Computational Biology

Lecture 11

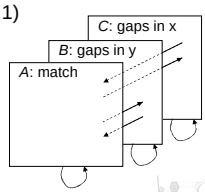
Saad Mneimneh

Alignment
Affine gap model

$$A(i,j) = s(i,j) + \max \begin{cases} A(i-1,j-1) \\ B(i-1,j-1) \\ C(i-1,j-1) \end{cases}$$

$$B(i,j) = \max \begin{cases} A(i-1,j) - e \\ B(i-1,j) - d \end{cases}$$

$$C(i,j) = \max \begin{cases} A(i,j-1) - e \\ C(i,j-1) - d \end{cases}$$



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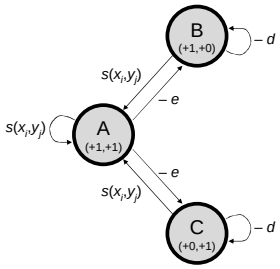
Finite state machine

An alignment corresponds to a path in the finite state machine



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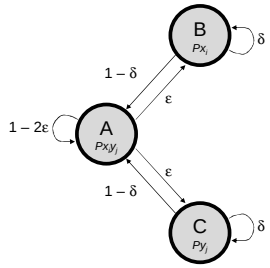
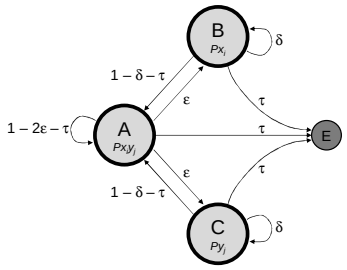
Probabilistic model HMM for related sequences

With transitional probabilities and emission probabilities, generates two sequences simultaneously



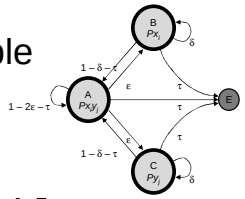
Modeling length

By adding an end state



Example

x = VLSPADK y = HLAESK



Possible alignment:

```
states:   A A A B B A A C A E
            | | | | | | | | |
emissions:  | | | | | | | | |
            | | | | | | | | |
x:          V L S P A D   K
y:          H L     A E S K
```

P = $(1-2\varepsilon-\tau)P_{VH}\cdot$
$(1-2\varepsilon-\tau)P_{LL}\cdot$
$\varepsilon P_S\cdot$
$\delta P_P\cdot$
$(1-\delta-\tau)P_{AA}\cdot$
$(1-2\varepsilon-\tau)P_{DE}\cdot$
$\varepsilon P_S\cdot$
$(1-\delta-\tau)P_{KK}\cdot$
τ

What is the most probable alignment (path in HMM)?

Viterbi algorithm

- All the algorithms we have seen for HMM apply, e.g. Viterbi
- But there is an extra dimension in the search space because of the extra emitted sequence
- Instead of using $v_k(i)$, we will use $v_k(i,j)$ because an observation x_i does not necessarily mean an observation for y_i.
- Imagine we have two clocks, one for x, and one for y, that work differently in different zones.
- Therefore, $v(i,j)$ can advance only in certain ways:
  - In zone A, both i and j advance.
  - In zone B, only i advances.
  - In zone C, only j advances.

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Viterbi

$v_A(0,0) = 1$, $v_A(i,0) = v_A(0,i) = 0$
$v_B(0,0) = 0$, $v_B(i,0) = \varepsilon\delta^{i-1}p_{x1}\ldots p_{xi}$, $v_B(0,j) = 0$
$v_C(0,0) = 0$, $v_C(i,0) = 0$, $v_C(0,j) = \varepsilon\delta^{j-1}p_{y1}\ldots p_{yj}$

for i=1..m, j=1..n

$$v_A(i,j) = Px_iy_j \cdot \max \begin{cases} (1-2\varepsilon-\tau)v_A(i-1,j-1) \\ (1-\delta-\tau)v_B(i-1,j-1) \\ (1-\delta-\tau)v_C(i-1,j-1) \end{cases}$$

$$v_B(i,j) = Px_i \cdot \max \begin{cases} \varepsilon v_A(i-1,j) \\ \delta v_B(i-1,j) \end{cases}$$

$$v_C(i,j) = Py_j \cdot \max \begin{cases} \varepsilon v_A(i,j-1) \\ \delta v_C(i,j-1) \end{cases}$$

$v_E = \tau.\max(v_A(m,n), v_B(m,n), v_C(m,n))$

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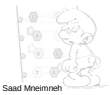
Observation

- Viterbi algorithm looks very similar to Needleman-Wunsch
- Let's investigate more this similarity
- Performing Viterbi in log space will definitely make it look like Needleman-Wunsch (multiplication → additive), let's do even more…
- Let's compute the log-odds ratio of the max probability of an alignment (path) to the probability of obtaining the sequences at random, therefore compute the maximum log-odds ratio.
  - Construct a model for random sequences
  - Perform Viterbi in log space with both models in mind
- We should then see almost the same algorithm



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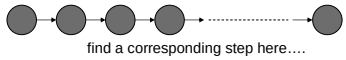
Two HMMs at the same time

alignment HMM path

$p = p_1.p_2.p_3……$

for each step here….

random HMM path

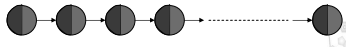


find a corresponding step here….

$p = q_1.q_2.q_3……$

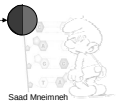
and associate steps together

alignment HMM path



$p = (p_1/q_1) . (p_2/q_2) . (p_3/q_3)……$

$\log p = \log (p_1/q_1) + \log (p_2/q_2) + \log (p_3/q_3)……$



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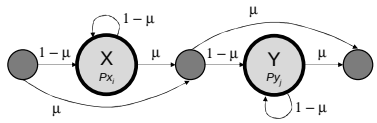
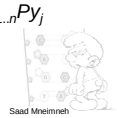
Random model

x and *y* are generated independently according to the individual probabilities Px_i and Py_i



$p(x,y \mid R) = \mu(1-\mu)^m \prod_{i=1..m} Px_i \,.\, \mu(1-\mu)^n \prod_{j=1..n} Py_j$

$= \mu^2(1-\mu)^{m+n} \prod_{i=1..m} Px_i \prod_{j=1..n} Py_j$



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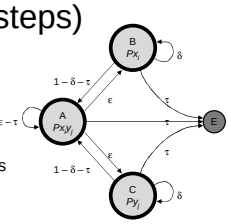
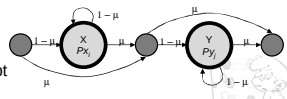
Aligned v.s. random (identifying steps)

- In the alignment model:
  - Each match step contributes $(1\text{-}2\varepsilon\text{-}\tau)Px_iy_j$ *(…depends)*
  - Each start gap step contributes εPx_i or εPy_j
  - Each additional gap step contributes δPx_i or δPy_j



- In the random model:
  - Each letter step contributes $(1\text{-}\mu)Px_i$ or $(1\text{-}\mu)Py_j$
  - All terms are counted except for a μ^2



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Aligned v.s. random (associating steps)

Alignment model	Random model
match x_i y_j	generate x_i and y_j
start gap in y with x_i	generate x_i
start gap in x with y_j	generate y_j
gap in y with x_i	generate x_i
gap in x with y_j	generate y_j

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Obtain p/q for each step…

match step

$$s(x_i, y_j) = \log \frac{Px_i y_j (1-2\varepsilon-\tau)}{(1-\mu)Px_i (1-\mu)Py_j} \cong \log \frac{Px_i y_j}{Px_i Py_j} + \log \frac{(1-2\varepsilon-\tau)}{(1-\mu)^2} \cong \log \frac{Px_i y_j}{Px_i Py_j}$$

corresponding random steps

gap step

$$d = -\log \frac{\delta Px_i}{(1-\mu)Px_i} = -\log \frac{\delta}{(1-\mu)} \cong -\log \delta$$

corresponding random step

start gap step

$$e = -\log \frac{\varepsilon Px_i}{(1-\mu)Px_i} \frac{1-\delta-\tau}{(1-2\varepsilon-\tau)} \cong -\log \varepsilon$$

corresponding random step

adjustment factor to correct for $s(x_i,y_j)$

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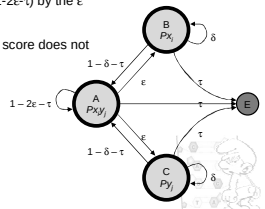
Start gap adjustment factor

- The contribution of state A assumes that a match always follows a match.
- If state A (match) is reached from state B or state C (a gap), then the term contributed to the probability of the path is $(1-\delta-\tau)\ Px_iPy_j$ and not $(1-2\varepsilon-\tau)Px_iPy_j$
- We correct this before it happens when we first open the gap (go from A to B or C) by multiplying $(1-\delta-\tau)/(1-2\varepsilon-\tau)$ by the ε contribution of the start gap
- But what if we never go back to A? Then the score does not exactly correspond to the log-odd ratio.



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log-odds ratio Viterbi (Needleman-Wunsch)

$v_A(0,0) = -2\log\mu$, $v_A(i,0) = v_A(0,i) = -\infty$
$v_B(0,0) = -\infty$, $v_B(i,0) = -e-(i-1)d$, $v_B(0,j) = -\infty$
$v_C(0,0) = -\infty$, $v_C(i,0) = -\infty$, $v_C(0,j) = -e-(j-1)d$

for i=1..m, j=1..n

$$V_A(i,j) = s(x_i,y_j) + \max \begin{cases} V_A(i-1,j-1) \\ V_B(i-1,j-1) \\ V_C(i-1,j-1) \end{cases}$$

$$V_B(i,j) = \max \begin{cases} V_A(i-1,j) - e \\ V_B(i-1,j) - d \end{cases}$$

$$V_C(i,j) = \max \begin{cases} V_A(i,j-1) - e \\ V_C(i,j-1) - d \end{cases}$$

We don't go back to state A.
The anticipated error did not occur.
Correct the adjustment.

$V_E = \max(V_A(m,n), V_B(m,n) - c, V_C(m,n) - c)$
$c = \log(1-\delta-\tau) - \log(1-2\varepsilon-\tau)$

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What is the meaning of the scores?

- From Viterbi, we obtained Needleman-Wuncsh with scores directly related to the parameters of a probabilistic model.

Needleman-Wunsch is just Viterbi with an appropriate transformation!

- We knew from before that the score is related to the log-odds ratio of probabilities. Now Viterbi gives more justification of this (we are actually after the most likely alignment compared to just a random instance!).
- We have a clear relation between the scores (even for gaps now) of Needleman-Wunsch and the parameters of a probabilistic model.
- The question now is: what do the model parameters ε, δ, τ, and μ really represent?

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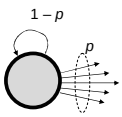
Duration of a state

Let us look at a single state with probability p of transitioning outside



What is the probability of staying in that state for a duration D.

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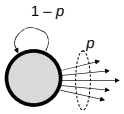
Duration of a state

$Pr[D=1]=p$
$Pr[D=2]=(1-p)p$
$Pr[D=3]=(1-p)(1-p)p$
.
.
.
$Pr[D=i]=(1-p)^{i-1}p$



i.e. geometric distribution

This is a disadvantage of a Markov Chain: it imposes a geometric distribution on the duration in a state, which might not be true.

There are ways around that… (see Durbin p. 69)

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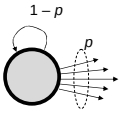
Mean duration

What is the mean duration?

$E[D] = 1/p$



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Therefore…

$2\varepsilon = 1/L_u$, L_u = mean length of ungapped regions

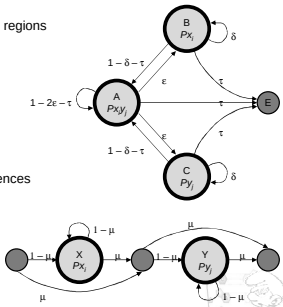
$L_u \nearrow$ $\varepsilon \searrow$ $\log \varepsilon \searrow$ $e \nearrow$

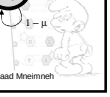
$1 - \delta = 1/L_g$, L_g = mean length of gap

$L_g \nearrow$ $\delta \nearrow$ $\log \delta \nearrow$ $d \searrow$

$\tau = 1/L_r$, L_r = mean length of related sequences (~ 0)

$\mu = 1/L$, L = mean length of a sequence (~ 0)





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