Motif Finding in DNA Sequences

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Our goal is to build a simple model which let's us identify "motifs" in DNA sequences. As input we are given a size k sample of sequences $x_i = (x_{i1}, x_{i2}, \ldots, x_{iw})$ (of length w, $i = 1, 2, \ldots, k$), where each x_{in} is one of four bases $\{A, C, G, T\}$, which we will identify respectively with $\{1, 2, 3, 4\}$.

The model assumes that the n-th term in a sequence is a random variable that follows the distribution $\theta_n = (\theta_{1n}, \theta_{2n}, \theta_{3n}, \theta_{4n})^T$, where

$$P(X_{in} = j) = \theta_{jn},$$

and obviously $\sum_{j=1}^{4} \theta_{jn} = 1$. The matrix $\theta = (\theta_1, \theta_2, \ldots, \theta_w)$ is called the position weight matrix of the motif distribution.
We also define a single separate background distribution $\theta^b = (\theta^b_1, \theta^b_2, \theta^b_3, \theta^b_4)^T$, where

$$P(X_{in} = j) = \theta^b_j,$$

meaning that the distribution is not dependent on n.

The model

Model assumption is that whether vector (sequence) X_i is generated from the motif or background distribution depends on the realisation of a latent variable $Z_i \in \{0, 1\}$, such that

$$P(Z_i = 0) = 1 - \alpha, \quad P(Z_i = 1) = \alpha,$$

where if $z_i = 1$, the sequence comes from the motif distribution, and if $z_i = 0$ - the background distribution is used. The variables Z_i are, of course, not observed.

We aim to estimate $\Theta = (\theta, \theta^b)$ (assume α is known), using the EM algorithm:

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Input: Matrix $X_{k \times k}$ with observations as rows
1 Initialise $\Theta^{(0)}$, set $t \leftarrow 0$.
2 E-step: For each observation $i = 1, \dots, k$ and class $j = 1, \dots, M$ calculate
      $Q_i^{(t)}(j) = P(Z_i = j | X; \Theta^{(t)})$.
3 M-step: Define
      $Q(\Theta, \Theta^{(t)}) := \sum_{i=1}^{k} \sum_{j=1}^{M} Q_i^{(t)}(j) \log P(x_i, Z_i = j; \Theta)$,
  maximise and update:
      $\Theta^{(t+1)} \leftarrow \arg\max_{\Theta} Q(\Theta, \Theta^{(t)})$.
4 If difference between $\Theta^{(t)}, \Theta^{(t+1)}$ small enough, $\hat{\Theta} \leftarrow \Theta^{(t+1)}$, and stop. Otherwise, $t \leftarrow t + 1$ and go to
  step 2.
Result: Estimate $\hat{\Theta}$
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Algorithm 1: Expectation Maximisation

E-step details

In our model, the values Q calculated in t-th E-step are

$$Q_i^{(t)}(0) = P(Z_i = 0 | x_i; \Theta^{(t)}) = \frac{P(Z_i = 0, x_i; \Theta^{(t)})}{P(x_i; \Theta^{(t)})} = \frac{P(x_i | Z_i = 0; \Theta^{(t)}) P(Z_i = 0; \Theta^{(t)})}{P(x_i; \Theta^{(t)})} = \frac{(1 - \alpha) \prod_{j=1}^{w} \theta_{x_{ij}}^{b,t}}{P(x_i; \Theta^{(t)})},$$

$$Q_i^{(t)}(1) = \frac{\alpha \prod_{j=1}^{w} \theta_{x_{ij}j}^{t}}{P(x_i; \Theta^{(t)})},$$

where of course $P(x_i, \Theta^{(t)}) = P(x_i | Z_i = 0; \Theta^{(t)}) + P(x_i | Z_i = 1; \Theta^{(t)}) = \prod_{j=1}^{w} \theta_{x_{ij}}^{b,t} + \prod_{j=1}^{w} \theta_{x_{ij}j}^{t}$.

M-step details

In the M-step we maximise the function Q defined as

$$Q(\Theta, \Theta^{(t)}) = \sum_{i=1}^{k} \sum_{j=0}^{1} Q_i^{(t)}(j) \log P(x_i, Z_i = j; \Theta),$$

with respect to Θ. It can be rewritten as follows

$$Q(\Theta, \Theta^{(t)}) = \sum_{i=1}^{k} Q_i^{(t)}(0) \log P(x_i, Z_i = 0; \Theta) + \sum_{i=1}^{k} Q_i^{(t)}(1) \log P(x_i, Z_i = 1; \Theta) =$$

$$= \sum_{i=1}^{k} Q_i^{(t)}(0) \log((1 - \alpha) \prod_{j=1}^{w} \theta_{x_{ij}}^{b}) + \sum_{i=1}^{k} Q_i^{(t)}(1) \log(\alpha \prod_{i=1}^{w} \theta_{x_{ij}j}).$$

The first sum is a function of θ^b only, and the second one - of θ, which means that to maximise $Q(\Theta, \Theta^{(t)})$ is to maximise each sum individually.

Consider the first sum $Q_1(\theta^b)$ dependent only on the background distribution. The task can be formulated as maximisation of $Q_q(\theta^b)$ with a single restriction

$$Q_q(\theta^b) \longrightarrow \max, \ \sum_{r=1}^{4} \theta_r^b = 1.$$

We can find extrema of the function using Lagrange's multipliers:

$$\begin{cases} L(\theta^b) = Q_1(\theta^b) - \lambda g(\theta^b) \\ g(\theta^b) = \theta_1^b + \theta_2^b + \theta_3^b + \theta_4^b - 1 \end{cases}$$

The derivative of L with respect to a set θ_r^b is

$$\frac{\partial L}{\partial \theta_r^b} = \frac{\partial}{\partial \theta_r^b}(\sum_{i=1}^{k} Q_i^{(t)}(0)(\log(1-\alpha) + \sum_{j=1}^{w} \log \theta_{x_{ij}}^b) - \lambda(\theta_1^b + \theta_2^b + \theta_3^b + \theta_4^b - 1)),$$

and since $\frac{\partial \log \theta_{x_{ij}}^b}{\partial \theta_r^b} = \begin{cases} 0, & \text{if } x_{ij} \neq r \\ \frac{1}{\theta_r^b}, & \text{if } x_{ij} = r \end{cases}$, we have

$$\frac{\partial L}{\partial \theta_r^b} = \sum_{i=1}^{k} (Q_i^{(t)}(0) \frac{1}{\theta_r^b} |\{j : x_{ij} = r\}|) - \lambda.$$

We equate the derivative to zero to get θ_r^b in closed form:

$$\theta_r^b = \frac{1}{\lambda} \sum_{i=1}^{k} Q_i^{(t)}(0) |\{j : x_{ij} = r\}|,$$

and utilising the restriction $\sum_{r=1}^{4} \theta_r^b = 1$, we also obtain $\lambda = w \sum_{i=1}^{k} Q_i^{(t)}(0)$, which concludes our search.

In similar fashion we aim to maximise $Q_2(\theta)$, dependent only on the parameters of the motif distribution. In this case, the potential solutions are subject to w restrictions

$$\begin{cases} L(\theta) = \sum_{i=1}^{k} Q_1^{(t)}(1)(\log \alpha + \sum_{j=1}^{w} \log \theta_{x_{ij}j}) - \sum_{i=1}^{w} \lambda_i g_i(\theta_i) \\ g_1(\theta_1) = \theta_{11} + \theta_{21} + \theta_{31} + \theta_{41} - 1 \\ \qquad \vdots \\ g_w(\theta_w) = \theta_{1w} + \theta_{2w} + \theta_{3w} + \theta_{4w} - 1 \end{cases}.$$

The derivative of l with respect to single θ_{rn} is

$$\frac{\partial L}{\partial \theta_{rn}} = \frac{\partial}{\partial \theta_{rn}}(\sum_{i=1}^{k} Q_i^{(t)}(1)(\log \alpha + \sum_{j=1}^{w} \log \theta_{x_{ij}j}) - \sum_{j=1}^{w} \lambda_j g_j(\theta_j)),$$

which, given $\frac{\partial \log \theta_{x_{ij}j}}{\partial \theta_{rn}} = \begin{cases} \frac{1}{\theta_{x_{in}n}}, & \text{if } j = n, x_{in} = r \\ 0, & \text{otherwise} \end{cases}$, simplifies to

$$\frac{\partial L}{\partial \theta_{rn}} = \sum_{i=1}^{k} Q_i^{(t)}(1) \frac{1}{\theta_{x_{in}n}} \mathbb{1}(x_{in} = r)) - \lambda_n.$$

Equating the derivative to zero yields:

$$\frac{\partial L}{\partial \theta_{rn}} = 0 \iff \sum_{i=1}^{k} Q_i^{(t)}(1) \frac{1}{\theta_{x_{in}n}} \mathbb{1}(x_{in} = r) = \sum_{i:\, x_{in}=r} Q_i^{(t)}(1) \frac{1}{\theta_{rn}} = \lambda_n \implies$$

$$\implies \theta_{rn} = \frac{1}{\lambda_n} \sum_{i\colon x_{in}=r} Q_i^{(t)}(1).$$

We still need λ_n to calculate the estimate. To obtain it, we use restriction $g_n(\theta_n) = \sum_{r=1}^{4} \theta_{rn} = 1$:

$$\sum_{r=1}^{4} \theta_{rn} = 1 \iff \sum_{r=1}^{4} \frac{1}{\lambda_n} \sum_{i\colon x_{in}=r} Q_i^{(t)}(1) = 1 \implies$$

$$\implies \lambda_n = \sum_{r=1}^{4} \sum_{i\colon x_{in}=r} Q_i^{(t)}(1) = \sum_{i=1}^{k} Q_i^{(t)}(1).$$

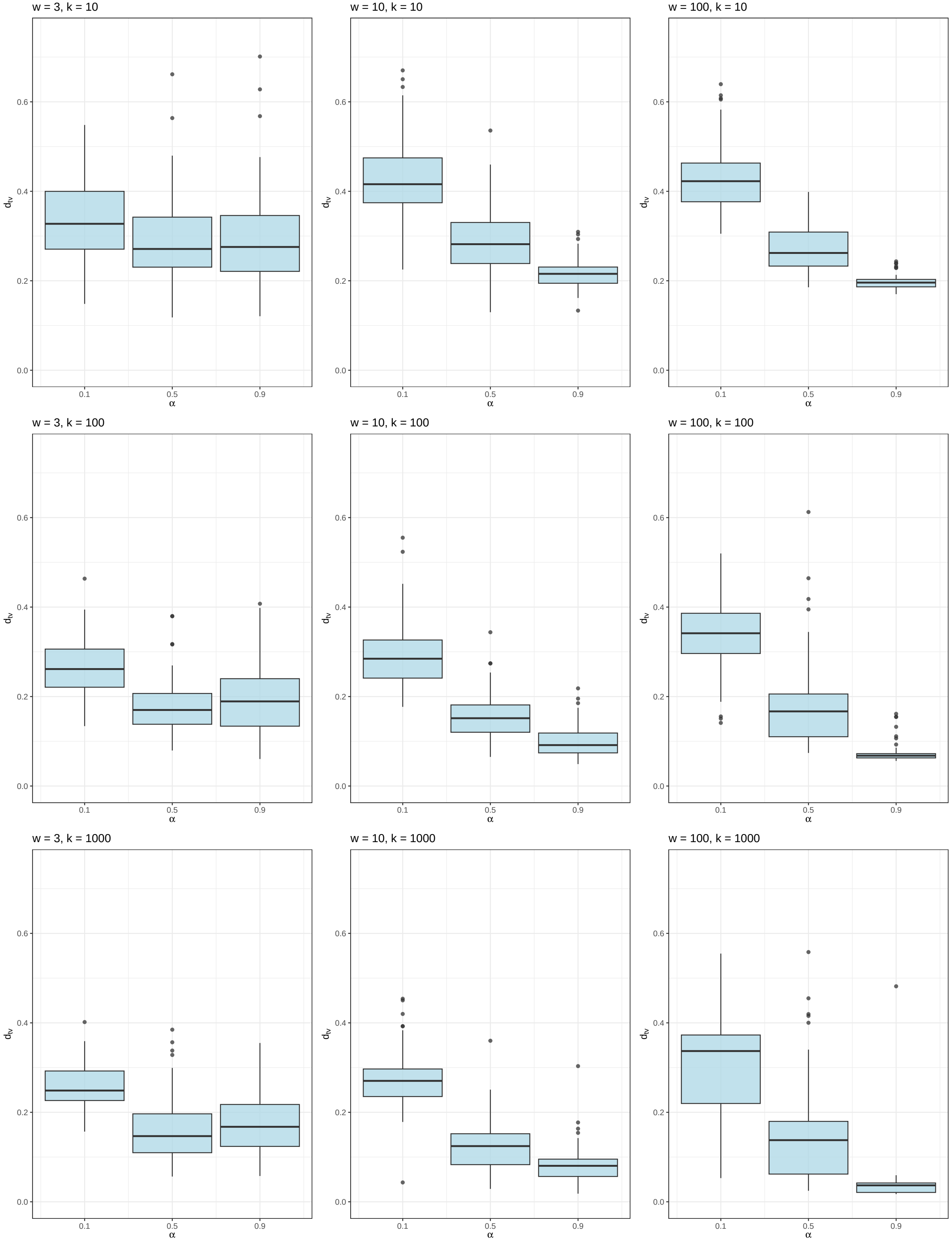
Notice that it does not depend on n ($\lambda_1 = \lambda_2 = \ldots = \lambda_w$). Having calculated λ_n we are able to evaluate θ_{rn}, which solves the problem in this step.

Algorithm performance

The program stops the algorithm, when d_{tv} between consecutive estimates reaches below 0.0001, or the number of iterations exceeds 1000. During simulations, regardless of parameters used, less than 250 iterations were always enough for convergence, excluding the outliers which went beyond 1000.

The algorithm was tested on data generated with different combinations of parameters: $w = 3, 10, 100$, $k = 10, 100, 1000$, $\alpha = 0.1, 0.5, 0.9$, with distributions generated randomly each time. Performence in terms of d_{tv} between estimates and true parameters, evaluated from 100 repetitions of the experiment for each case, in the graph below.

Boxplots of total variance distance for each combination of parameters



w = 3, k = 10

w = 10, k = 10

w = 100, k = 10

w = 3, k = 100

w = 10, k = 100

w = 100, k = 100

w = 3, k = 1000

w = 10, k = 1000

w = 100, k = 1000

In general, both larger dimensions w and sample size k positively influence the estimation, especially, when the probability α of vector being sampled from the motif distribution is high. Estimation yields worse results when α is small, meaning very few observations were sampled from the motif distribution.