

Insert title

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ABSTRACT

Abstract (200 words minimum)

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1 Introduction

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2 Methods

2.1 Pair Hidden Markov Model

We model a pair of RNA sequences

$$X = x_1, \dots, x_{L_X}, \quad Y = y_1, \dots, y_{L_Y},$$

over alphabet $\mathcal{A} = \{A, C, G, U\}$. Their alignment is represented by a hidden state sequence

$$Z = (z_1, \dots, z_T), \quad z_t \in \mathcal{S} = \{M, X, Y\},$$

where M denotes a match (or substitution), X an insertion in X (gap in Y), and Y an insertion in Y (gap in X).

We associate to each step t a pair of prefix indices (i_t, j_t) specifying how many characters of X and Y have been consumed. The state z_t determines which symbols are emitted and how indices advance:

$$(i_{t+1}, j_{t+1}) = \begin{cases} (i_t + 1, j_t + 1), & z_t = M, \\ (i_t + 1, j_t), & z_t = X, \\ (i_t, j_t + 1), & z_t = Y. \end{cases}$$

A path Z is valid if all characters are consumed, i.e. $(i_T, j_T) = (L_X, L_Y)$.

2.1.1 Emission model

For $z_t \in \{M, X, Y\}$ we define emission distributions

$$e_M(x, y) = P(\text{emit } (x, y) \mid z_t = M), \quad e_X(x) = P(\text{emit } x \mid z_t = X), \quad e_Y(y) = P(\text{emit } y \mid z_t = Y),$$

with normalizations $\sum_{x,y \in \mathcal{A}} e_M(x, y) = 1$, $\sum_{x \in \mathcal{A}} e_X(x) = 1$, $\sum_{y \in \mathcal{A}} e_Y(y) = 1$. At step t the emission probability is

$$e_{z_t} = \begin{cases} e_M(x_{i_t+1}, y_{j_t+1}), & z_t = M, \\ e_X(x_{i_t+1}), & z_t = X, \\ e_Y(y_{j_t+1}), & z_t = Y. \end{cases}$$

2.1.2 Start, transition, and end distributions

The HMM parameters are:

- Start distribution

$$\pi(s) = P(z_1 = s), \quad s \in \mathcal{S},$$

taken as uniform ($\pi(M) = \pi(X) = \pi(Y) = \frac{1}{3}$) unless noted.

- Transition matrix

$$a_{uv} = P(z_{t+1} = v \mid z_t = u), \quad u, v \in \mathcal{S},$$

with $\sum_v a_{uv} = 1$ and constraints $a_{XY} = a_{YX} = 0$ (no direct transitions between insert states), allowing an affine gap penalty via distinct gap-open ($M \rightarrow X/Y$) and gap-extend ($X \rightarrow X, Y \rightarrow Y$) probabilities.

- End distribution

$$\rho(s) = P(\text{end} \mid z_T = s), \quad s \in \mathcal{S}.$$

2.1.3 Joint probability and log-space parameterization

For any valid path $Z = (z_1, \dots, z_T)$,

$$P(X, Y, Z) = \pi(z_1) \left[\prod_{t=1}^{T-1} a_{z_t z_{t+1}} \right] \left[\prod_{t=1}^T e_{z_t} \right] \rho(z_T).$$

The marginal likelihood sums over all valid alignments,

$$P(X, Y) = \sum_{Z \in \mathcal{Z}(X, Y)} P(X, Y, Z),$$

where $\mathcal{Z}(X, Y)$ is the set of paths that consume both sequences.

All probabilities are represented in log-space: $\log \pi(s)$, $\log a_{uv}$, $\log \rho(s)$, $\log e_M(x, y)$, $\log e_X(x)$, $\log e_Y(y)$. Then

$$\log P(X, Y, Z) = \log \pi(z_1) + \sum_{t=1}^{T-1} \log a_{z_t z_{t+1}} + \sum_{t=1}^T \log e_{z_t} + \log \rho(z_T).$$

2.2 Parameter estimation from aligned sequences

We estimate emission and transition parameters from reference alignments. Each alignment yields strings $\tilde{X}, \tilde{Y} \in (\mathcal{A} \cup \{-\})^L$.

2.2.1 Column-wise state labeling

For each column ℓ we assign a state

$$s_\ell = \begin{cases} M & \tilde{x}_\ell \in \mathcal{A}, \tilde{y}_\ell \in \mathcal{A}, \\ X & \tilde{x}_\ell \in \mathcal{A}, \tilde{y}_\ell = -, \\ Y & \tilde{x}_\ell = -, \tilde{y}_\ell \in \mathcal{A}, \\ \emptyset & \text{otherwise (e.g. both gaps).} \end{cases}$$

Columns with $s_\ell = \emptyset$ are ignored; transitions are not propagated across them.

2.2.2 Sufficient statistics

We collect counts

$$\begin{aligned} c_M(a, b) &= \#\{\ell : s_\ell = M, \tilde{x}_\ell = a, \tilde{y}_\ell = b\}, \\ c_X(a) &= \#\{\ell : s_\ell = X, \tilde{x}_\ell = a\}, \\ c_Y(b) &= \#\{\ell : s_\ell = Y, \tilde{y}_\ell = b\}, \\ c_{\text{tr}}(u, v) &= \#\{\ell : s_\ell = u, s_{\ell+1} = v, u, v \in \mathcal{S}\}, \end{aligned}$$

skipping ℓ with $s_\ell = \emptyset$.

2.2.3 Emissions with pseudocounts

With pseudocount $\eta \geq 0$ and $\mathcal{A} = \{A, C, G, U\}$, define

$$T_M(a) = \sum_{b \in \mathcal{A}} (c_M(a, b) + \eta).$$

Then

$$e_M(a, b) = \begin{cases} \frac{c_M(a, b) + \eta}{T_M(a)}, & T_M(a) > 0, \\ \frac{1}{|\mathcal{A}|}, & T_M(a) = 0. \end{cases}$$

For insertions, with $T_X = \sum_a (c_X(a) + \eta)$ and $T_Y = \sum_b (c_Y(b) + \eta)$,

$$e_X(a) = \begin{cases} \frac{c_X(a) + \eta}{T_X}, & T_X > 0, \\ \frac{1}{|\mathcal{A}|}, & T_X = 0, \end{cases} \quad e_Y(b) = \begin{cases} \frac{c_Y(b) + \eta}{T_Y}, & T_Y > 0, \\ \frac{1}{|\mathcal{A}|}, & T_Y = 0. \end{cases}$$

In implementation we store $\log e_M, \log e_X, \log e_Y$, with zero probabilities encoded as $-\infty$.

2.2.4 Transitions and affine-gap parameters

Raw transition estimates are

$$\tilde{a}_{uv} = \begin{cases} 0, & (u, v) \in \{(X, Y), (Y, X)\}, \\ \frac{c_{\text{tr}}(u, v) + \eta}{\sum_w (c_{\text{tr}}(u, w) + \eta)}, & \text{if denominator} > 0, \\ 0, & \text{otherwise,} \end{cases}$$

followed by row-wise renormalization over allowed v (excluding $X \rightarrow Y$ and $Y \rightarrow X$) to obtain a_{uv} . Again, $\log a_{uv}$ is stored, with $-\infty$ for zero entries.

We summarize affine-gap parameters as

$$\delta = a_{MX} + a_{MY}, \quad \epsilon_X = a_{XX}, \quad \epsilon_Y = a_{YY}, \quad \epsilon = \frac{1}{2}(\epsilon_X + \epsilon_Y).$$

2.3 Forward–backward inference

We perform log-space dynamic programming on the grid $0 \leq i \leq L_X$, $0 \leq j \leq L_Y$ using tables $F_s(i, j)$ and $B_s(i, j)$ for $s \in \{M, X, Y\}$, where (i, j) encodes consumed prefixes. We use the log-sum-exp operator

$$\text{LSE}(v_1, \dots, v_k) = \log \left(\sum_{m=1}^k e^{v_m} \right)$$

for stable accumulation.

2.3.1 Forward recursion

Initialize all $F_s(i, j) = -\infty$. The first emissions are

$$F_X(1, 0) = \log \pi(X) + \log e_X(x_1), \quad F_Y(0, 1) = \log \pi(Y) + \log e_Y(y_1), \quad F_M(1, 1) = \log \pi(M) + \log e_M(x_1, y_1),$$

if the corresponding indices are in range.

For $1 \leq i \leq L_X$, $1 \leq j \leq L_Y$, the recurrences (omitting impossible moves) are

$$\begin{aligned} F_M(i, j) &= \text{LSE}\left(F_M(i-1, j-1) + \log a_{MM}, F_X(i-1, j-1) + \log a_{XM}, F_Y(i-1, j-1) + \log a_{YM}\right) + \log e_M(x_i, y_j), \\ F_X(i, j) &= \text{LSE}\left(F_M(i-1, j) + \log a_{MX}, F_X(i-1, j) + \log a_{XX}\right) + \log e_X(x_i), \\ F_Y(i, j) &= \text{LSE}\left(F_M(i, j-1) + \log a_{MY}, F_Y(i, j-1) + \log a_{YY}\right) + \log e_Y(y_j). \end{aligned}$$

The forward log-partition is

$$\log Z_f = \text{LSE}(F_M(L_X, L_Y) + \log \rho(M), F_X(L_X, L_Y) + \log \rho(X), F_Y(L_X, L_Y) + \log \rho(Y)).$$

2.3.2 Backward recursion

Initialize all $B_s(i, j) = -\infty$ and at (L_X, L_Y) set

$$B_M(L_X, L_Y) = \log \rho(M), \quad B_X(L_X, L_Y) = \log \rho(X), \quad B_Y(L_X, L_Y) = \log \rho(Y).$$

For $0 \leq i \leq L_X$, $0 \leq j \leq L_Y$, let $\mathbf{1}[\cdot]$ denote an indicator and include only in-bounds moves. Then

$$\begin{aligned} B_M(i, j) &= \text{LSE}\left(\mathbf{1}[i < L_X, j < L_Y](\log a_{MM} + \log e_M(x_{i+1}, y_{j+1}) + B_M(i+1, j+1)), \right. \\ &\quad \mathbf{1}[i < L_X](\log a_{MX} + \log e_X(x_{i+1}) + B_X(i+1, j)), \\ &\quad \left. \mathbf{1}[j < L_Y](\log a_{MY} + \log e_Y(y_{j+1}) + B_Y(i, j+1))\right), \end{aligned}$$

$$\begin{aligned} B_X(i, j) &= \text{LSE}\left(\mathbf{1}[i < L_X, j < L_Y](\log a_{XM} + \log e_M(x_{i+1}, y_{j+1}) + B_M(i+1, j+1)), \right. \\ &\quad \mathbf{1}[i < L_X](\log a_{XX} + \log e_X(x_{i+1}) + B_X(i+1, j)) \Big), \end{aligned}$$

$$\begin{aligned} B_Y(i, j) &= \text{LSE}\left(\mathbf{1}[i < L_X, j < L_Y](\log a_{YM} + \log e_M(x_{i+1}, y_{j+1}) + B_M(i+1, j+1)), \right. \\ &\quad \left. \mathbf{1}[j < L_Y](\log a_{YY} + \log e_Y(y_{j+1}) + B_Y(i, j+1))\right), \end{aligned}$$

using $a_{XY} = a_{YX} = 0$. The backward log-partition is

$$\log Z_b = \text{LSE}(\log \pi(M) + \log e_M(x_1, y_1) + B_M(1, 1), \log \pi(X) + \log e_X(x_1) + B_X(1, 0), \log \pi(Y) + \log e_Y(y_1) + B_Y(0, 1)).$$

We use $\log Z = \frac{1}{2}(\log Z_f + \log Z_b)$ as a numerically stable estimate of $\log P(X, Y)$.

2.4 Viterbi decoding (MAP alignment)

The maximum a posteriori alignment is

$$Z^* = \arg \max_{Z \in \mathcal{Z}(X, Y)} P(X, Y, Z) = \arg \max_{Z \in \mathcal{Z}(X, Y)} \log P(X, Y, Z).$$

2.4.1 Dynamic programming

For $0 \leq i \leq L_X$, $0 \leq j \leq L_Y$ and $s \in \{M, X, Y\}$ define

$$V_{i,j}^s = \max_{Z: (i_T, j_T) = (i, j), z_T = s} \log P(X_{1:i}, Y_{1:j}, Z),$$

with $V_{i,j}^s = -\infty$ if no such path exists.

Initialization at $(0, 0)$ is $V_{0,0}^M = V_{0,0}^X = V_{0,0}^Y = -\infty$. First non-empty cells:

$$V_{1,0}^X = \log \pi(X) + \log e_X(x_1), \quad V_{0,1}^Y = \log \pi(Y) + \log e_Y(y_1), \quad V_{1,1}^M = \log \pi(M) + \log e_M(x_1, y_1).$$

Leading gaps are filled via

$$\begin{aligned} V_{i,0}^X &= \log e_X(x_i) + \max\{V_{i-1,0}^M + \log a_{MX}, V_{i-1,0}^X + \log a_{XX}\}, \quad i = 2, \dots, L_X, \\ V_{0,j}^Y &= \log e_Y(y_j) + \max\{V_{0,j-1}^M + \log a_{MY}, V_{0,j-1}^Y + \log a_{YY}\}, \quad j = 2, \dots, L_Y. \end{aligned}$$

For $1 \leq i \leq L_X$, $1 \leq j \leq L_Y$:

$$\begin{aligned} V_{i,j}^M &= \log e_M(x_i, y_j) + \max\{V_{i-1,j-1}^M + \log a_{MM}, V_{i-1,j-1}^X + \log a_{XM}, V_{i-1,j-1}^Y + \log a_{YM}\}, \\ V_{i,j}^X &= \log e_X(x_i) + \max\{V_{i-1,j}^M + \log a_{MX}, V_{i-1,j}^X + \log a_{XX}\}, \\ V_{i,j}^Y &= \log e_Y(y_j) + \max\{V_{i,j-1}^M + \log a_{MY}, V_{i,j-1}^Y + \log a_{YY}\}. \end{aligned}$$

2.4.2 Termination and traceback

At (L_X, L_Y) we add end probabilities:

$$\ell^* = \max_{s \in \{M, X, Y\}} (V_{L_X, L_Y}^s + \log \rho(s)),$$

with optimal final state

$$s^* = \arg \max_{s \in \{M, X, Y\}} (V_{L_X, L_Y}^s + \log \rho(s)).$$

We store backpointers during the DP and trace back from (L_X, L_Y, s^*) to $(0, 0)$, then reverse the sequence of moves to recover the optimal alignment.

2.5 Maximum expected accuracy (MEA) alignment

We also compute an alignment that maximizes the expected number of correctly aligned nucleotide pairs under the posterior over paths.

2.5.1 Posterior match probabilities

For $1 \leq i \leq L_X$, $1 \leq j \leq L_Y$, let $M_{ij} = 1$ if x_i is aligned to y_j in state M along some path, and define

$$P_{ij} = P(M_{ij} = 1 \mid X, Y).$$

Using forward and backward probabilities restricted to the match state,

$$P_{ij} = \frac{\alpha_M(i, j) \beta_M(i, j)}{P(X, Y)},$$

where $\alpha_M(i, j)$ is the forward probability of being in M aligning (x_i, y_j) , $\beta_M(i, j)$ is the corresponding backward probability, and $P(X, Y)$ is the marginal likelihood. We arrange P_{ij} in a matrix $P \in [0, 1]^{(L_X+1) \times (L_Y+1)}$ with $P[0, \cdot] = P[\cdot, 0] = 0$.

2.5.2 Objective and weighting

An alignment A is a set of index pairs $A \subseteq \{1, \dots, L_X\} \times \{1, \dots, L_Y\}$, where $(i, j) \in A$ iff x_i is aligned to y_j . Its expected accuracy is

$$\mathbb{E}[\text{acc}(A) | X, Y] = \sum_{(i,j) \in A} P_{ij}.$$

We introduce weights $w_{ij} = f(P_{ij}; \gamma)$ and maximize

$$A^* = \arg \max_A \sum_{(i,j) \in A} w_{ij}.$$

Examples of f include:

- Power ($\gamma > 0$): $w_{ij} = P_{ij}^\gamma$,
- Threshold ($\gamma \in (0, 1]$): $w_{ij} = P_{ij} - (1 - \gamma)$,
- ProbCons-style ($\gamma > 0.5$): $w_{ij} = 2\gamma P_{ij} - 1$,
- Log-odds ($\gamma \in (0, 1)$):

$$w_{ij} = \log \frac{P_{ij}}{1 - P_{ij}} + \log \frac{\gamma}{1 - \gamma}.$$

Let W be the matrix with entries $W[i, j] = w_{ij}$ and $W[0, \cdot] = W[\cdot, 0] = 0$.

2.5.3 Dynamic programming and reconstruction

We view MEA alignment as a maximum-weight path on the grid $\{0, \dots, L_X\} \times \{0, \dots, L_Y\}$: diagonal steps align (x_i, y_j) with weight $W[i, j]$, and horizontal/vertical steps are gaps with weight 0.

Let $D(i, j)$ be the maximum total weight for prefixes $x_{1:i}, y_{1:j}$, with

$$D(0, 0) = 0, \quad D(i, 0) = 0, \quad D(0, j) = 0.$$

For $1 \leq i \leq L_X, 1 \leq j \leq L_Y$,

$$D(i, j) = \max\{D(i - 1, j - 1) + W[i, j], D(i - 1, j), D(i, j - 1)\}.$$

The MEA score is $D(L_X, L_Y)$. Storing the maximizing move (diagonal/up/left) at each cell and tracing back from (L_X, L_Y) to $(0, 0)$ yields the MEA alignment.

3 Results

3.1 Synthetic Data

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3.2 Real Data

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4 Discussion

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References

Figures

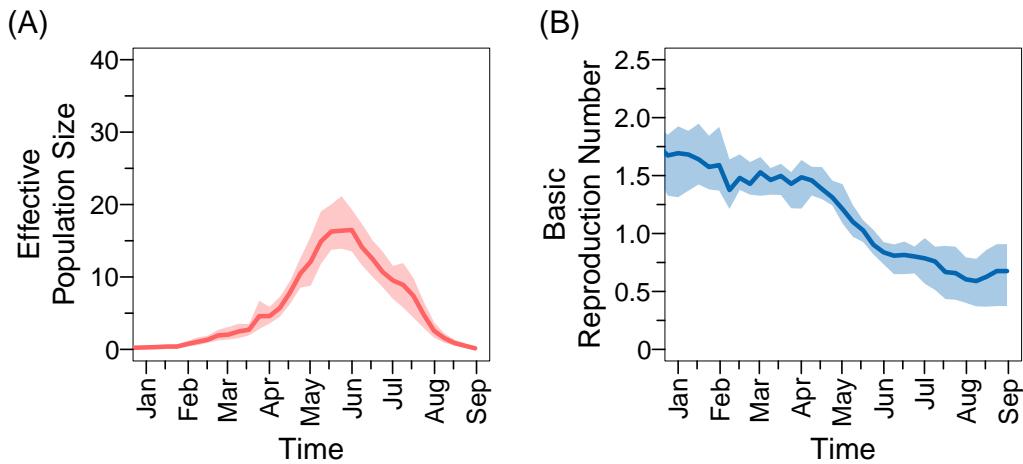


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Tables

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Algorithms