# R'HOM
# Programs to segment DNA sequences into homogeneous regions / Recherche d'HOMogénéités dans une séquence d'ADN

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## Contents

## 1 Introduction

R'HOM is a set of programs to segment a DNA sequence into a finite number of homogeneous regions. Each region can be composed of several segments. The models used are Hidden Markov Models, HMM (M1-Mk). Segment arrangement is represented by an unobservable first order Markov chain, the hidden state chain (M1). The homogeneous regions are described by different models, more precisely by k-order Markov chains (Mk). Each model has characteristic statistical properties and take into account the local composition in oligonucleotides of length k+1 of the DNA sequence.

Several iterative algorithms are proposed to, on one hand, reconstruct the hidden state chain, that is to identify and locate the homogeneous regions of a given sequence (or a set of sequences), and on the other hand, to estimate the model parameters (state and observation transitions), in order to characterize these regions. When R'HOM is used on a set of sequences, the sequences are assumed to be independently generated using an unique set of parameters for all sequences (leading to a global estimation).

The deterministic EM (Expectation-Maximization) algorithm gives a maximum likelihood estimation. To take into account available information on the model parameters, we also proposed a bayesian estimation with Dirichlet priors (on state and observation transitions) using MCMC (Markov Chain Monte Carlo) methods, more precisely Gibbs sampling. These two iterative procedures, EM and MCMC methods, don't require any learning set of presegmented sequences to give a segmentation of the sequence.

**Keywords:** DNA sequence heterogeneity, DNA segmentation, Hidden Markov Models, maximum likelihood estimation, bayesian estimation, EM algorithm, MCMC methods (Gibbs sampling)

## 2 Programs

The corresponding programs are:

- *rhom.em* is the only one documented here,
- *rhom.gibbs* a new version is still under construction,
- *seq.graph* produces a graphical display of the estimated state probabilities for all sequence positions, and all segment classes. This representation allows us to visualise the detected homogeneous regions, that can be superimposed on the DNA features. The precise localisation of these regions are also avalaible.
- *rhom.extract* allows to extract the sequences corresponding to each homogeneous region.

## 3 References

### 3.1 related to R'HOM program

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### 3.2 other references on DNA segmentation without learning set

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## 4 Hidden Markov Models, HMM

### 4.1 Model description

The models used to describe DNA sequence heterogeneities are Hidden Markov Models (M1-Mk). These models allow to segment a sequence into a finite number, **nstate**, regions, that can be composed of several segments, without any prior knowledge about their content, size or localization. Segment arrangement corresponds to an underlying structure of the sequence modelized by an hidden Markov chain with **nstate** states, called the hidden state chain. A DNA sequence is represented by a finite series $X_1X_2...X_n$, each letter $X_i$ taken from an alphabet $\mathcal{A}$ with **nmodal** modalities (several **type** of alphabet are considered, for instance **nmodal**=4 letters a,c,g,t,...), and the corresponding hidden states by a finite series $S_1S_2...S_n$, each $S_i$ taking **nstate** possible values.
For all the models, the hidden states are generated according to an homogeneous first order Markov chain, MC, (M1), with finite state space $\mathcal{S} = \{1, ..., nstate\}$, that is the probability of generating a state at a given position depends only on the previous state. Moreover, the transition probabilities from a state u to a state v, denoted by $\pi_s(u, v)$ are homogeneous: they don't depend on the sequence position.

$$\pi_s(u,v) = P(S_i = v \mid S_{i-1} = u), u, v \in \mathcal{S}, \forall i = 1, 2, ... \text{ with } \sum_{v\in\mathcal{S}} \pi_s(u,v) = 1$$

We denote by $\pi_s$ the MC transition matrix of size $nstate \times nstate$, and $\mu_s$ the initial distribution (of size $nstate$), that can be chosen as the stationary distribution (and thus not estimated).

$$\begin{array}{rrcl} & \mu_s(v) & = & P(S_1 = v) \\ \text{that we choose as} & \mu_s(v) & = & P(S_i = v), v \in \mathcal{S}, \forall i = 1, 2, ... \text{ with } \sum_{v\in\mathcal{S}} \mu_s(v) = 1 \end{array}$$

The letters of the sequence, $X_i$, appear with a law that depends on the hidden state $S_i$. Several models are considered.

### 4.2 M1-M0 model

Conditionally on the actual state, we can assume that the letters are drawn independently. The probability of generating a letter $a$ depends only on the associated state $u$ of the letter. $\pi_o$ represents the matrix of these probabilities of size $nstate \times nmodal$. Each term $\pi_o(u, a)$ of the matrix is defined by

$$\pi_o(u,a) = P(X_i = a \mid S_i = u), u \in \mathcal{S}, a \in \mathcal{A}, \forall i = 1, 2, ... \text{ with } \sum_{a\in\mathcal{A}} \pi_o(u,a) = 1$$

The M1-M0 model takes into account the local letter composition of the sequence.

### 4.3 M1-M1 model

Conditionally on the actual state, the M1-M1 model assumes a first order markovian dependence between the letters. The probability of generating a letter $b$ depends only on the previous letter $a$ and the associated state $u$ of the letter $b$. $\pi_o$ represents the transition matrix of the CM of size $nstate \times nmodal \times nmodal$. Each term $\pi_o(u,a,b)$ of the matrix is defined by

$$\pi_o(u,a,b) = P(X_i = b \mid X_{i-1} = a, S_i = u), u \in \mathcal{S}, a, b \in \mathcal{A}, \forall i = 1,2,... \text{ with } \sum_{b \in \mathcal{A}} \pi_o(u,a,b) = 1$$

$\mu_o$ denotes the MC initial distribution (size $nstate \times nmodal$) that can be chosen as the stationary distribution

$$\mu_o(u,a) = P(X_i = a \mid S_i = u), u \in \mathcal{S}, a \in \mathcal{A}, \forall i = 1,2,... \text{ with } \sum_{a \in \mathcal{A}} \mu_o(u,a) = 1$$

The M1-M1 model takes into account the local dinucleotide composition of the sequence.

### 4.4 M1-Mk model

Conditionally on the actual state, the M1-Mk model assumes a k-order markovian dependence between the letters. The probability of generating a letter $a_{k+1}$ depends only on the k previous letter $a_k, ..., a_1$ and the associated state $u$ of the letter $a_{k+1}$. $\pi_o$ represents the transition matrix of the CM (of size $nstate \times nmodal \times ... \times nmodal$). Each term $\pi_o(u, a_1, ..., a_k, a_{k+1})$ of the matrix is defined by

$$\begin{aligned}\pi_o(u, a_1, ..., a_k, a_{k+1}) &= P(X_i = a_{k+1} \mid X_{i-1} = a_k, ..., X_{i-k} = a_1, S_i = u), \\ &\quad u \in \mathcal{S}, a_1, ..., a_{k+1} \in \mathcal{A}, \forall i = 1,2,... \text{ with } \sum_{a_{k+1} \in \mathcal{A}} \pi_o(u, a_1, ..., a_k, a_{k+1}) = 1\end{aligned}$$

$\mu_o$ denotes the MC initial distribution that can be chosen as the stationary distribution

$$\begin{aligned}\mu_o(u, a_1, ..., a_k) &= P(X_1 = a_1, ..., X_k = a_k \mid S_k = u), u \in \mathcal{S}, \\ &\quad a_1, ..., a_k \in \mathcal{A}, \forall i = 1,2,... \text{ with } \sum_{a_1,...a_k \in \mathcal{A}} \mu_o(u, a_1, ..., a_k) = 1\end{aligned}$$

The M1-M1 model takes into account the local k+1-nucleotide composition of the sequence.

### 4.5 Model choice

The choice of the order $k$ of the model M1-Mk depends on the information (local oligonucleotide composition) that ones want to take into account to characterize the homogeneous regions.
For instance, the M1-M2 model fits on the local trinucleotide composition of the sequence.

## 5 rhom.em: Segmentation of a DNA sequence with HMM by the EM algorithm

### 5.1 Algorithm

For a given M1-Mk model, rhom.em uses the iterative EM algorithm to reconstruct the hidden state sequence and give an approximation of the maximum likelihood estimator (MLE) $\hat{\theta}$ of the model parameters $\theta = (\pi_s, \pi_o)$. The $m^{th}$ EM iteration consists in:

- E step: compute $P(S_i = u, S_{i+1} = v \mid X, \theta^{(m)})$ with $X = X_1 \dots X_n$, for all sequence position $i$ and all segment class $u, v$. This is done using the forward - backward recurrence of Baum-Welch algorithm.

- M step: update $\theta$ by choosing $\theta^{(m+1)} = \arg\max_{\theta} E(\log P(X, S \mid \theta) \mid \theta^{(m)}, X)$, the conditional expectation of the complete log likelihood. This maximization step leads to the intuitive estimators:
$$\pi_s^{(m+1)}(u,v) = \frac{\sum_{i=1}^{n-1} P(S_i = u, S_{i+1} = v \mid X, \theta^{(m)})}{\sum_{i=1}^{n-1} P(S_i = u \mid X, \theta^{(m)})}$$
$$\pi_o^{(m+1)}(v, a_1, \dots, a_{k+1}) = \frac{\sum_{i=k+1}^{n} P(S_i = v \mid X, \theta^{(m)}) 1_{\{X_i = a_{k+1}, X_{i-1} = a_k, \cdots, X_{i-k} = a_1\}}}{\sum_{i=k+1}^{n} P(S_i = v \mid X, \theta^{(m)}) 1_{\{X_{i-1} = a_k, \cdots, X_{i-k} = a_1\}}}$$

Starting from an initial value of the model parameters $\theta^{(0)}$, E and M steps are alternated until an iteration $M$ for which the difference between the loglikelihood value $\log P(X \mid \theta^{(M)})$ of two successive iterations is less than an arbitrary threshold epsilon. Finaly $\hat{\theta} = \theta^{(M)}$ and state sequence is reconstructed with the state probabilities $P(S_i = u \mid X, \theta^{(M)})$.
Contiguous positions associated to the same segment class $v$, $v = \arg\max_{u \in \mathcal{S}} P(S_i = u \mid X, \theta^{(M)})$, are identified as an homogeneous segment of class $v$. All homogeneous segments of class $v$ are characterized by the same $k+1$-nucleotide composition $\hat{\pi_o}(v, a_1, ..., a_k)$.

## 5.2 Usage

```
> rhom.em -model <model_desc> -seq <seq_list> -em <em_param>
> rhom.em -h
```

## 5.3 Arguments description

- -h gives only the syntax of the command.

- -model <model_desc> is the name of the input file that contains the model description.

- -seq <seq_list> is the name of the file that contains the paths of the sequences constituting the analyse set.

- -em <em_param> is the name of the input file containing the informations needed to initialize and to run EM. The user can give its own initial values for the parameters, or multiple random initializations can be used, followed by likelihood based selection of the best final results.

# 6 Input files

The input files contain lists of keywords that must be specified. Comments, always preceded by a "#", can be introduced in the files. A keyword can be followed by a ":", but no space character has to be introduced between the keyword and the ":"

## 6.1 -seq Sequence file

The file <seq_list> contains the names of the files containing the sequences to study. The sequences don't have to be in the same directory, but the corresponding output files are created in the same directory as the sequence. Each sequence must only contain the following characters: a, A, c, C, g, G, t, T (ignoring the case). Numeric characters are ignored.

**example** of sequence list file, <seq_list>:

```
sequence1.gb
sequence2.gb
```

**Sequence format** Several formats are considered.

- fasta:

  ```
  > title
  agctgtgt...
  ```

  Warning the fasta file must contain only one sequence.

- GenBank: only the keywords LOCUS and ORIGIN are take into account, other are ignored.

- EMBL: only the keywords ID and SQ are take into account, other are ignored.

- yet another format:

  ```
  title #
  agctgtgtaa ...
  ```

## 6.2 -model Model description

This file contains the model description with the following keywords:

- **model:** integer greater than 0 defining the order k of the M1-Mk model.
- **type:** integer defining the type of the letter alphabet (inducing the modality number of the letters, nmodal)

  0: alphabet a, g, c, t (in this order!), nmodal=4

  1: alphabet W, S (W=a+t, S=g+c), nmodal=2

  2: alphabet R, Y (R=a+g, Y= c+t), nmodal=2

  3: amino-acid alphabet, nmodal=20
- **nstate:** interger greater than 1 corresponding to the number of segment classes, that is the number of hidden states in your model.

**example** of model description file, <model_desc>:

```
#M1-M2 with 4 hidden states
model: 2 # M1-M2
type: 0 #alphabet a, g, c, t
nstate: 4 #4 hidden states
```

## 6.3 -em EM Algorithm Parameters

This file contains the informations needed to run and initialize EM. The user can give its own initial values for the parameters, or multiple random initializations can be used, followed by likelihood based selection of the best final results. The keywords are:

- niter: integer defining the maximal number of EM iterations
- eps: real defining the stopping criteria. EM is stopped when the difference of two consecutive values of the loglikelihood is less than epsilon or when niter is reached.

  only when the user specifies its own starting values:

- pis: the matrix $\pi_s$ (nstate $\times$ nstate) of the initial values of the state transitions. The sum of each raw must be equal to 1.
- mus: the vector $\mu_s$ (size nstate) of the initial values of the initial state distribution. The sum of all the elements must be equal to 1.
- pio: the matrix $\pi_o$ (nstate $\times$ nmodal $\times$ nmodal $\ldots$ nmodal) of the initial values of the observation transitions. The sum of each raw is equal to 1.
- muo: the matrix $\mu_o$ (size nstate * nmodal * ... *nmodal) of the initial values of the initial observation distribution. For each state, the sum of all the elements must be equal to 1.

  only when multiple random initializations are used:

- pis_sel: real between 0 and 1. pis_sel corresponds to the value of the diagonal elements of the state transition matrix. Usually pis_sel is chosen close to 1 to start with initial segment length not too small. The others values are set to (1-pis_sel)/(nstate-1).
- nb_sel: integer defining the number of considered random starting points.
- niter_sel: integer defining the iteration number achieved for each random path (from each starting point).

  The best path (with the highest loglikelihood value) will be kept for which niter iterations will be achieved. The inial values of observation transitions pio are generated at random between 0.5/nmodal and 0.5/nmodal + 0.5 (extremal initial values are discarded).

**example** of initialization EM file, <em_param.naleat>

with specified starting values (for the preceding model description):

```
#algo EM with 100 iterations. M1-M2 with 4 hidden states. Stopping criteria fixed to 10e-3
niter 100
eps 10e-3

pis #Initial values of state transitions (nstate*nstate=4 * 4)
#state 1 state 2   state 3     state 4
0.948854    0.0502678   0.000877813 1.30941e-28 #state 1
0.0938233   0.896385 1.93881e-57 0.00979151 # state 2
1.4473e-105 1.02748e-93 0.998933 0.00106683 # state 3
0.0308109   2.0568e-06  0.00484188  0.964345 #state 4
```

```
mus #Initial values of initial state distribution (1*nstate=1 * 4)
#state 1 state 2   state 3     state 4
0.301835 0.146496 0.496712 0.0551699

pio #Initial values of observation transitions (4*4*4=nstate*nmodal*nmodal)
#state 1
#a       g        c       t
0.250679 0.199376 0.28703 0.262915 # aa
0.262325 0.104503 0.0636073 0.569565 # ag
0.348552 0.0376766 0.356861 0.25691 # ac
0.290229 0.276766 0.253169 0.179837  # at
0.171719 0.263213 0.180284 0.384785  # ga
0.35131 0.421945 0.082876 0.143869  # gg
1.03216e-07 0.227579 0.340905 0.431516 # gc
0.166153 0.428288 0.128137 0.277423 # gt
0.563403 0.148526 0.171301 0.116769 # ca
0.532434 4.38999e-07 0.170677 0.296889  # cg
0.681336 7.41972e-10 0.161307 0.157356  # cc
0.398021 0.117946 0.188856 0.295177  # ct
0.462522 0.250213 0.194246 0.0930196  # ta
0.443759 0.318182 0.139334 0.0987249 # tg
0.722646 0.0339112 0.243443 2.72926e-41 # tc
0.229728 0.227167 0.254991 0.288114 # tt
#state2
0.460708 0.30662 0.216851 0.0158213
...
#state 3
0.225592 0.263064 0.331467 0.179877
...
#state 4
0.312473 0.143202 0.0801305 0.464194
...

muo #Initial values of initial observation distribution
#(4*4=nstate*nmodal)
#state 1
#a       g        c       t
0.12904 0.0747909 0.079439 0.0792296 #a
0.0706479 0.0487123 0.0194636 0.0588641 #g
0.100936 0.00959239 0.0561533 0.0380135 #c
0.0615724 0.0647921 0.0497819 0.0589715 #t
#state2
0.165736 0.0854782 0.0434868 0.0376994
...
#state 3
0.158642 0.0614003 0.0349861 0.0958986
...
#state 4
0.0276459 0.00812737 0.078968 0.0256395
```

<u>with use of multiple random initialization (for the preceding model description):</u>

```
#algo EM with 100 iterations. M1-M2 with 4 hidden states.
```

```
#Stopping criteria fixed to 10e-3
niter 100
eps 10e-3

pis_sel 0.99
#the diagonal elements of pis are set to 0.99
# Mean length of each region = 100 bp.
niter_sel 100
nb_sel 10
#10 starting points are selected at random for which 100 iterations are made.
#The best path is kept for which niter=100 iterations are made.
```

## 7 Output files

The command:

```
> rhom.em -model <model_desc> -seq <seq_list> -em <em_param>
```

creates the following output files:

- <seq_list>.trace
- <seq1>.rhom, <seq2>.rhom,..., <seqn>.rhom when the file <seq_list> contains the n sequences <seq1>, ..., <seqn>.

The structure of these output files are the same for a random or specified initialization. When a random initialisation is used, two additional files are created:

- <seq_list>.select.likelihoods
- <seq_list>.select.models

### 7.1 .trace file

This file contains informations about the model and algorithm descriptions, initial values of the parameters, successive values of the loglikelihood and the stopping criteria for each iteration, and the final values of the parameters.

**example** of content. The lines of comments beginning by # are added for the user comprehension.

```
hidden state number (nstate): 4
observation modality number (nmodal): 4
maximal iteration number (niter): 100 (working on A,G,C,T)
Markov model order: M1-M2
Algorithm: EM
sequence list file: fic_seq
number of sequences: 2
total sequence length: 8002 sequence files:
    sequence1.gb
    sequence2.gb

#initial values of pis
pis: 0.948854 0.0502678 0.000877813 1.30941e-28 ...

#initial values of mus
```

```
mus: 0.301771 0.146465 0.496606 0.0551582

#initial values of pio
pio: 0.250679 0.199376 0.28703 0.262915 0.262325 0.104503...

#initial values of muo
muo: 0.128932 0.0747283 0.0793725 0.0791633 0.0707193...

iteration: 1 loglikelihood: -9833.24
iteration: 2 loglikelihood:-9833.22
diff: 0.0205511

#final values of pis
pis: 0.948683 0.0504397 0.000876873 1.88526e-28 0.0943041 ...

#final values of mus
mus: 0.301963 0.146351 0.496714 0.055186

#final values of pio
pio: 0.250553 0.199383 0.287258 0.262807 0.262736 0.104441 ...

#final values of muo
muo: 0.128992 0.0748365 0.0794692 0.079204 0.0706376 0.0487347 ...


Iteration number: 63 epsilon and loglikelihood diff: 10e-3 0.000205511
```

## 7.2 .rhom files

R'HOM produces as many .rhom output files as sequences in the file <seq_list>. The name of each output file is sequence_name.rhom. Each file contains a description of the model and the algorithm parametrization, the state probabilities $P(S_i = u \mid X, \hat{\theta})$ estimated with EM, for each position $i$ of the sequence, and all segment class $u$, final parameter estimations, and also characteristic informations of the algorithm.

**example** of content of a .rhom file where lines of comments beginning by # are added for the reader comprehension.

```
#title and length of the sequence
L43967  #  4001
#type nmodal model nstate algorithm number of self-      number of iter
#                         code      complementary states made
  0    4      2       4     0         0                    2
#type of file (ouptut file of the final results)
0

#estimated state probabilities for all sequence position
#state 1   state 2    state 3   state4
0.00649628 0.00113897  0.991456 0.000908642 # position 1
0.00618641 0.000945452 0.992516 0.000352241 # position 2
0.00586888 0.000870091 0.993261 5.00163e-133 # position 3
...
0.000521638 8.84279e-05 0.997984 0.00140579 # position 4001
```

```
# final values of pis
0.948683 0.0504397 0.000876873 1.88526e-28
0.0943041 0.895884 8.89759e-58 0.0098116
1.67912e-106 8.06319e-95 0.998933 0.00106682
0.0308272 1.2522e-06 0.00484352 0.964328

#final values of mus
0.301963 0.146351 0.496714 0.055186

#final values of pio
#state 1
0.250553 0.199383 0.287258 0.262807 0.262736 0.104441 0.0635067...
#state 2
0.461027 0.306671 0.216449 0.0158531 0.12538 0.473632 0.328604...
#state 3
0.46024 0.155891 0.10354 0.280329 0.254131 0.147643 0.163976...
#state 4
7.45071e-51 2.86447e-126 0.576877 0.423123 0.528608 3.81939e-67 ...

#final values of muo
#state 1
0.128992 0.0748365 0.0794692 0.079204 0.0706376 0.0487347 ...
#state 2
0.165878 0.0854007 0.0433873 0.0377102 0.0692985 0.105744 ...
#state 3
0.158642 0.0614002 0.0349862 0.0958989 0.0369068 0.0236469 ...
#state 4
0.0276532 0.00813249 0.0789714 0.025657 0.0157272 0.0166258 ...

#epsilon final value of stopping criteria
10       0.0205511
```

**Remark:** this version of R'HOM doesn't consider the possibility of self-complementary states. The number of self-complementary states is set to 0.

## 7.3 .select files

Created only for a random initialization.

### 7.3.1 .select.likelihoods file

This file contains the loglikelihood value at the **niter_sel** iteration for each of the tested **nb_sel** model (that is for each random starting point), and also specified the selected model.

**example** of a .select.likelihoods file. The lines of comments beginning by # are added for the reader comprehension.

```
#nb_sel=10 random starting points are considered for which niter_sel=100 iter are made
#loglikelihood value at the iter niter_sel=100 for the nb_sel=10 tested models.
0 loglikelihood -9851.42
1 loglikelihood -9883.1
```

```
2 loglikelihood -9851.94
3 loglikelihood -9879.17
4 loglikelihood -9876.09
5 loglikelihood -9860.59
6 loglikelihood -9894
7 loglikelihood -9897.08
8 loglikelihood -9848.08
9 loglikelihood -9872.34

Best start point used: 8
```

### 7.3.2 .select.models file

This file contains the parameter values at the **niter_sel** iteration for each of the tested **nb_sel** model (that is for each random starting point). These values can be used as starting points to study local maxima.

**example** of a .select.models file where the lines of comments beginning by # are added for the reader comprehension.

```
#nb_sel=10 random starting points are considered for which niter_sel=100 iter are made
#parameter values at the iter niter_sel=100 for the nb_sel=10 tested models.

pis_sel: 0.99 niter_sel: 100 nb_sel: 10

++++++++++++++++++++++++++++++++
model 0

pis:
0.977557 0.0118793 0.00523414 0.00532981
1.46568e-83 0.994239 0.00190493 0.00385653
0.0006573 0.000402097 0.998941 5.83319e-103
0.00257132 6.11516e-68 8.89454e-50 0.997429

mus:
0.0505506 0.139142 0.497305 0.313215

pio:
1.29304e-135 1.37341e-203 0.376415 0.623585 0.390377 0.405173 ...

muo: 0.0263328 0.0237873 0.0648022 0.0305001 0.032571 0.031781 ...

++++++++++++++++++++++++++++++++
model 1

...

++++++++++++++++++++++++++++++++
model 9

pis:
0.998959 0.000506626 0.000533938 5.87165e-85 ...
mus:
```

```
0.5038 0.252605 0.188987 0.0548021
pio:
0.317425 0.230929 0.271109 0.180538 0.217473 0.231578 ...
muo:
0.1288 0.0707994 0.0692565 0.0611432 0.0640931 0.0613545 ...
```

## 8 Acknoledgments

We thank Annie Bouvier and Fabrice Lepage for their help in R'HOM program developement.