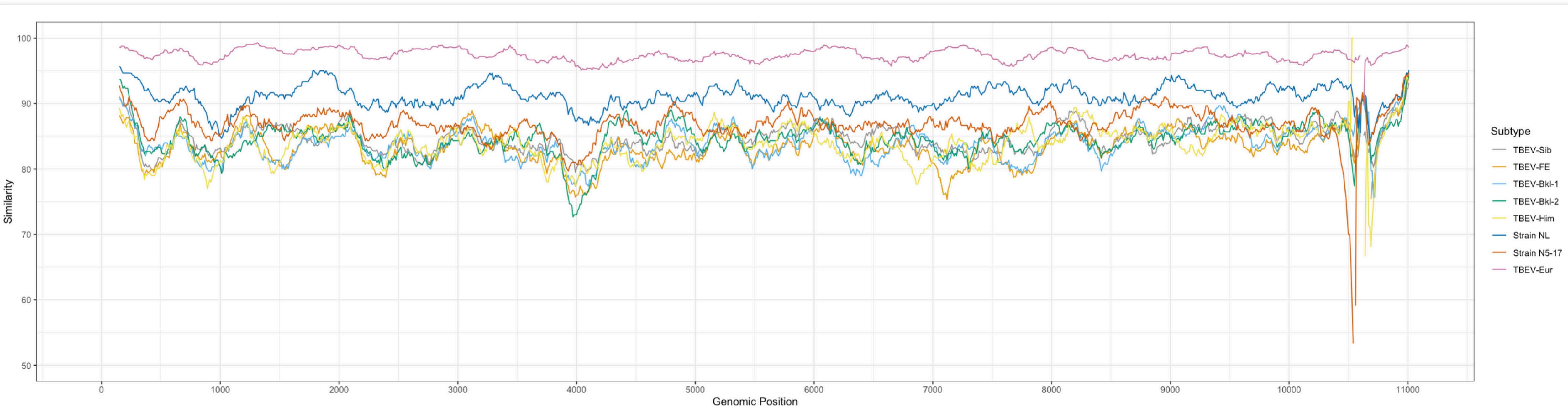


- At least 6 subtypes
- Disease severity
FE > Sib > EUR

TBEV subtype diversity

Sequence-level comparison of known TBEV subtypes vs Neudoerfl strain (300nt windows; 10nt steps)

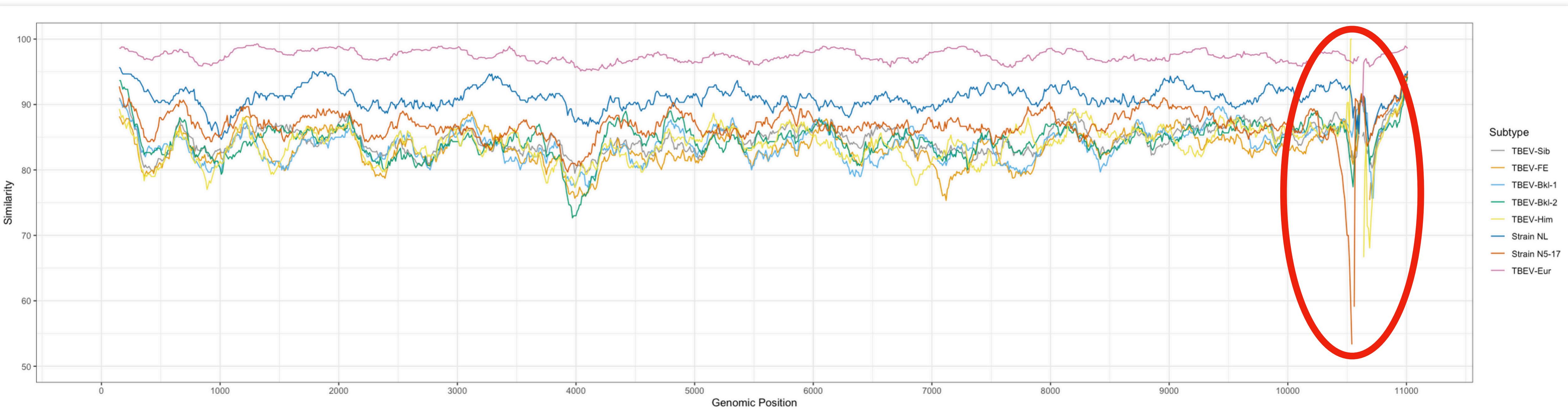
RNAsimplot
technology preview



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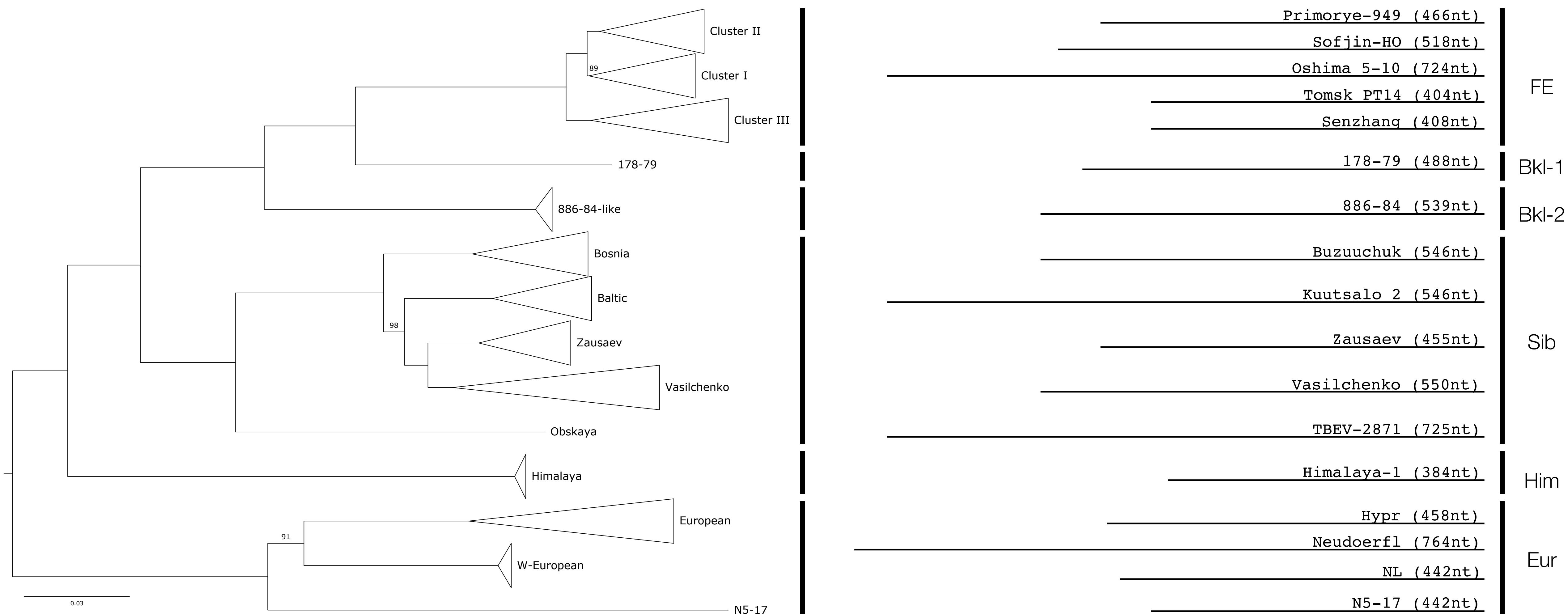
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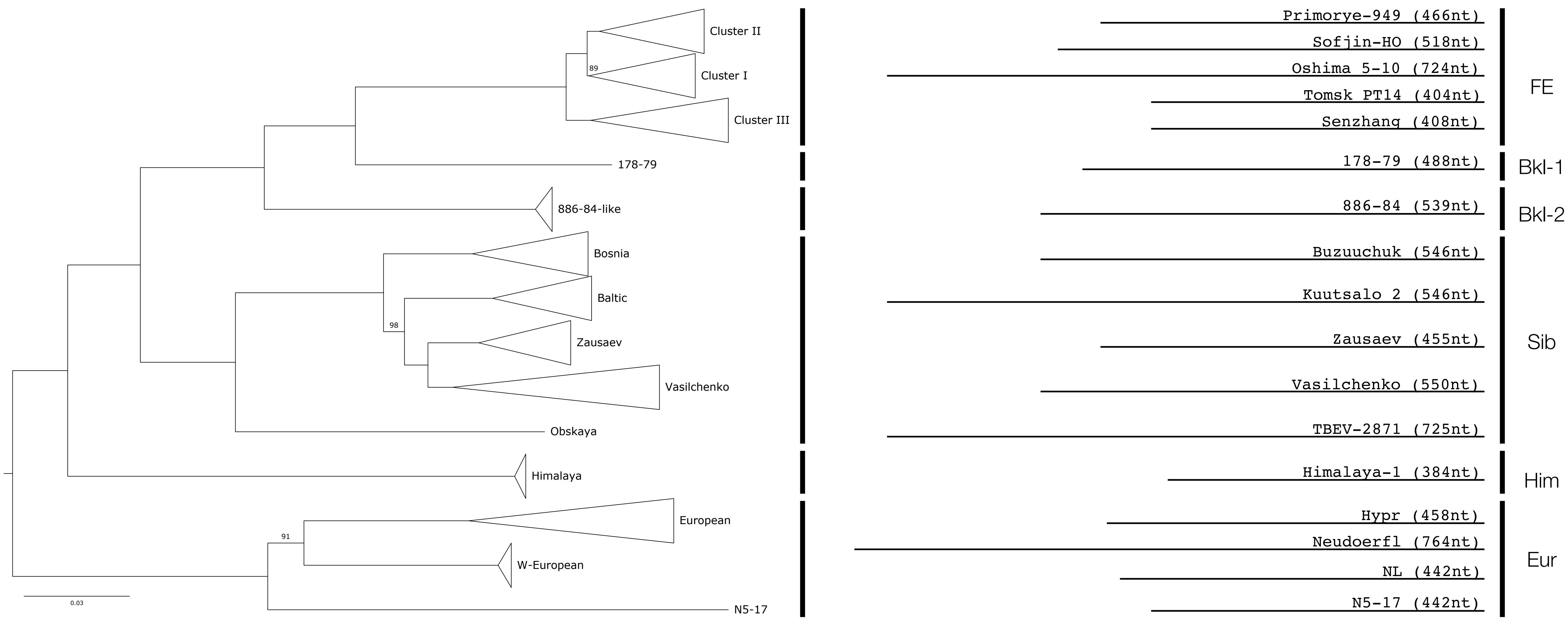
TBEV subtype diversity: 3'UTR

Tick-borne encephalitis virus subtypes differ in 3'UTR length



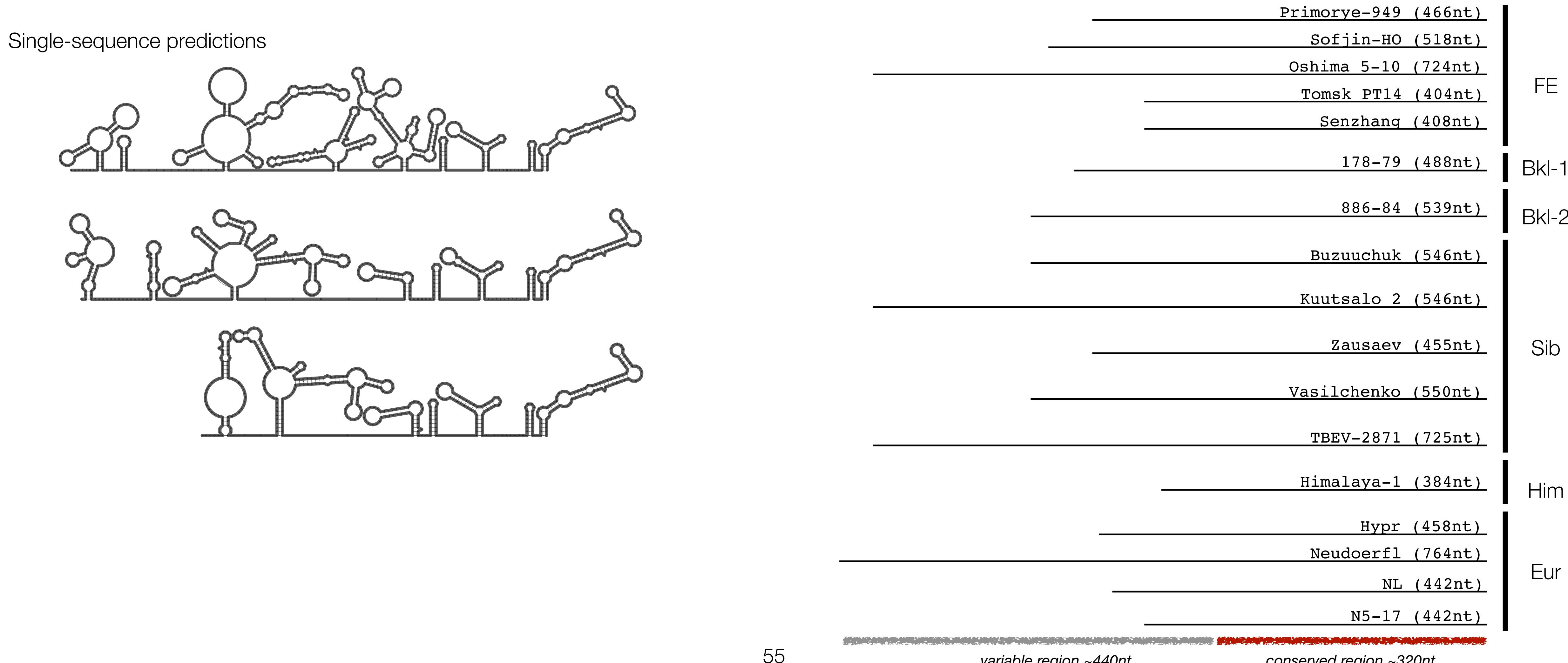
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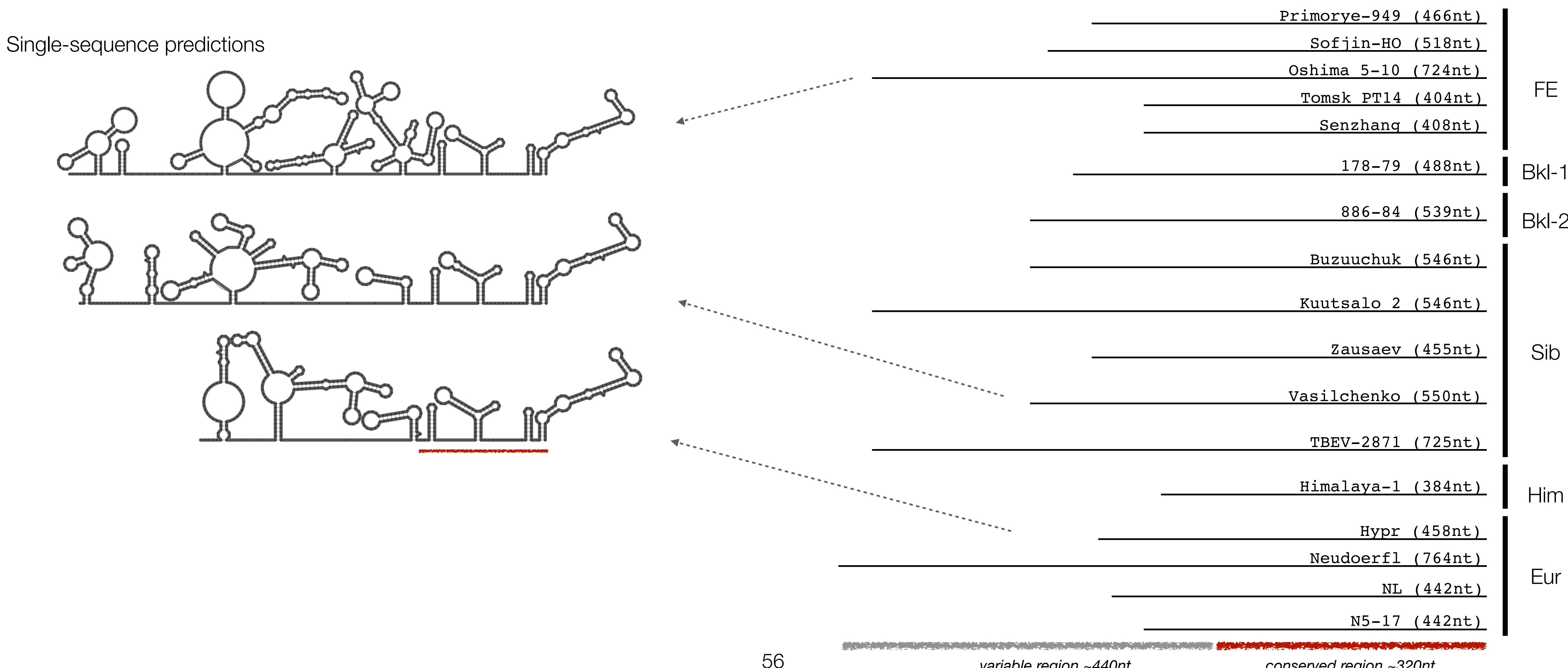
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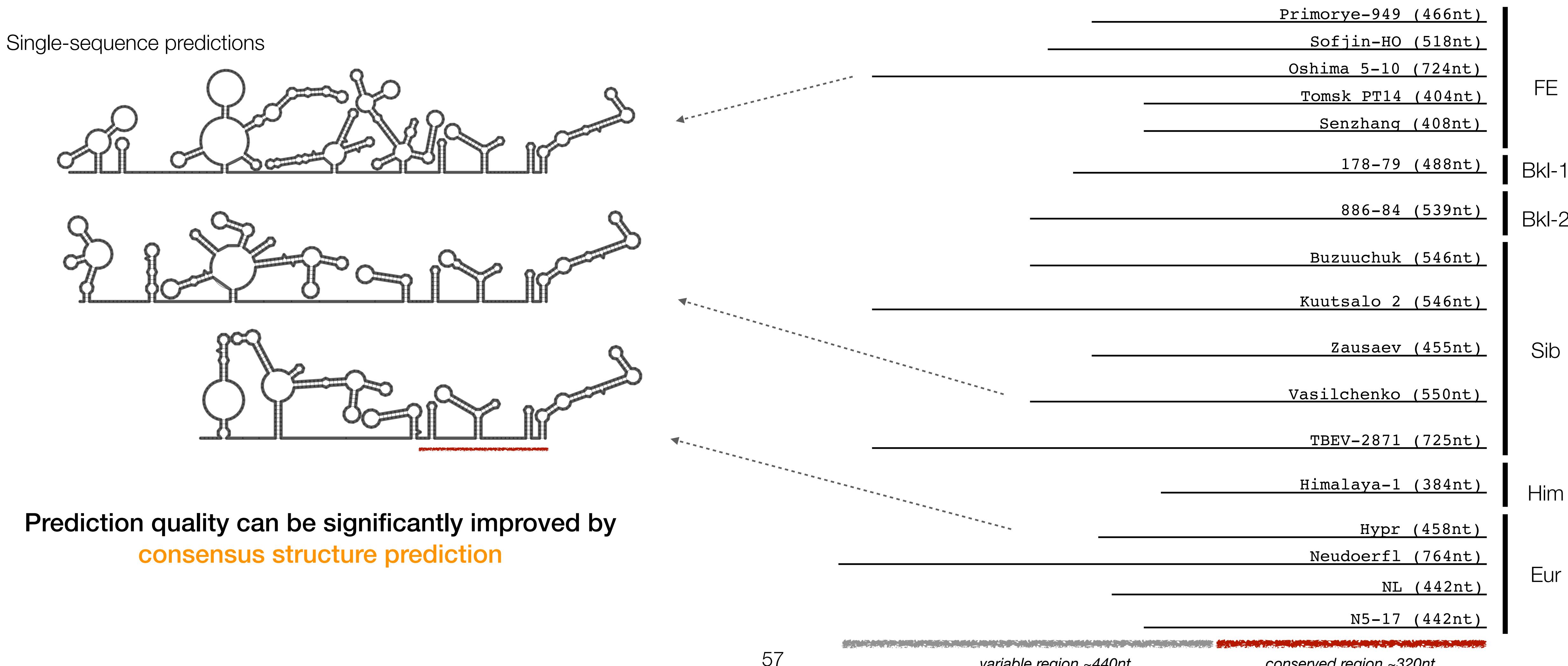
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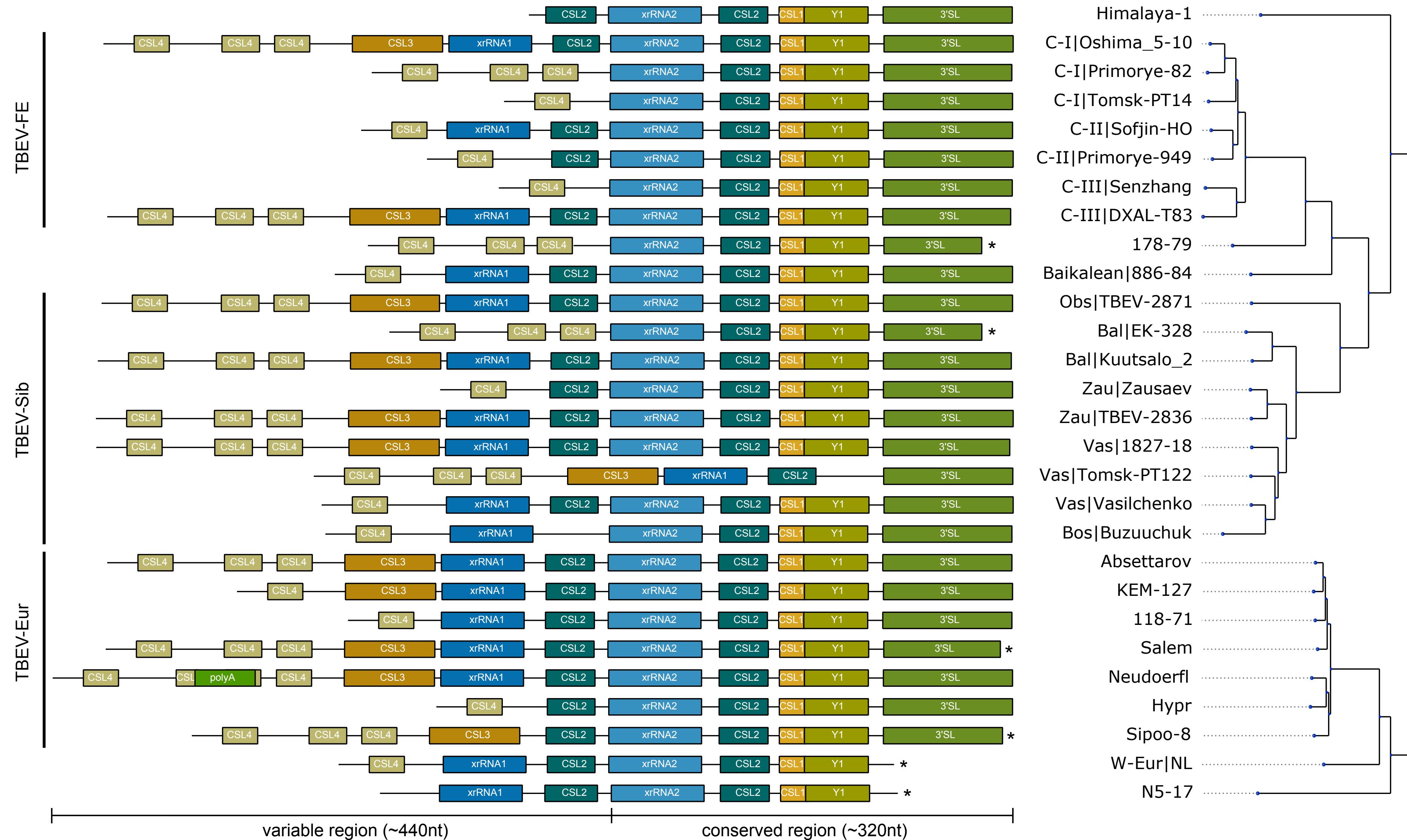


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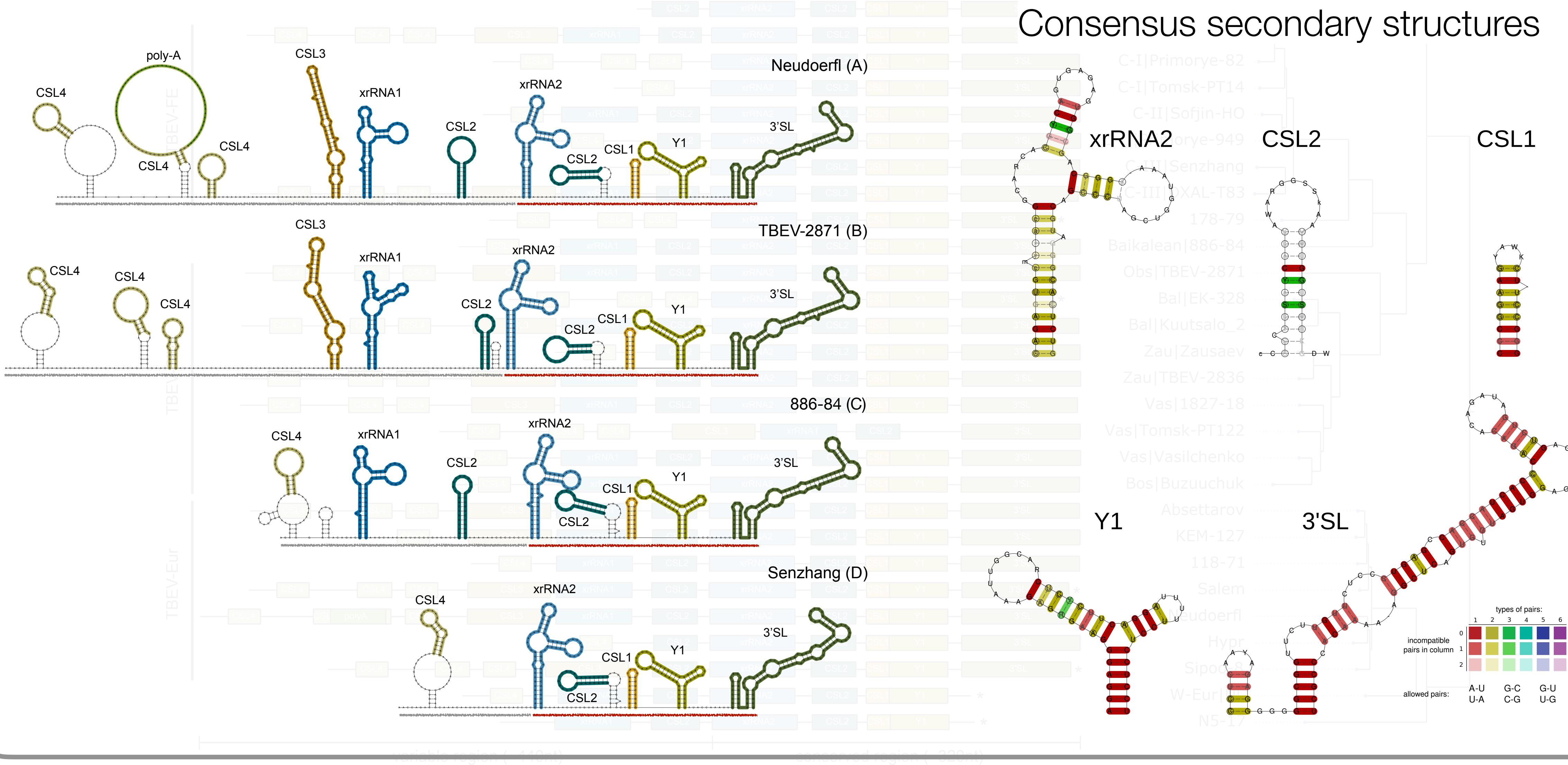
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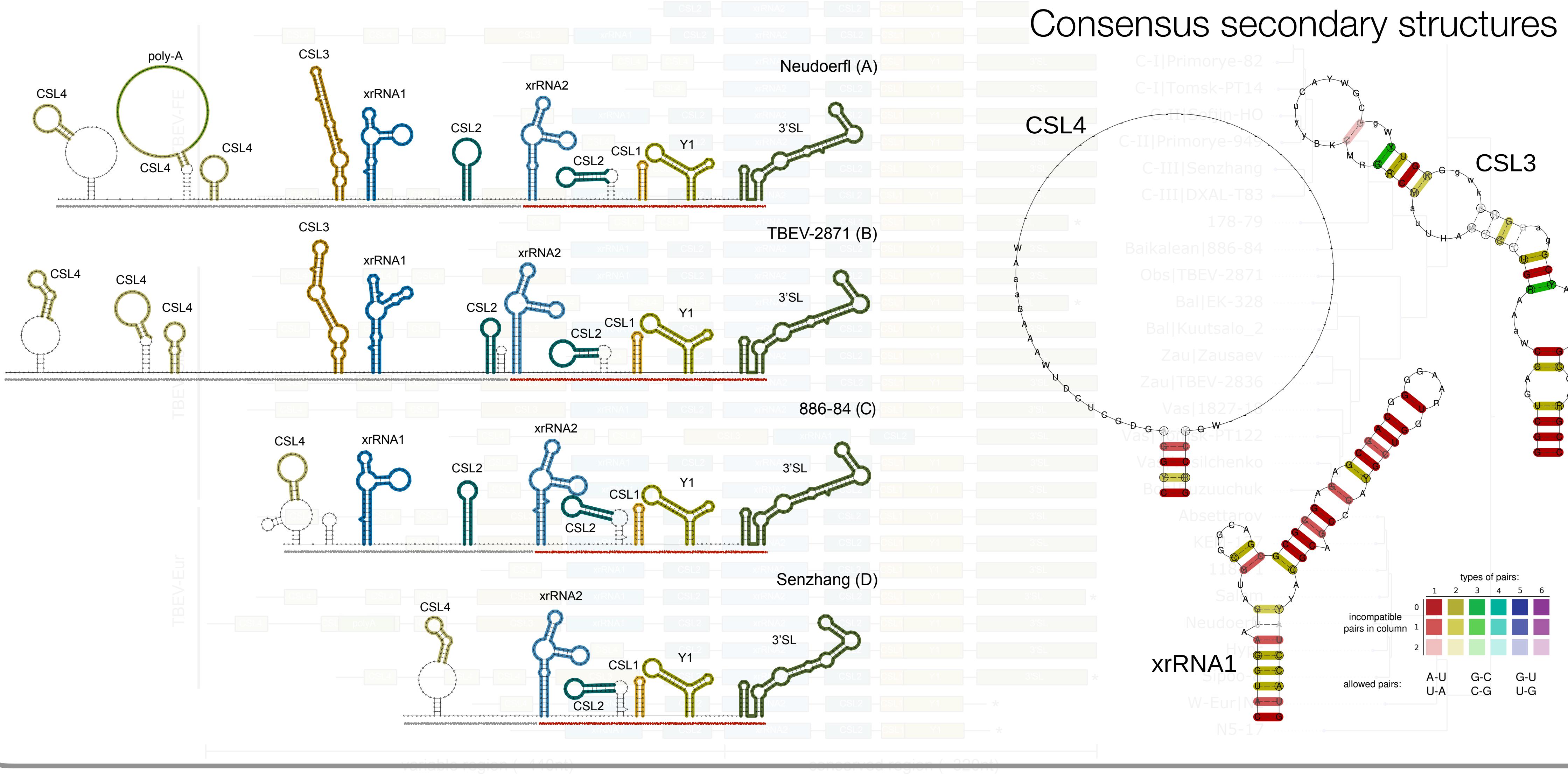
Conserved RNA elements in TBEV 3'UTRs



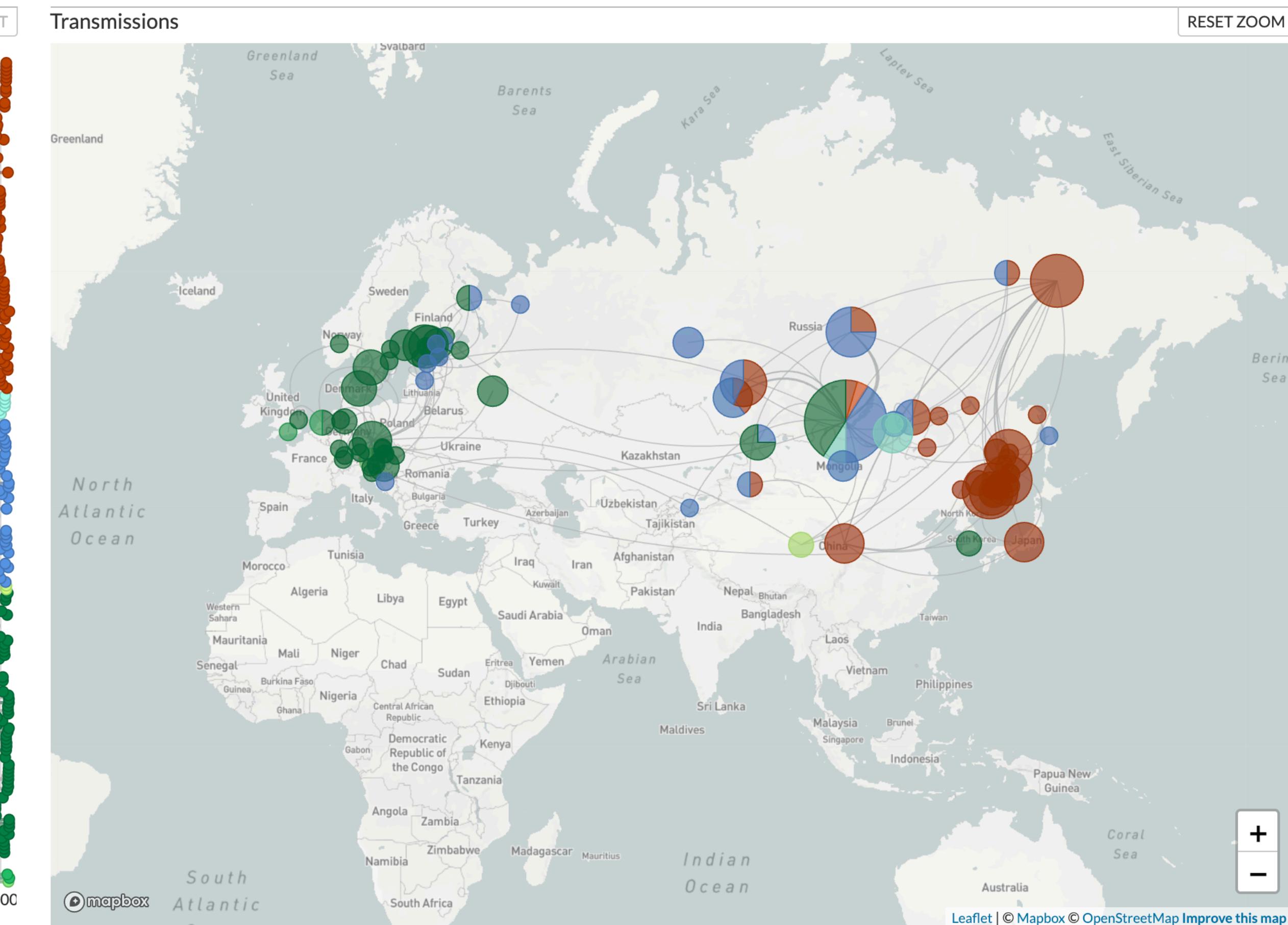
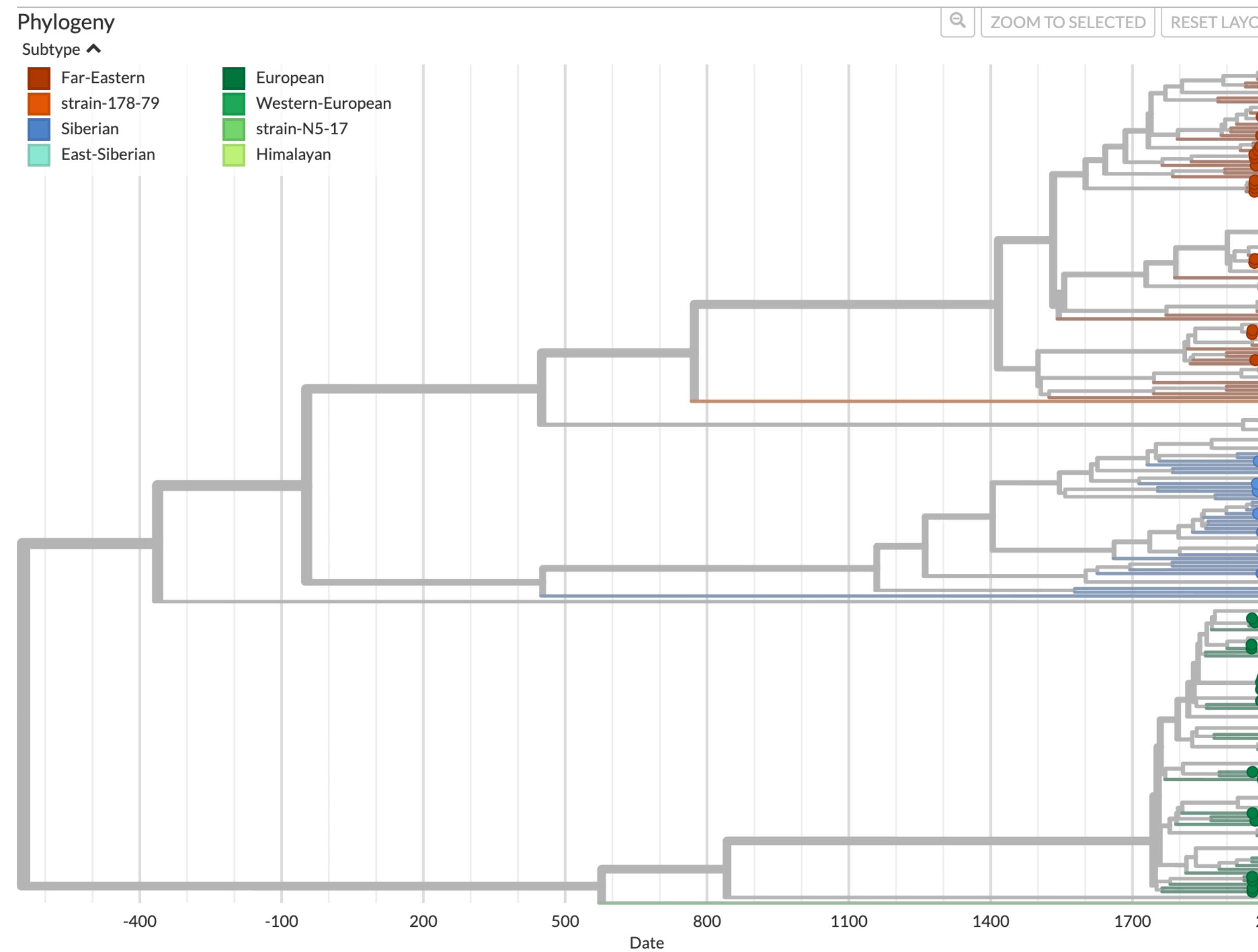
TBEV 3'UTR: Conserved region elements



TBEV 3'UTR: Variable region elements



TBEV molecular epidemiology



<https://nextstrain.org/groups/ViennaRNA/TBEVnext>

Summary

- The **ViennaRNA** Package provides efficient implementations for RNA structure prediction
- Structural alignments and covariance models are used to find conserved RNAs
- Pervasive conservation of functional RNA structures in TBEV 3'UTRs
- **ViennaRNA** Web Services are available at

<http://rna.tbi.univie.ac.at/>

Acknowledgements

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Lena Kutschera
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