A Maximum-Likelihood Formulation and EM Algorithm for the Protein Multiple Alignment Problem

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4. The algorithm yields the posterior distribution over the set of all multiple alignments. The most probable one of them is considered as the final result.

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Markov chain of amino acid evolution represented by transition probabilities matrix for the accepted evolutionary step

$$\mathbf{\Psi} = \left(\psi(\alpha^j | \alpha^i), \alpha^i, \alpha^j \in A \right) (20 \times 20), \ \sum_{\alpha^j \in A} \psi(\alpha^j | \alpha^i) = 1 \text{ for all } \alpha^i \in A$$

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Dayhoff's main assumptions on the Markov chain:

– ergodicity, namely, existence of a final probability distribution over A

$$\xi(\alpha^j) = \sum_{\alpha^i \in A} \xi(\alpha^i) \psi(\alpha^j | \alpha^i) \text{ for all } \alpha^j \in A$$

– reversibility, namely, invariance to time inversion

$$\xi(\alpha^i) \psi(\alpha^j | \alpha^i) = \xi(\alpha^j) \psi(\alpha^i | \alpha^j) \text{ for all } \alpha^i, \alpha^j \in A$$

Notations

$A = \left\{ \alpha^1, ..., \alpha^{20} \right\}$ – the set (alphabet) of amino acids

$\boldsymbol{\omega} = (\omega_t \in A, t = 1, ..., N_{\boldsymbol{\omega}})$ – amino acid sequence of length $N_{\boldsymbol{\omega}}$

n – an integer called the order of the multiple alignment, namely, the assumed number of common columns .

$\Omega_{\geq n}$ – the set of all amino acid sequences of length $N_{\boldsymbol{\omega}} \geq n$

Ω_n – the set of all amino acid sequences of fixed length $N_{\boldsymbol{\omega}} = n$

$\Omega^*_{\geq n} = \left\{ \boldsymbol{\omega}_j, N_j \geq n, \ j = 1, ..., M \right\}$ – the given finite set of amino acid sequences to be aligned

Hypothesis 1

Each sequence in $\boldsymbol{\omega}_j = (\omega_{jt} \in A, t = 1, \ldots, N_j \geq n) \in \Omega^*_{\geq n}$ has evolved from a specific ancestor $\boldsymbol{\vartheta}_j = (\vartheta_{ji} \in A, i = 1, \ldots, n) \in \Omega_n$ through independent known random transformation $\varphi_{N_j}(\boldsymbol{\omega} \mid \boldsymbol{\vartheta}_j)$, $\sum_{\boldsymbol{\omega} \in \Omega_{N_j}} \varphi_{N_j}(\boldsymbol{\omega} \mid \boldsymbol{\vartheta}_j) = 1$.

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Hypothesis 2

The length n of the random ancestors $\boldsymbol{\vartheta}_j \in \Omega_n$ is fixed, and their elements $(\vartheta_{j1},..., \vartheta_{jn})$ are drawn from the amino acid alphabet A in accordance with a common sequence of independent probability distributions

$$\left(\beta_i(\vartheta), i = 1,..., n\right),\ \vartheta \in A,\ \sum_{\vartheta \in A} \beta(\vartheta) = 1.$$

The sequence of these distributions forms a probabilistic profile of the “fuzzy” common ancestor

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For the accepted family of transformation distributions $\varphi_{N_j}(\boldsymbol{\omega} \mid \boldsymbol{\vartheta}_j)$, it is required to estimate the common probabilistic profile $\overline{\boldsymbol{\beta}} = \left(\boldsymbol{\beta}_i \in \mathbb{R}^{20}, i = 1,..., n\right)$ of the preset length n.

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The final multiple alignment

Combination of individual pair-wise alignments of the given sequences with the found common profile.

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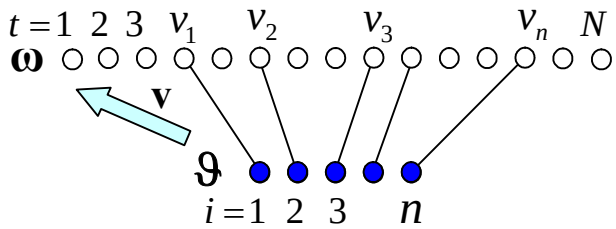
1. Random structure of the transformation: Unilateral alignment of the ancestor to the resulting sequence  	$\mathbf{v}=(v_1,\ldots,v_n)\in\mathbb{V}_{N\|n}$, $v_n\le N$ A preset probability distribution: $q_{N\|n}(\mathbf{v})=q_{N\|n}(v_1,\ldots,v_n)$

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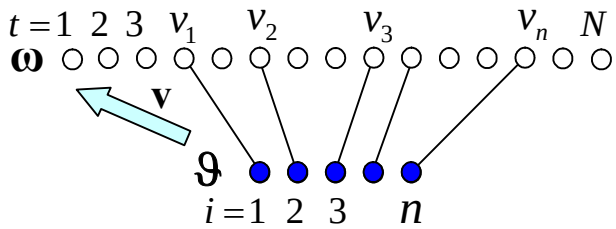
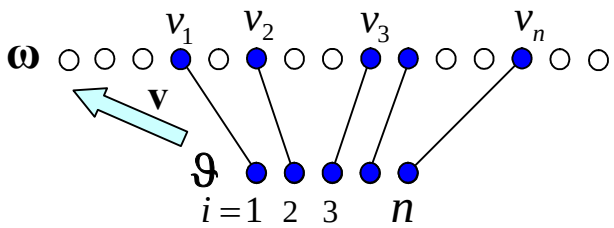
1. Random structure of the transformation: Unilateral alignment of the ancestor to the resulting sequence  	$\mathbf{v}=(v_1,\ldots,v_n)\in\mathbb{V}_{N\mid n},\quad v_n\le N$ A preset probability distribution: $q_{N\mid n}(\mathbf{v})=q_{N\mid n}(v_1,\ldots,v_n)$
2. Random key subsequence  	$\bar{\boldsymbol{\omega}}_{\mathbf{v}}=(\omega_{v_1},\ldots,\omega_{v_n}),$ $\eta_n(\bar{\boldsymbol{\omega}}_{\mathbf{v}}\mid\vartheta,\mathbf{v})=\prod_{i=1}^{n}\underbrace{\psi(\omega_{v_i}\mid\vartheta_i)}_{\text{Dayhoff's conditional probabilities}}$

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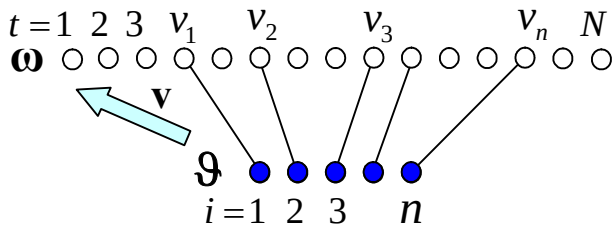
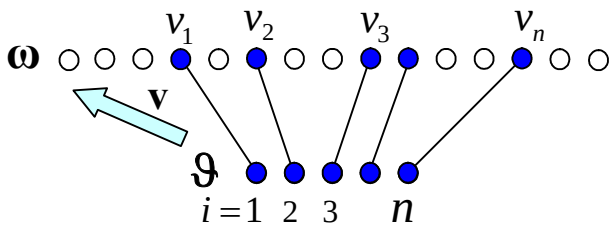
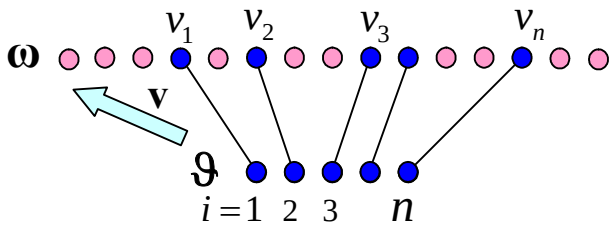
1. Random structure of the transformation: Unilateral alignment of the ancestor to the resulting sequence  	$\mathbf{v}=(v_1,\ldots,v_n)\in\mathbb{V}_{N\mid n},\quad v_n\le N$ A preset probability distribution: $q_{N\mid n}(\mathbf{v})=q_{N\mid n}(v_1,\ldots,v_n)$
2. Random key subsequence  	$\bar{\boldsymbol{\omega}}_{\mathbf{v}}=(\omega_{v_1},\ldots,\omega_{v_n}),$ $\eta_n(\bar{\boldsymbol{\omega}}_{\mathbf{v}}\mid\vartheta,\mathbf{v})=\prod_{i=1}^{n}\underbrace{\psi(\omega_{v_i}\mid\vartheta_i)}_{\text{Dayhoff's conditional probabilities}}$
3. Random additional subsequence  	Absolutely randomly drawn amino acids

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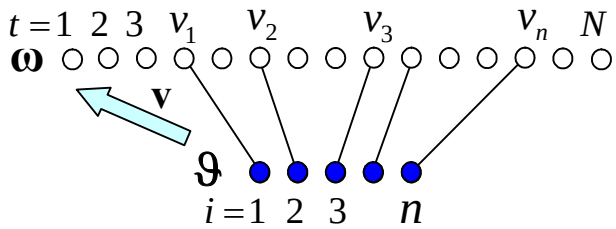
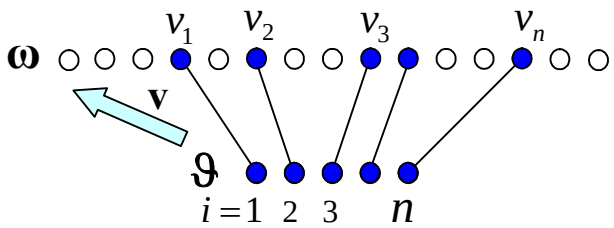
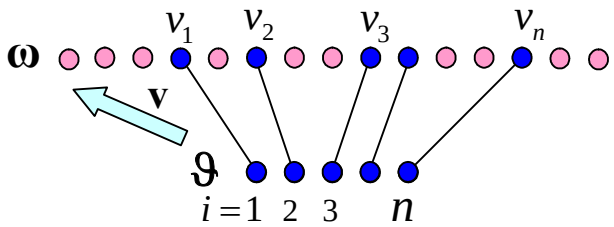
1. Random structure of the transformation: Unilateral alignment of the ancestor to the resulting sequence  	$\mathbf{v}=(v_1,\ldots,v_n)\in\mathbb{V}_{N\mid n},\quad v_n\le N$ A preset probability distribution: $q_{N\mid n}(\mathbf{v})=q_{N\mid n}(v_1,\ldots,v_n)$
2. Random key subsequence  	$\bar{\boldsymbol{\omega}}_{\mathbf{v}}=(\omega_{v_1},\ldots,\omega_{v_n}),$ $\eta_n(\bar{\boldsymbol{\omega}}_{\mathbf{v}}\mid\vartheta,\mathbf{v})=\prod_{i=1}^{n}\underbrace{\psi(\omega_{v_i}\mid\vartheta_i)}_{\text{Dayhoff's conditional probabilities}}$
3. Random additional subsequence  	Absolutely randomly drawn amino acids
All in all, we have the resulting parametric conditional distribution family of a single protein in terms of the unknown common probabilistic profile: $\zeta_{N\mid n}(\boldsymbol{\omega}\mid\bar{\boldsymbol{\beta}},\mathbf{v})$	

Maximum-likelihood estimation of the common profile

The general scenario once again:

$\Omega^*_{\geq n} = \left\{ \boldsymbol{\omega}_j,\ N_j \geq n,\ j = 1,\ldots,M \right\}$ – the given finite set of amino acid sequences independently generated from the unknown probabilistic profile $\overline{\boldsymbol{\beta}} = \left(\boldsymbol{\beta}_i \in \mathbb{R}^{20},\ i = 1,\ldots,n \right)$ to be estimated.

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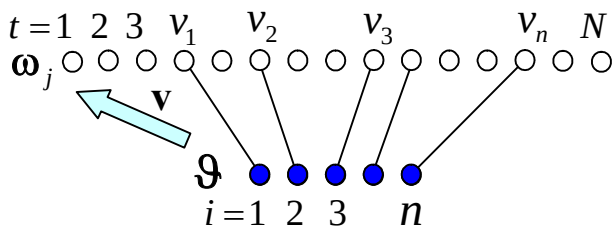
Random structure of the transformation: Unilateral alignment of the ancestor to the resulting sequence  	$\mathbf{v}_j = (v_{j,1},\ldots,v_{j,n}) \in \mathbb{V}_{N_j\|n},\ \ v_n \leq N_j$ A preset probability distribution: $q_{N\|n}(\mathbf{v}) = q_{N\|n}(v_1,\ldots,v_n)$

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Let $\overline{\boldsymbol{\beta}}_s = (\boldsymbol{\beta}_{1,s},\ldots,\boldsymbol{\beta}_{n,s})$ be approximation to the solution at step s. Then, the a posteriori probabilities of the events $\mathbf{v}_{j,i} = t$ are completely defined: $p_{it}(\overline{\boldsymbol{\beta}}_s, \boldsymbol{\omega}_j) = P(v_{j,i} = t \mid \overline{\boldsymbol{\beta}}_s, \boldsymbol{\omega}_j)$

Maximum-likelihood estimation of the common profile

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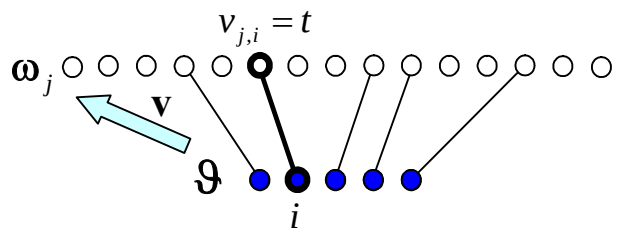

$\mathbf{v}_j = (v_{j,1},\ldots,v_{j,n}) \in \mathbb{V}_{N_j|n},\quad v_{j,n} \leq N_j$

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Theorem. This choice provides that the inequality $F(\Omega^*_{\geq n} \mid \overline{\boldsymbol{\beta}}_{s+1}) > F(\Omega^*_{\geq n} \mid \overline{\boldsymbol{\beta}}_s)$ holds true at each step s while $\nabla_{\overline{\boldsymbol{\beta}}} F(\Omega^*_{\geq n} \mid \overline{\boldsymbol{\beta}}_s) \neq \mathbf{0}$; if $\nabla_{\overline{\boldsymbol{\beta}}} F(\Omega^*_{\geq n} \mid \overline{\boldsymbol{\beta}}_s) = \mathbf{0}$ then $F(\Omega^*_{\geq n} \mid \overline{\boldsymbol{\beta}}_{s+1}) = F(\Omega^*_{\geq n} \mid \overline{\boldsymbol{\beta}}_s)$.

Choosing the length of the common profile

Each of n columns in the common profile is a probability distribution over the amino acid alphabet.
The idea: The most appropriate n must provide the minimum average entropy of these distribution:

$$\hat{n} = \arg\min_{n} \left(-\frac{1}{n} \sum_{i=1}^{n} \sum_{k=1}^{20} \beta_i^k \ln \beta_i^k \right)$$

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The n-column profile $\hat{\bar{\beta}}$ found as the maximum-likelihood estimate:

$$\hat{\bar{\beta}} = \arg\max_{\bar{\beta}} \ln F(\Omega^*_{\geq n} \mid \bar{\beta})$$

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For each protein $j = 1,\ldots,M$, this is a standard dynamic programming problem.

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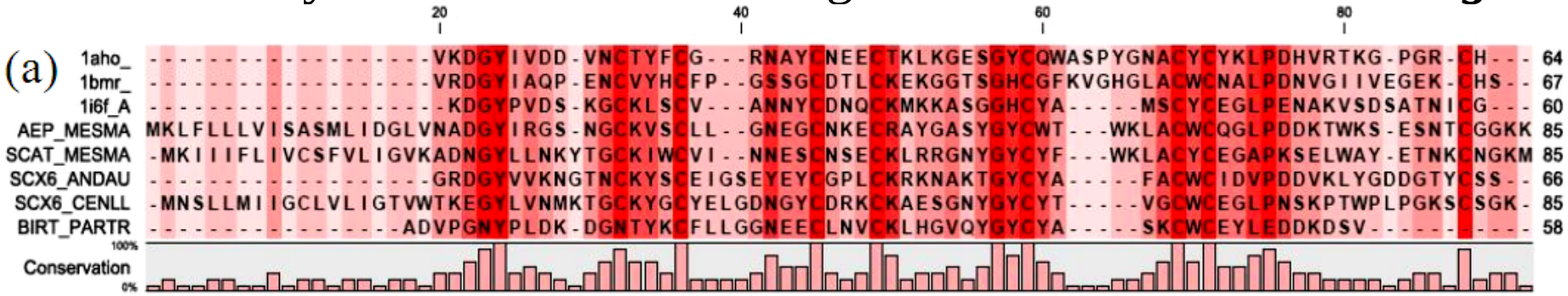

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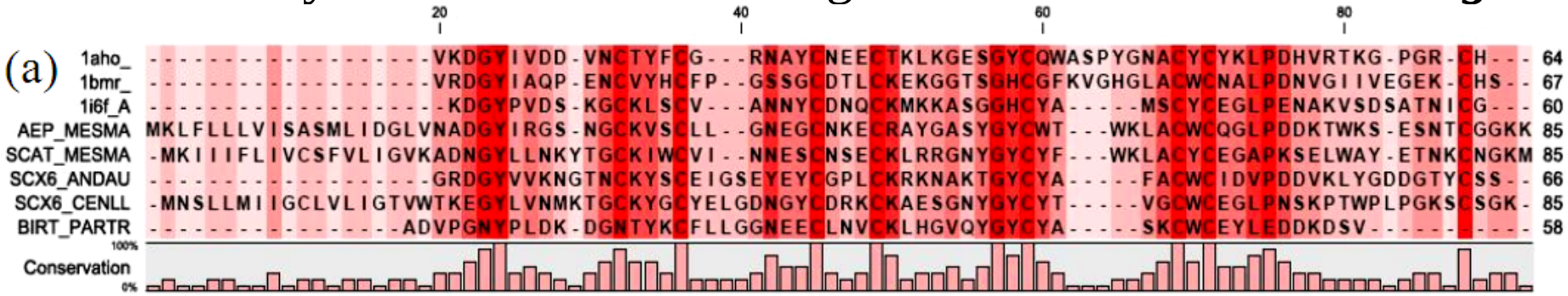

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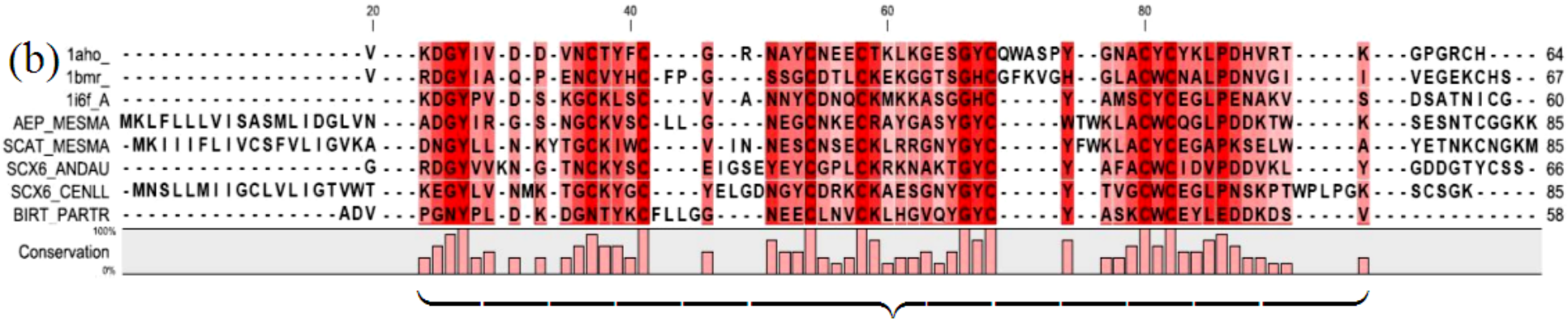

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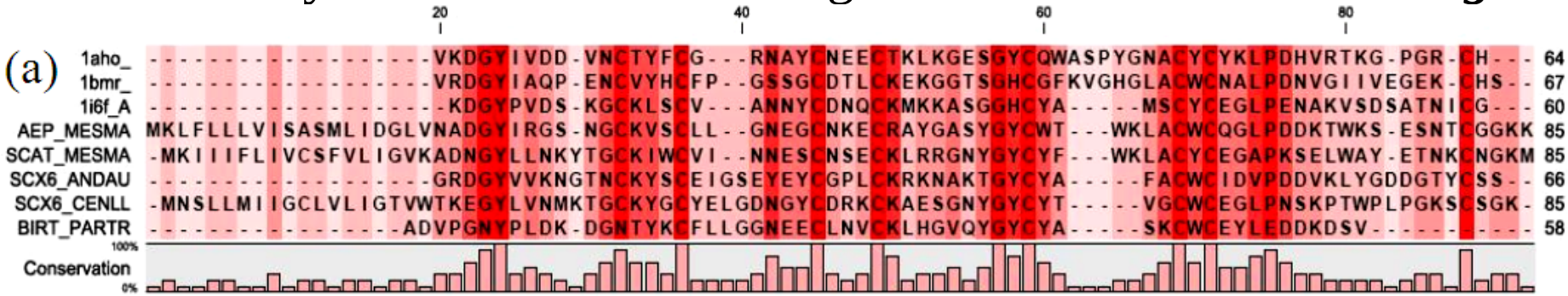

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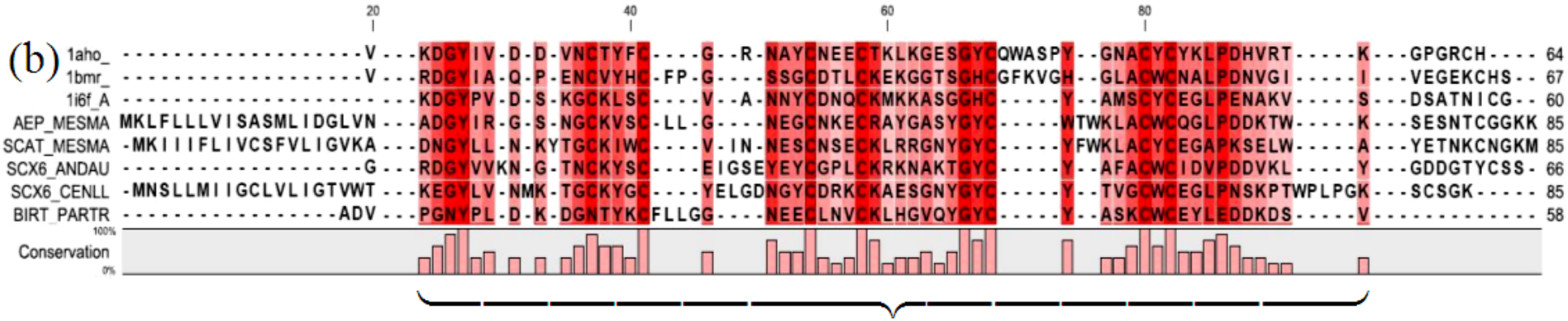

- Prediction accuracy assessment:
  - **SP** – sum of pairs score,
  - **TC** – total column score.

Experimental comparison of multiple alignment procedures in BAliBase 3.0

Set	Family	CLUSTALW	DIALIGN	ProbAlign	The proposed approach
RV11	1aab	0.92/0.96	0.91/0.93	0.83/0.87	**0.99/0.99**
	1aboA	0.00/0.38	0.00/0.00	0.00/**0.54**	0.00/0.45
	1bbt3	0.00/0.20	0.00/0.00	**0.29/0.42**	0.28/0.36
	1csy	0.37/0.42	0.31/0.37	0.46/0.56	**0.51/0.56**
	1dox	0.00/0.24	0.40/0.46	0.62/0.71	**0.64/0.75**
RV12	1axo	0.29/0.54	0.54/0.64	0.69/0.87	**0.87/0.93**
	1fj1A	**1.00/1.00**	0.69/0.76	0.79/0.84	**1.00/1.00**
	1hfh	0.68/0.78	0.39/0.53	**0.78/0.85**	0.75/**0.85**
	1hpi	0.59/0.72	0.37/0.57	0.40/0.55	**0.75/0.82**
	1krn	0.53/0.69	0.47/0.68	0.60/0.75	**0.79/0.88**
RV20	1idy	0.00/**0.62**	0.00/0.00	0.00/0.33	0.00/0.60
	1pamA	0.43/0.77	0.29/0.58	**0.74/0.84**	0.69/0.83
	1pgtA	**0.47**/0.49	0.14/0.52	0.26/**0.69**	0.27/0.68
	1tvxA	0.00/**0.64**	0.00/0.00	0.00/0.41	0.00/0.46
	1ubi	0.00/**0.68**	0.00/0.03	**0.09**/0.49	0.08/0.48
	mean	0.35/0.61	0.30/0.41	0.44/0.65	**0.51/0.71**

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Statistics of comparing the proposed approach with ProbAlign

	TC / SP
The number of cases when our proposed approach is better or equal	11(73%) / 10(67%)
The mean increment of scores	0.112 / 0.127
The mean percentage increment of scores	23% / 21%
The mean decrement of scores	0.025 / 0.036
The mean percentage decrement of scores	6% / 7.1%

Conclusions

- The proposed formal approach to multiple alignment is based on a deliberately simplified model of protein evolution.
- The iterative procedure of solving the respective optimization problem is based on the well-known EM algorithm.
- The first experiments have shown that this approach outperforms, in average, other methods of multiple alignment by mean values of TC and SP scores.
- It does not yield the best scores for all considered cases, but as a rule, our method shows small decreasing and large increasing of scores in comparison to other methods.