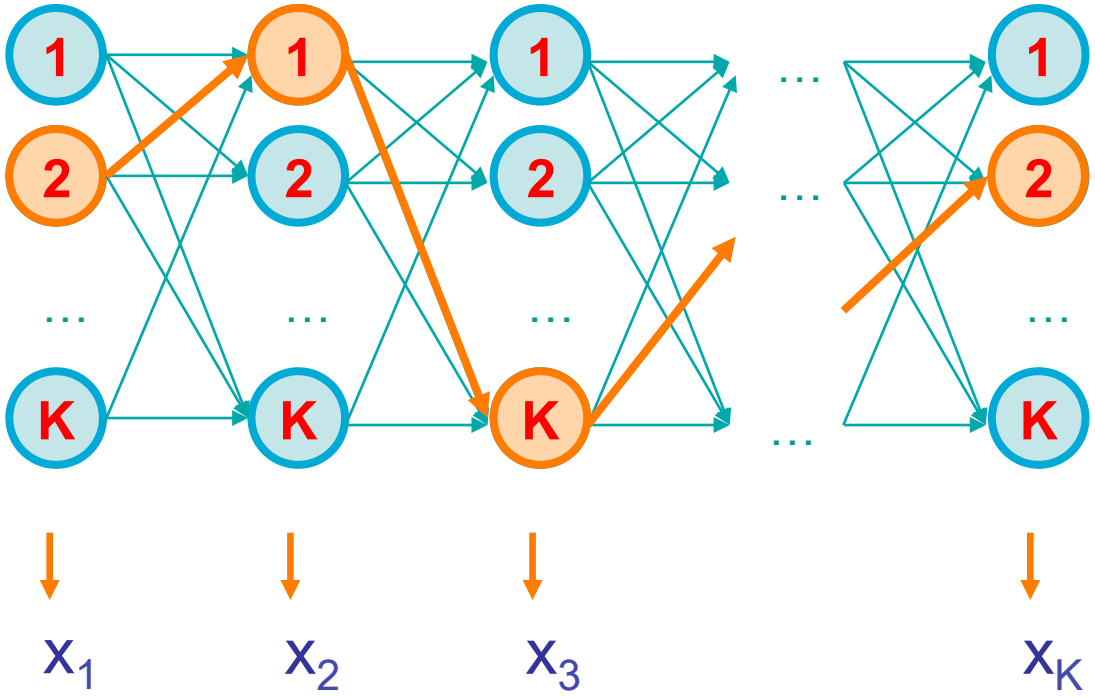
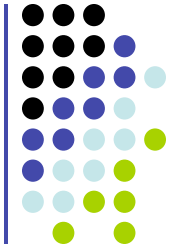
Hidden Markov Models



Viterbi, Forward, Backward



VITERBI

Initialization:

$V_0(0) = 1$

$V_k(0) = 0$, for all $k > 0$

Iteration:

$V_l(i) = e_l(x_i)\ \max_k V_k(i\text{-}1)\ a_{kl}$

Termination:

$P(x, \pi^*) = \max_k V_k(N)$

FORWARD

Initialization:

$f_0(0) = 1$

$f_k(0) = 0$, for all $k > 0$

Iteration:

$f_l(i) = e_l(x_i) \sum_k f_k(i\text{-}1)\ a_{kl}$

Termination:

$P(x) = \sum_k f_k(N)$

BACKWARD

Initialization:

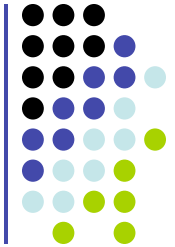
$b_k(N) = 1$, for all k

Iteration:

$b_l(i) = \sum_k e_l(x_i{+}1)\ a_{kl}\ b_k(i{+}1)$

Termination:

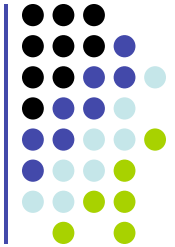
$P(x) = \sum_k a_{0k}\ e_k(x_1)\ b_k(1)$



Learning

Re-estimate the parameters of the model based on training data

Two learning scenarios



1. Estimation when the "right answer" is known

   Examples:

   GIVEN: a genomic region $x = x_1 \ldots x_{1,000,000}$ where we have good (experimental) annotations of the CpG islands

   GIVEN: the casino player allows us to observe him one evening, as he changes dice and produces 10,000 rolls

2. Estimation when the "right answer" is unknown

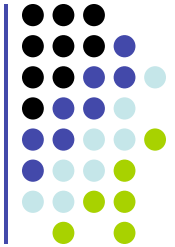
   Examples:

   GIVEN: the porcupine genome; we don't know how frequent are the CpG islands there, neither do we know their composition

   GIVEN: 10,000 rolls of the casino player, but we don't see when he changes dice

QUESTION: Update the parameters θ of the model to maximize $P(x|\theta)$

1. When the states are known



Given $x = x_1 \ldots x_N$
for which the true $\pi = \pi_1 \ldots \pi_N$ is known,

Define:

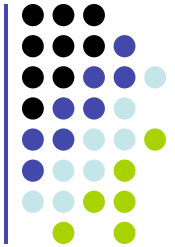
A_{kl} = # times k→l transition occurs in π
$E_k(b)$ = # times state k in π emits b in x

We can show that the maximum likelihood parameters θ (maximize $P(x|\theta)$) are:

$$a_{kl} = \frac{A_{kl}}{\sum_i A_{ki}}$$

$$e_k(b) = \frac{E_k(b)}{\sum_c E_k(c)}$$

1. When the states are known



Intuition: When we know the underlying states,
Best estimate is the normalized frequency of
transitions & emissions that occur in the training data

Drawback:

Given little data, there may be **overfitting**:
$P(x|\theta)$ is maximized, but θ is unreasonable
0 probabilities – BAD

Example:

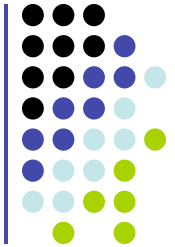
Given 10 casino rolls, we observe

x = 2, 1, 5, 6, 1, 2, 3, 6, 2, 3
π = F, F, F, F, F, F, F, F, F, F

Then:

$a_{FF} = 1$; $a_{FL} = 0$
$e_F(1) = e_F(3) = .2$;
$e_F(2) = .3$; $e_F(4) = 0$; $e_F(5) = e_F(6) = .1$

Pseudocounts



Solution for small training sets:

Add pseudocounts

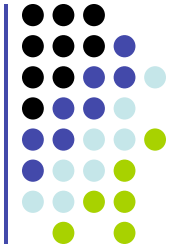
A_{kl}	= # times k→l transition occurs in π	+ r_{kl}
$E_k(b)$	= # times state k in π emits b in x	+ $r_k(b)$

r_{kl}, $r_k(b)$ are pseudocounts representing our prior belief

Larger pseudocounts ⇒ Strong priof belief

Small pseudocounts (ε < 1): just to avoid 0 probabilities

2. When the states are hidden

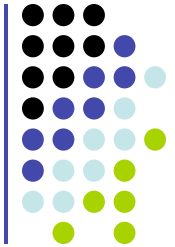


We don't know the true A_{kl}, $E_k(b)$

Idea:

- We estimate our "best guess" on what A_{kl}, $E_k(b)$ are
  - Or, we start with random / uniform values
- We update the parameters of the model, based on our guess
- We repeat

2. When the states are hidden



Starting with our best guess of a model M, parameters θ:

Given $x = x_1 \ldots x_N$

for which the true $\pi = \pi_1 \ldots \pi_N$ is unknown,

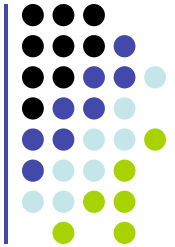
We can get to a provably more likely parameter set θ

i.e., θ that increases the probability $P(x \mid \theta)$

Principle: EXPECTATION MAXIMIZATION

1. Estimate A_{kl}, $E_k(b)$ in the training data
2. Update θ according to A_{kl}, $E_k(b)$
3. Repeat 1 & 2, until convergence

Estimating new parameters



To estimate A_{kl}: (assume "$| \theta_{CURRENT}$", in all formulas below)

At each position i of sequence x, find probability transition k→l is used:

$$P(\pi_i = k, \pi_{i+1} = l \mid x) = [1/P(x)] \times P(\pi_i = k, \pi_{i+1} = l, x_1 \ldots x_N) = Q/P(x)$$

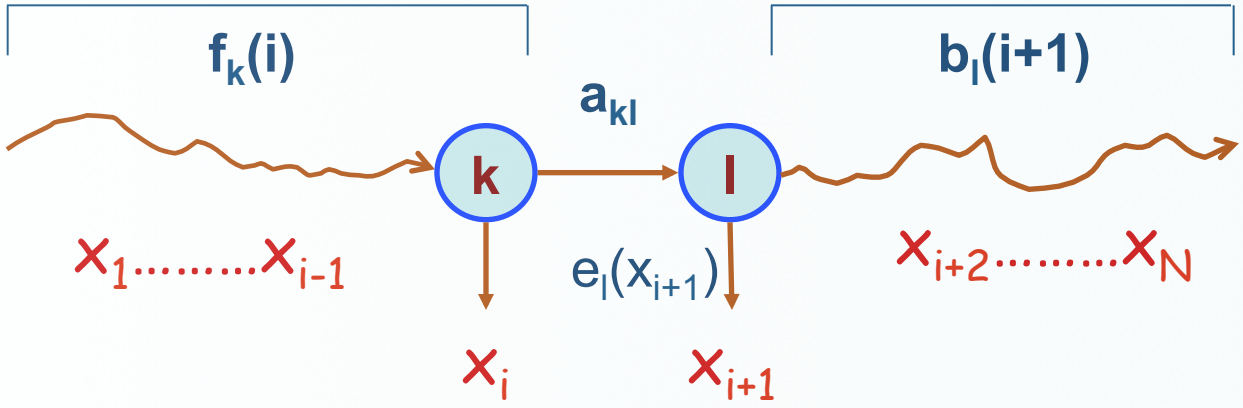
where
$$Q = P(x_1 \ldots x_i, \pi_i = k, \pi_{i+1} = l, x_{i+1} \ldots x_N) =$$
$$= P(\pi_{i+1} = l, x_{i+1} \ldots x_N \mid \pi_i = k)\, P(x_1 \ldots x_i, \pi_i = k) =$$
$$= P(\pi_{i+1} = l, x_{i+1} x_{i+2} \ldots x_N \mid \pi_i = k)\, f_k(i) =$$
$$= P(x_{i+2} \ldots x_N \mid \pi_{i+1} = l)\, P(x_{i+1} \mid \pi_{i+1} = l)\, P(\pi_{i+1} = l \mid \pi_i = k)\, f_k(i) =$$
$$= b_l(i+1)\, e_l(x_{i+1})\, a_{kl}\, f_k(i)$$

So:
$$\mathbf{P(\pi_i = k, \pi_{i+1} = l \mid x, \theta) = \frac{f_k(i)\, a_{kl}\, e_l(x_{i+1})\, b_l(i+1)}{P(x \mid \theta_{CURRENT})}}$$

Estimating new parameters

- So, A_{kl} is the E[# times transition k→l, given current θ]

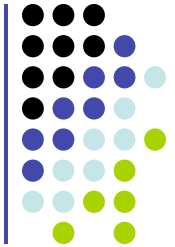
$$A_{kl} = \sum_i P(\pi_i = k, \pi_{i+1} = l \mid x, \theta) = \sum_i \frac{f_k(i)\, a_{kl}\, e_l(x_{i+1})\, b_l(i+1)}{P(x \mid \theta)}$$



- Similarly,

$$E_k(b) = [1/P(x \mid \theta)] \sum_{\{i \mid x^i = b\}} f_k(i)\, b_k(i)$$

The Baum-Welch Algorithm



Initialization:

Pick the best-guess for model parameters

(or arbitrary)

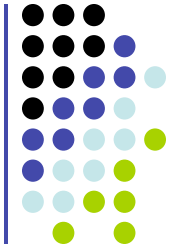
Iteration:

1. Forward
2. Backward
3. Calculate A_{kl}, $E_k(b)$, given $\theta_{CURRENT}$
4. Calculate new model parameters θ_{NEW} : a_{kl}, $e_k(b)$
5. Calculate new log-likelihood $P(x \mid \theta_{NEW})$

GUARANTEED TO BE HIGHER BY EXPECTATION-MAXIMIZATION

Until $P(x \mid \theta)$ does not change much

The Baum-Welch Algorithm



Time Complexity:

iterations $\times$ $O(K^2N)$

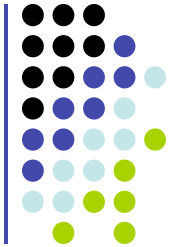
- Guaranteed to increase the log likelihood $P(x \mid \theta)$

- Not guaranteed to find globally best parameters

  Converges to local optimum, depending on initial conditions

- Too many parameters / too large model: Overtraining

Alternative: Viterbi Training



Initialization: Same

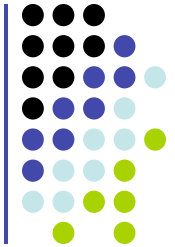
Iteration:

1. Perform Viterbi, to find π^*
2. Calculate A_{kl}, $E_k(b)$ according to π^* + pseudocounts
3. Calculate the new parameters a_{kl}, $e_k(b)$

Until convergence

Notes:

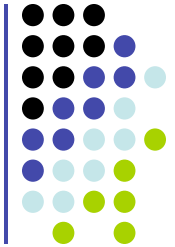
- Not guaranteed to increase $P(x \mid \theta)$
- Guaranteed to increase $P(x \mid \theta, \pi^*)$
- In general, worse performance than Baum-Welch



Pair-HMMs and CRFs

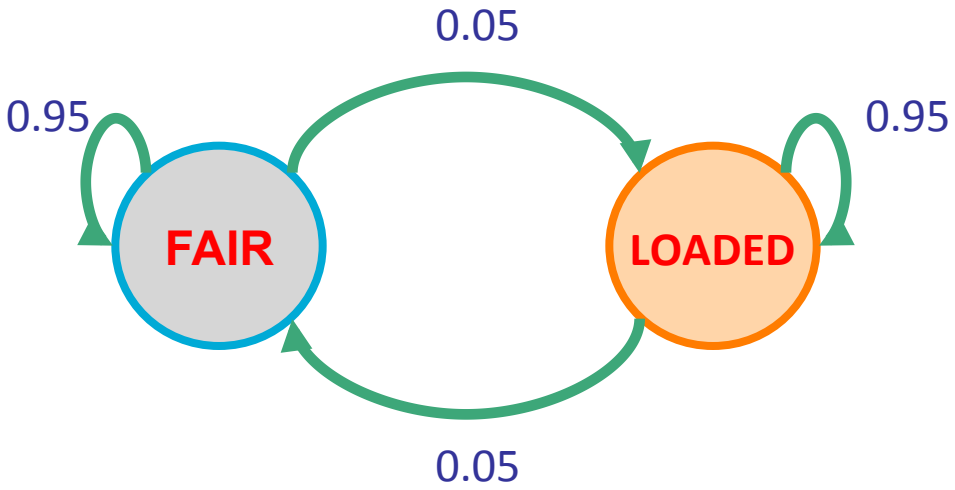
Slide Credits: Chuong B. Do

Quick recap of HMMs

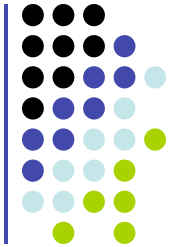


- Formally, an HMM = (Σ, Q, A, a_0, e).
  - alphabet: $\Sigma = \{b_1, \ldots, b_M\}$
  - set of states: $Q = \{1, \ldots, K\}$
  - transition probabilities: $A = [a_{ij}]$
  - initial state probabilities: a_{0i}
  - emission probabilities: $e_i(b_k)$

- Example:

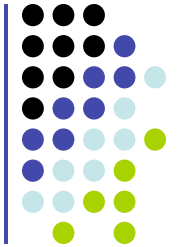


Pair-HMMs

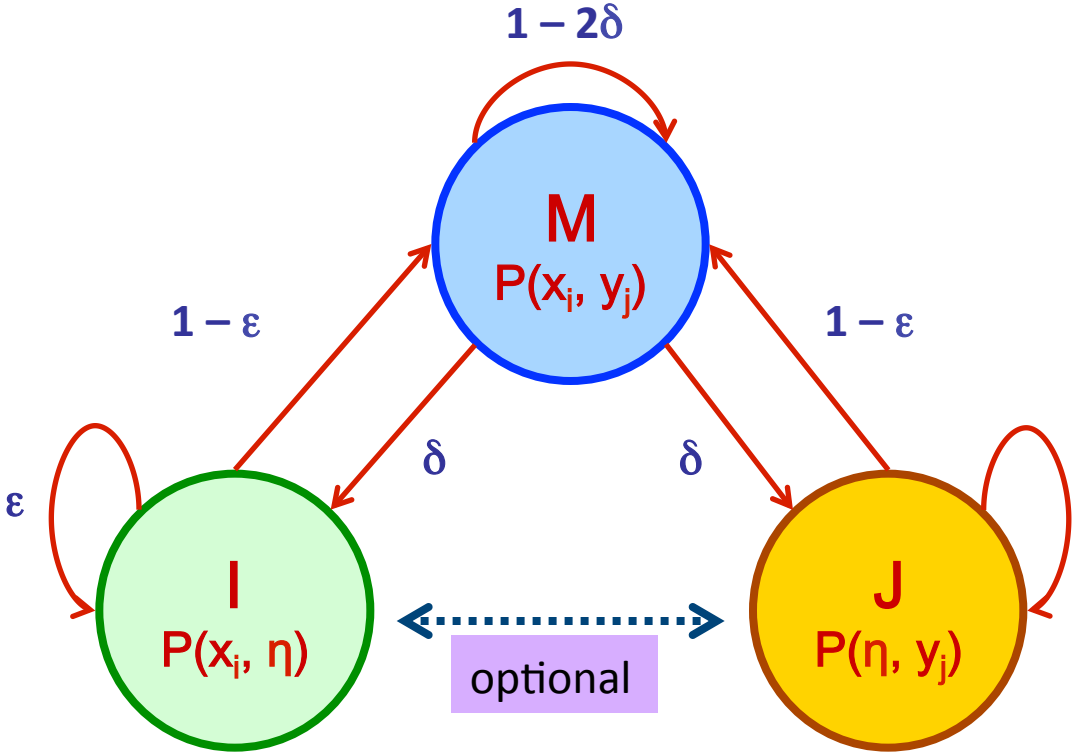


- Consider the HMM = $((\Sigma_1 \cup \{\eta\}) \times (\Sigma_2 \cup \{\eta\}), Q, A, a_0, e)$.
- Instead of emitting a pair of letters, in some states we may emit a letter paired with η (the empty string)
  - For simplicity, assume η is never emitted for both observation sequences simultaneously
  - Call the two observation sequences x and y

Application: sequence alignment



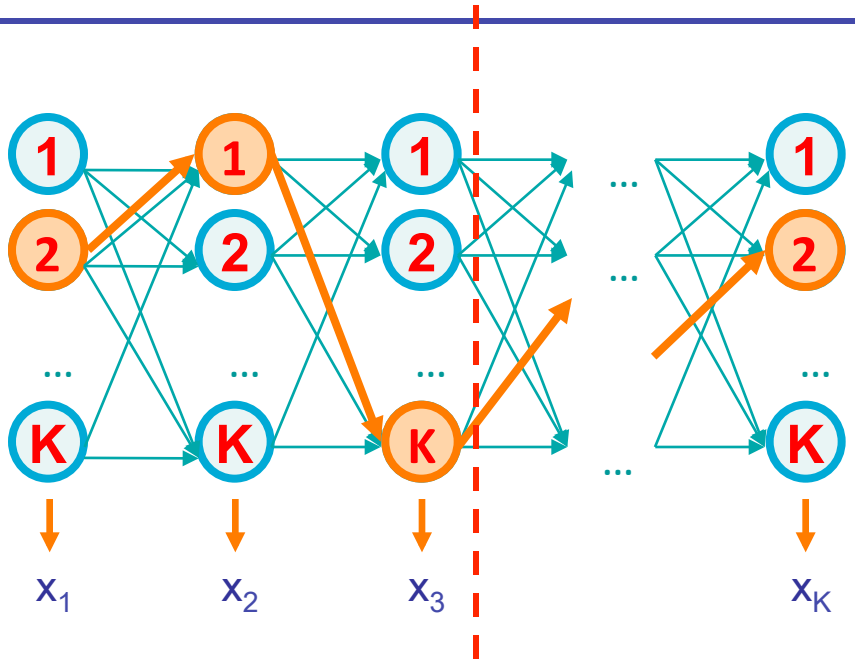
- Consider the following pair-HMM:



$\forall c \in \Sigma, P(\eta, c) = P(c, \eta) = Q(c)$

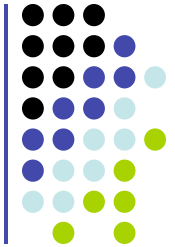
- **QUESTION**: What are the interpretations of P(c,d) and Q(c) for $c,d \in \Sigma$?
- **QUESTION**: What does this model have to do with alignments?
- **QUESTION**: What is the average length of a gapped region in alignments generated by this model? Average length of matched regions?

Recap: Viterbi for single-sequence HMMs



- Algorithm:
  - $V_k(i) = \max_{\pi 1 \ldots \pi i-1} P(x_1 \ldots x_{i-1}, \pi_1 \ldots \pi_{i-1}, x_i, \pi_i = k)$
  - Compute using dynamic programming!

(Broken) Viterbi for pair-HMMs



- In the single sequence case, we defined

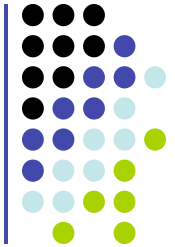
$$V_k(i) = \max_{\pi 1 \ldots \pi i-1} P(x_1 \ldots x_{i-1}, \pi_1 \ldots \pi_{i-1}, x_i, \pi_i = k)$$

$$= e_k(x_i) \cdot \max_j a_{jk} V_j(i - 1)$$

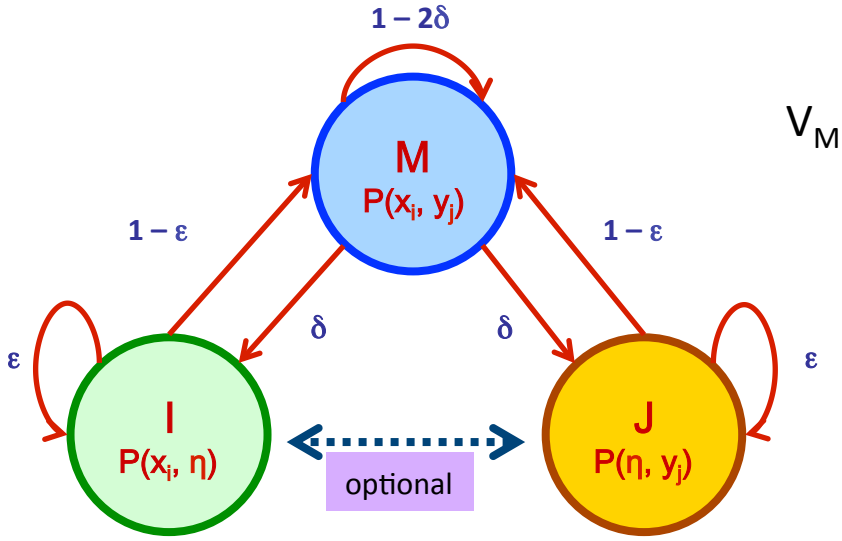
- In the pairwise case,

  $(x_1, y_1) \ldots (x_{i-1}, y_{i-1})$ no longer correspond to the first i – 1 letters of x and y

(Fixed) Viterbi for pair-HMMs



- Consider this special case:



$\forall c \in \Sigma, P(\eta, c) = P(c, \eta) = Q(c)$

$$V_M(i, j) = P(x_i, y_j) \max \begin{cases} (1 - 2\delta)\, V_M(i - 1, j - 1) \\ (1 - \varepsilon)\, V_I(i - 1, j - 1) \\ (1 - \varepsilon)\, V_J(i - 1, j - 1) \end{cases}$$

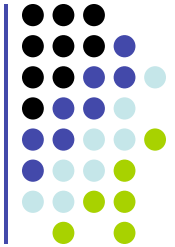
$$V_I(i, j) = Q(x_i) \max \begin{cases} \delta\, V_M(i - 1, j) \\ \varepsilon\, V_I(i - 1, j) \end{cases}$$

$$V_J(i, j) = Q(y_j) \max \begin{cases} \delta\, V_M(i, j - 1) \\ \varepsilon\, V_J(i, j - 1) \end{cases}$$

- Similar for **forward/backward** algorithms
  - (see Durbin et al for details)

QUESTION: What's the computational complexity of DP?

Connection to NW with affine gaps



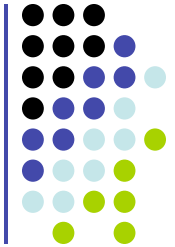
$$V_M(i, j) = P(x_i, y_j) \max \begin{cases} (1 - 2\delta)\, V_M(i - 1, j - 1) \\ (1 - \varepsilon)\, V_I(i - 1, j - 1) \\ (1 - \varepsilon)\, V_J(i - 1, j - 1) \end{cases}$$

$$V_I(i, j) = Q(x_i) \max \begin{cases} \delta\, V_M(i - 1, j) \\ \varepsilon\, V_I(i - 1, j) \end{cases}$$

$$V_J(i, j) = Q(y_j) \max \begin{cases} \delta\, V_M(i, j - 1) \\ \varepsilon\, V_J(i, j - 1) \end{cases}$$

- **QUESTION**: How would the optimal alignment change if we divided the probability for every single alignment by $\prod_{i=1 \ldots |x|} Q(x_i) \prod_{j = 1 \ldots |y|} Q(y_j)$?

Connection to NW with affine gaps



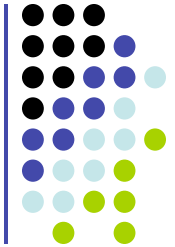
$$V_M(i, j) = \frac{P(x_i, y_j)}{Q(x_i)\,Q(y_j)} \max \begin{cases} (1 - 2\delta)\, V_M(i - 1, j - 1) \\ (1 - \varepsilon)\, V_I(i - 1, j - 1) \\ (1 - \varepsilon)\, V_J(i - 1, j - 1) \end{cases}$$

$$V_I(i, j) = \max \begin{cases} \delta\, V_M(i - 1, j) \\ \varepsilon\, V_I(i - 1, j) \end{cases}$$

$$V_J(i, j) = \max \begin{cases} \delta\, V_M(i, j - 1) \\ \varepsilon\, V_J(i, j - 1) \end{cases}$$

- Account for the extra terms “along the way.”

Connection to NW with affine gaps



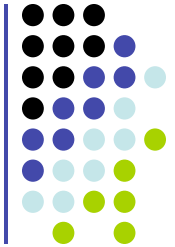
$$\log V_M(i, j) = \log \frac{P(x_i, y_i)}{Q(x_i)\, Q(y_j)} + \max \begin{cases} \log (1 - 2\delta) + \log V_M(i - 1, j - 1) \\ \log (1 - \varepsilon) + \log V_I(i - 1, j - 1) \\ \log (1 - \varepsilon) + \log V_J(i - 1, j - 1) \end{cases}$$

$$\log V_I(i, j) = \max \begin{cases} \log \delta + \log V_M(i - 1, j) \\ \log \varepsilon + \log V_I(i - 1, j) \end{cases}$$

$$\log V_J(i, j) = \max \begin{cases} \log \delta + \log V_M(i, j - 1) \\ \log \varepsilon + \log V_J(i, j - 1) \end{cases}$$

- Take logs, and ignore a couple terms.

Connection to NW with affine gaps



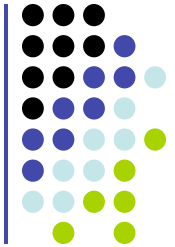
$$M(i, j) = S(x_i, y_j) + \max \begin{cases} M(i-1, j-1) \\ I(i-1, j-1) \\ J(i-1, j-1) \end{cases}$$

$$I(i, j) = \max \begin{cases} d + M(i-1, j) \\ e + I(i-1, j) \end{cases}$$

$$J(i, j) = \max \begin{cases} d + M(i, j-1) \\ e + J(i, j-1) \end{cases}$$

- Rename!

A simple example



- Let's work out an example, assume seq. identity 88%
  - Calculate match & mismatch scores
  - P(A, A) + … + P(T, T) = 0.88, therefore P(A, A) = 0.22
  - P(A, C) + … + P(G, T) = 0.12, therefore P(x, y, x != y) = 0.01
  - Match score
    - $\log(0.22 / 0.25^2) = 1.25846$
  - Mismatch score
    - $\log(.01 / .25^2) = - 1.83258$
  - When is a score of an ungapped aligned region = 0?
    - Assume a fraction p of matches
    - $1.25846p – 1.83258(1 – p) = 0$
    - Therefore, $p = 1.83258/(1.25846 + 1.83258) = 0.5929$