# String Alignment

CMSC423 Fall 2015
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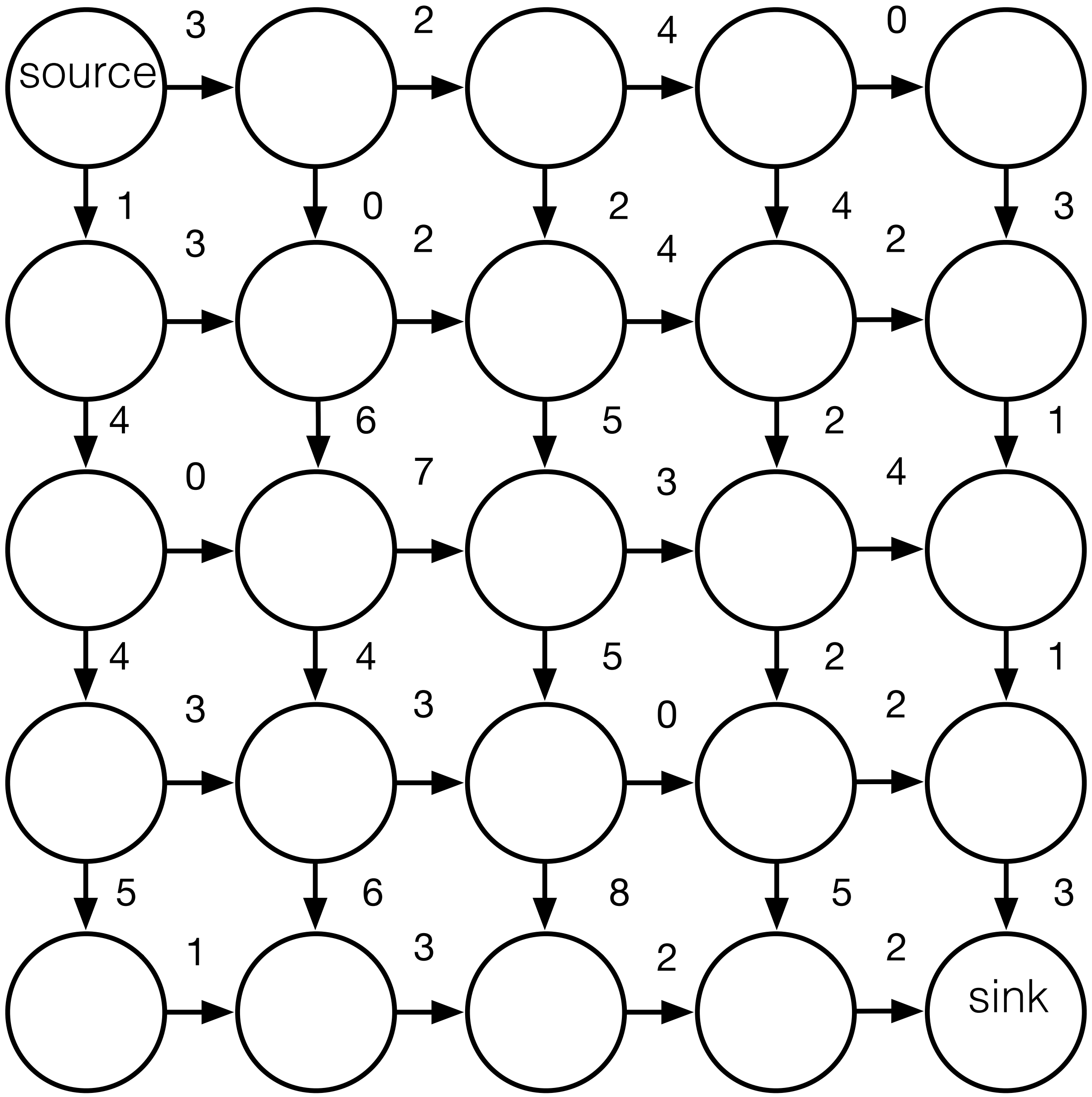
# Recursive Solution to Longest Path in a Grid

move from top DOWN

$$s_{i,j} = \max \begin{cases} s_{i-1,j} + \mathrm{DOWN}_{i,j} \\ s_{i,j-1} + \mathrm{RIGHT}_{i,j} \end{cases}$$

move from left RIGHT

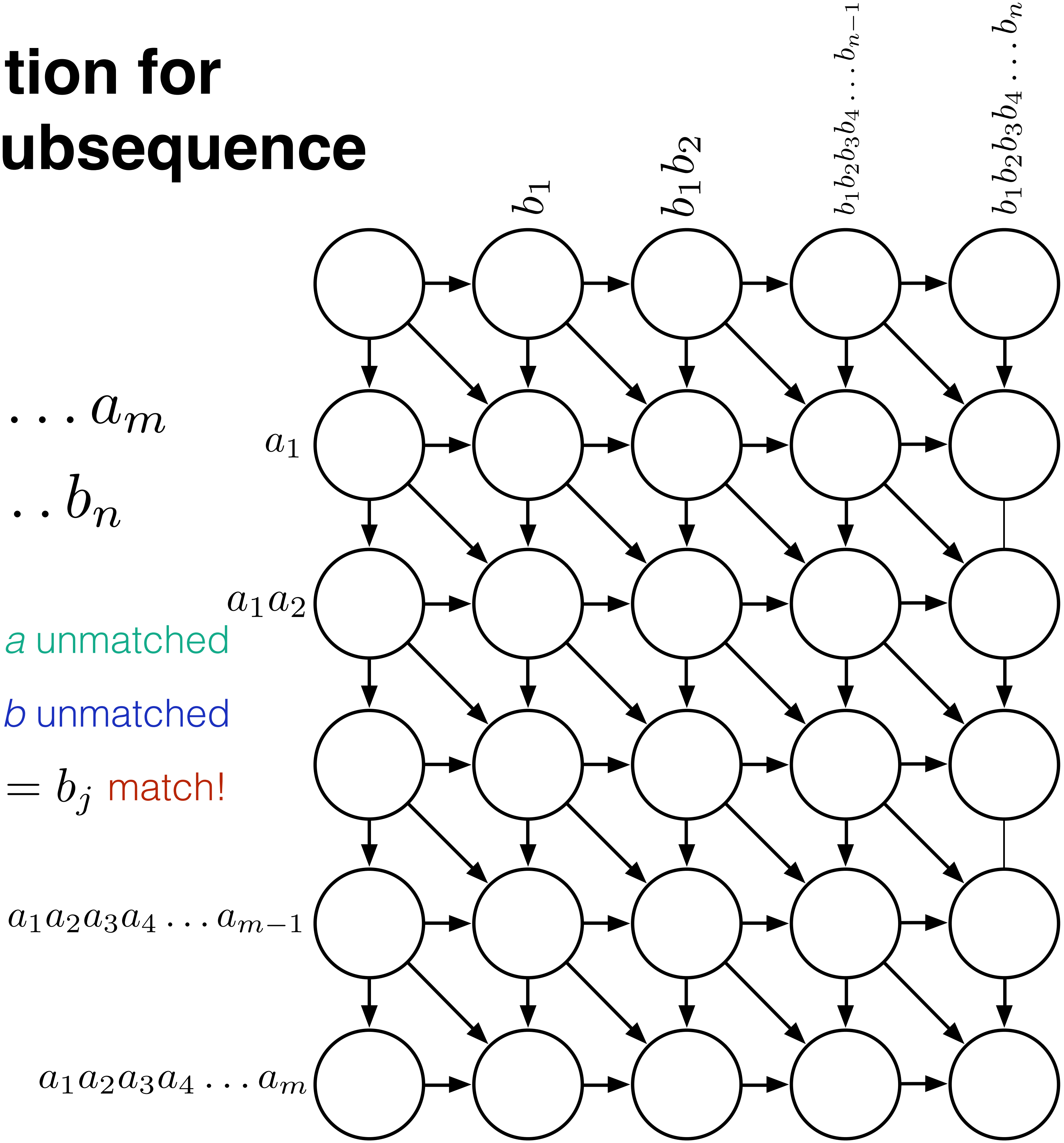


# Recursive Solution for Longest Common Subsequence

$$a = a_1a_2a_3a_4\ldots a_m$$

$$b = b_1b_2b_3b_4\ldots b_n$$

$$s_{i,j} = \max\begin{cases} s_{i-1,j} & \text{char in } a \text{ unmatched} \\ s_{i,j-1} & \text{char in } b \text{ unmatched} \\ s_{i-1,j-1}+1, \ \text{if } a_i = b_j & \text{match!} \end{cases}$$



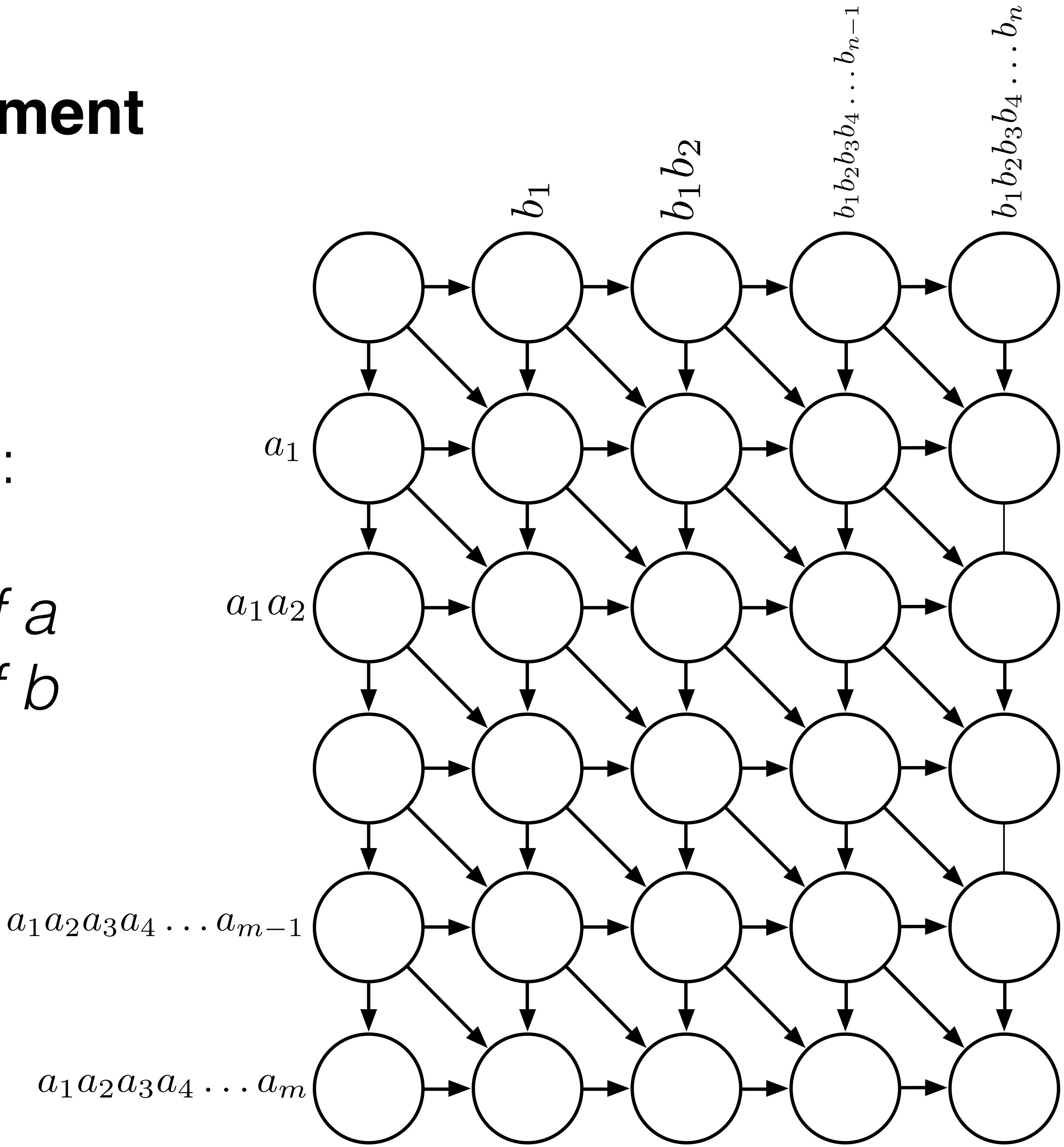
$s_{i,j}$ is length of LCS of:

***prefix*** *of length i of a*
***prefix*** *of length j of b*

# Global Alignment

$s_{i,j}$ is the score of optimally aligning:

***prefix*** *of length i of a*
***prefix*** *of length j of b*

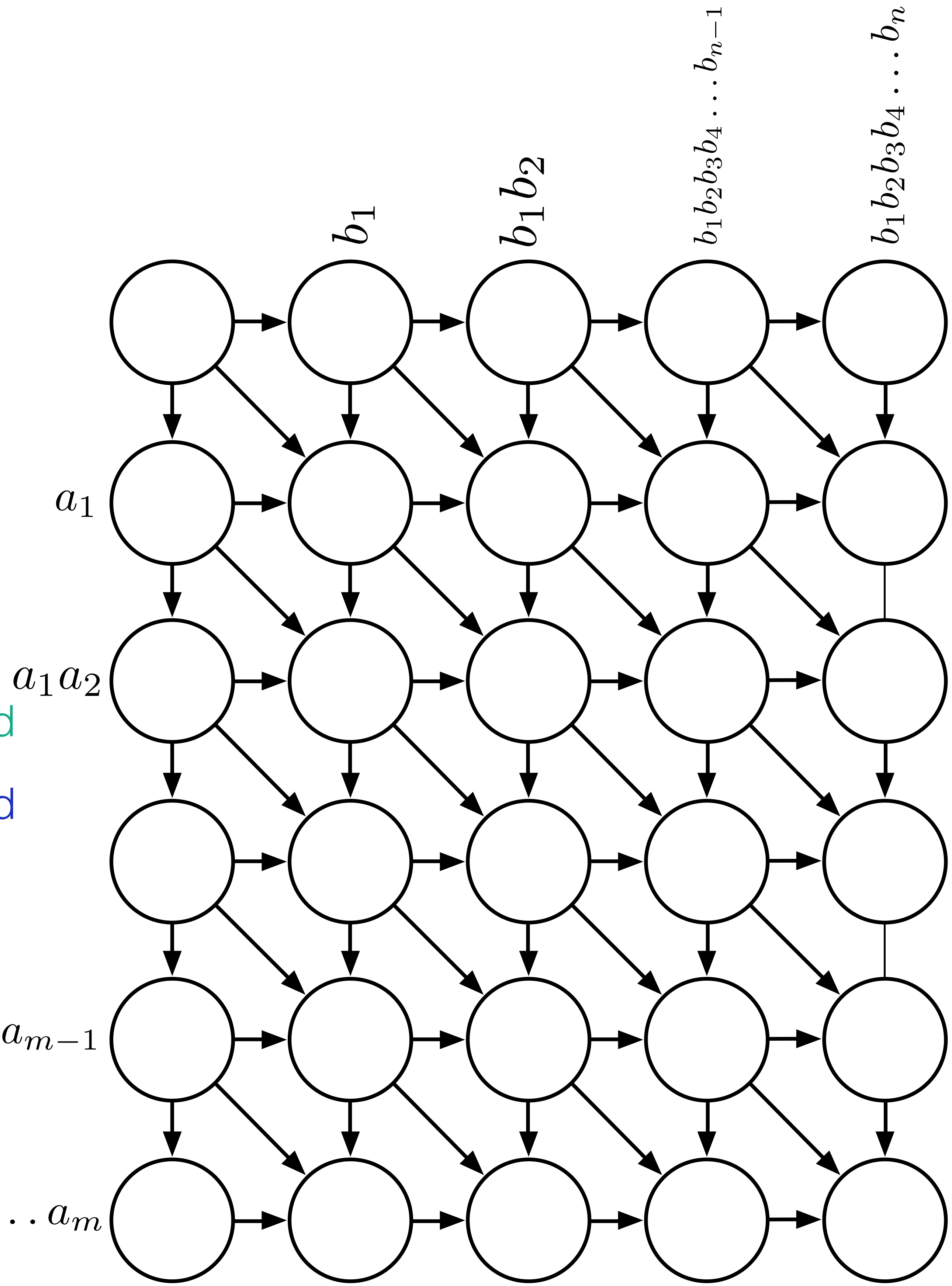


# Global Alignment

Generalizing LCS:

- *scoring alignments*
- *gap penalty*

$$s_{i,j} = \max \begin{cases} s_{i-1,j} - \sigma & \text{char in } a \text{ unmatched} \\ s_{i,j-1} - \sigma & \text{char in } b \text{ unmatched} \\ s_{i-1,j-1} + \text{SCORE}(a_i, b_j), & \text{align!} \end{cases}$$


$b_1$
$b_1 b_2$
$b_1 b_2 b_3 b_4 \ldots b_{n-1}$
$b_1 b_2 b_3 b_4 \ldots b_n$
$a_1$
$a_1 a_2$
$a_1 a_2 a_3 a_4 \ldots a_{m-1}$
$a_1 a_2 a_3 a_4 \ldots a_m$

# Guiding principles of scores in alignments

- Sequence is said to have diverged from a common ancestor through mutations
  - Substitutions
  - Insertions and deletions (gaps)

- Score evolutionarily close alignments higher than those that are not

- That is we compute the **likelihood ratio** of an alignment given the two sequences are related versus not related

# Log odds score

- Let $X$ be a random variable representing an alignment
- Let $M_1$ and $M_2$ be two probabilistic models for $X$
- Log odds score $S(X)$

$$S(X) = \log \frac{P(X|M_1)}{P(X|M_2)}$$

- If $S(X)>0$, $X$ is more likely to come from model $M_1$
- If $S(X)<0$, $X$ is more likely to come from model $M_2$

# What are $M_1$ and $M_2$ in our sequence alignment problem

- $M_1$: foreground model, that is the sequences are “related by evolution”.

- $M_2$: background model, that is the sequences are unrelated

- Need to compute the probability of an alignment $X$, under the two models $M_1$ and $M_2$

- Assume alignments on **protein sequences** with no gaps.

# $M_1$: foreground model

- Assume each pair of aligned positions evolved from a common ancestor
- Let $p_{ab}$ be the probability of observing a pair *{a,b}*
- Probability of an alignment between $x$ and $y$ is

$$P(x,y|M_1) = \prod_{i=1}^{n} p_{x_i y_i}$$

# $M_2$: background model

- Assume the individual amino acids at a position are independent of the amino acid in another position.
- Let $q_a$ be the probability of amino acid a
- The probability of an n-character alignment of $x$ and $y$ is

$$P(x, y|M_2) = \prod_{i=1}^{n} q_{x_i} \prod_{i=1}^{n} q_{y_i}$$

# Computing the log odds ratio to score an alignment

- The score of an alignment is the log odds ratio of the two sequences from $M_1$ and $M_2$

$$S = \log \frac{P(x, y|M_1)}{P(x, y|M_2)}$$

$$S = \log \frac{\prod_{i=1}^{n} p_{x_i y_i}}{\prod_{i=1}^{n} q_{x_i} q_{y_i}}$$

# Computing the log odds ratio to score an alignment

$$S = \sum_{i=1}^{n} \log \frac{p_{x_i y_i}}{q_{x_i} q_{y_i}}$$

Score of an alignment

$$s(a,b) = \log \frac{p_{a,b}}{q_a q_b}$$

Substitution matrix entry

# Some common substitution matrices

- BLOSUM matrices [Henikoff and Henikoff, 1992]
  - BLOSUM45
  - BLOSUM50
  - BLOSUM62
    - Number represents percent identity of sequences used to construct substitution matrices
- PAM [Dayhoff et al, 1978]
- Empirically, BLOSUM62 works the best

# How to estimate the probabilities?

- Need a good set of confirmed alignments

- Depends upon what we know about when the two sequences might have diverged

    - $p_{ab}$ for closely related species is likely to be low if $a != b$

    - $p_{ab}$ for species that have diverged a long time ago is likely close to the background.

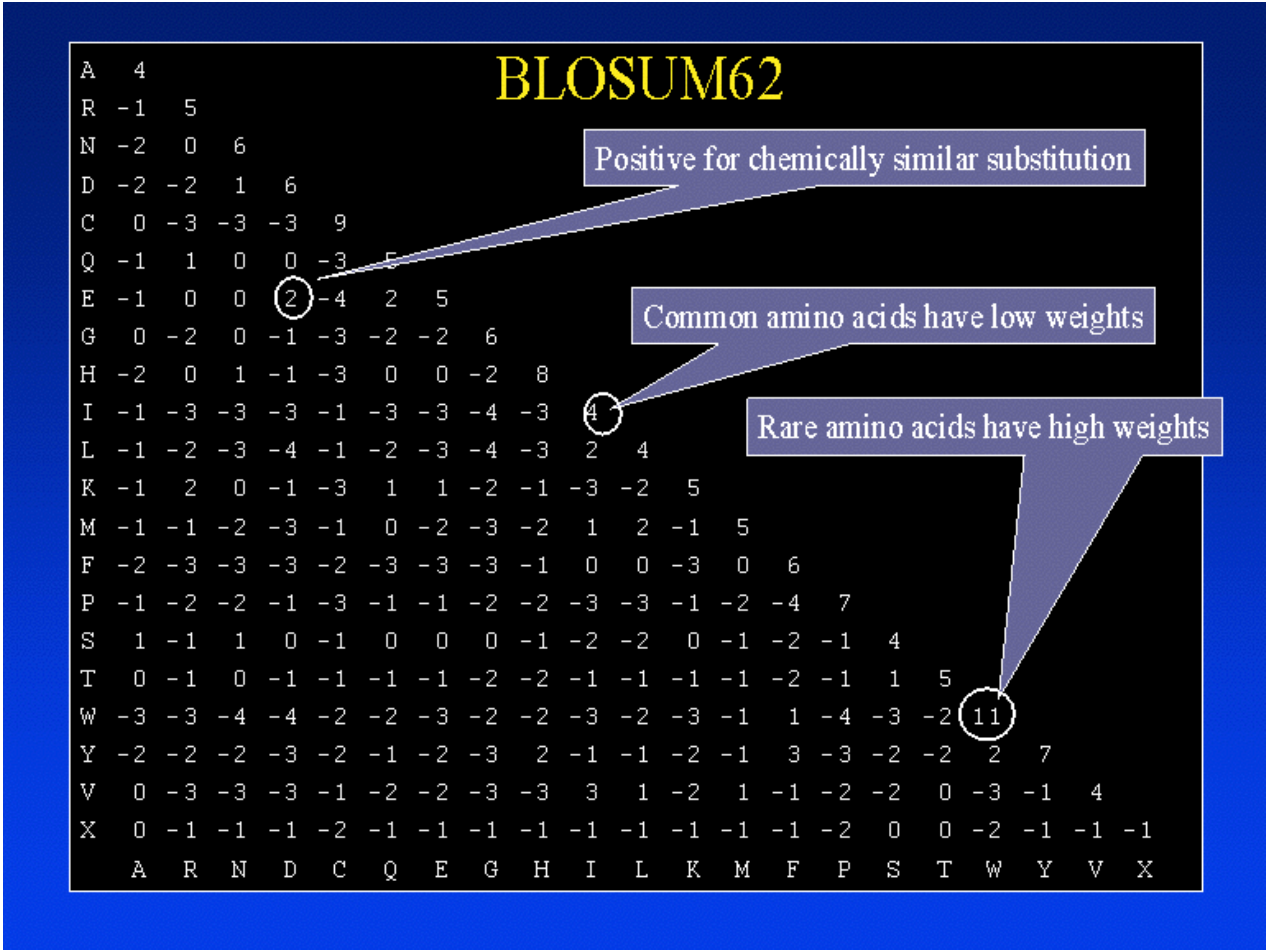
# BLOSUM matrices

- BLOck Substitution Matrix
- Derived from a set of aligned ungapped regions from protein families called BLOCKS
- Cluster proteins such that they have no less than L % of similarity

# Different BLOSUM matrices

- BLOSUM50
  - Proteins >50% similarity are in the same group
- BLOSUM62
  - Proteins >62% similarity are in the same group

# Example substitution scoring matrix (BLOSUM62)



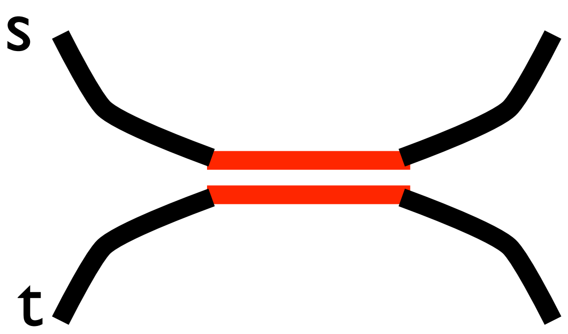
BLOSUM62

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 4 | | | | | | | | | | | | | | | | | | | | |
| R | -1 | 5 | | | | | | | | | | | | | | | | | | | |
| N | -2 | 0 | 6 | | | | | | | | | | | | | | | | | | |
| D | -2 | -2 | 1 | 6 | | | | | | | | | | | | | | | | | |
| C | 0 | -3 | -3 | -3 | 9 | | | | | | | | | | | | | | | | |
| Q | -1 | 1 | 0 | 0 | -3 | 5 | | | | | | | | | | | | | | | |
| E | -1 | 0 | 0 | 2 | -4 | 2 | 5 | | | | | | | | | | | | | | |
| G | 0 | -2 | 0 | -1 | -3 | -2 | -2 | 6 | | | | | | | | | | | | | |
| H | -2 | 0 | 1 | -1 | -3 | 0 | 0 | -2 | 8 | | | | | | | | | | | | |
| I | -1 | -3 | -3 | -3 | -1 | -3 | -3 | -4 | -3 | 4 | | | | | | | | | | | |
| L | -1 | -2 | -3 | -4 | -1 | -2 | -3 | -4 | -3 | 2 | 4 | | | | | | | | | | |
| K | -1 | 2 | 0 | -1 | -3 | 1 | 1 | -2 | -1 | -3 | -2 | 5 | | | | | | | | | |
| M | -1 | -1 | -2 | -3 | -1 | 0 | -2 | -3 | -2 | 1 | 2 | -1 | 5 | | | | | | | | |
| F | -2 | -3 | -3 | -3 | -2 | -3 | -3 | -3 | -1 | 0 | 0 | -3 | 0 | 6 | | | | | | | |
| P | -1 | -2 | -2 | -1 | -3 | -1 | -1 | -2 | -2 | -3 | -3 | -1 | -2 | -4 | 7 | | | | | | |
| S | 1 | -1 | 1 | 0 | -1 | 0 | 0 | 0 | -1 | -2 | -2 | 0 | -1 | -2 | -1 | 4 | | | | | |
| T | 0 | -1 | 0 | -1 | -1 | -1 | -1 | -2 | -2 | -1 | -1 | -1 | -1 | -2 | -1 | 1 | 5 | | | | |
| W | -3 | -3 | -4 | -4 | -2 | -2 | -3 | -2 | -2 | -3 | -2 | -3 | -1 | 1 | -4 | -3 | -2 | 11 | | | |
| Y | -2 | -2 | -2 | -3 | -2 | -1 | -2 | -3 | 2 | -1 | -1 | -2 | -1 | 3 | -3 | -2 | -2 | 2 | 7 | | |
| V | 0 | -3 | -3 | -3 | -1 | -2 | -2 | -3 | -3 | 3 | 1 | -2 | 1 | -1 | -2 | -2 | 0 | -3 | -1 | 4 | |
| X | 0 | -1 | -1 | -1 | -2 | -1 | -1 | -1 | -1 | -1 | -1 | -1 | -1 | -1 | -2 | 0 | 0 | -2 | -1 | -1 | -1 |
| | A | R | N | D | C | Q | E | G | H | I | L | K | M | F | P | S | T | W | Y | V | X |

Positive for chemically similar substitution

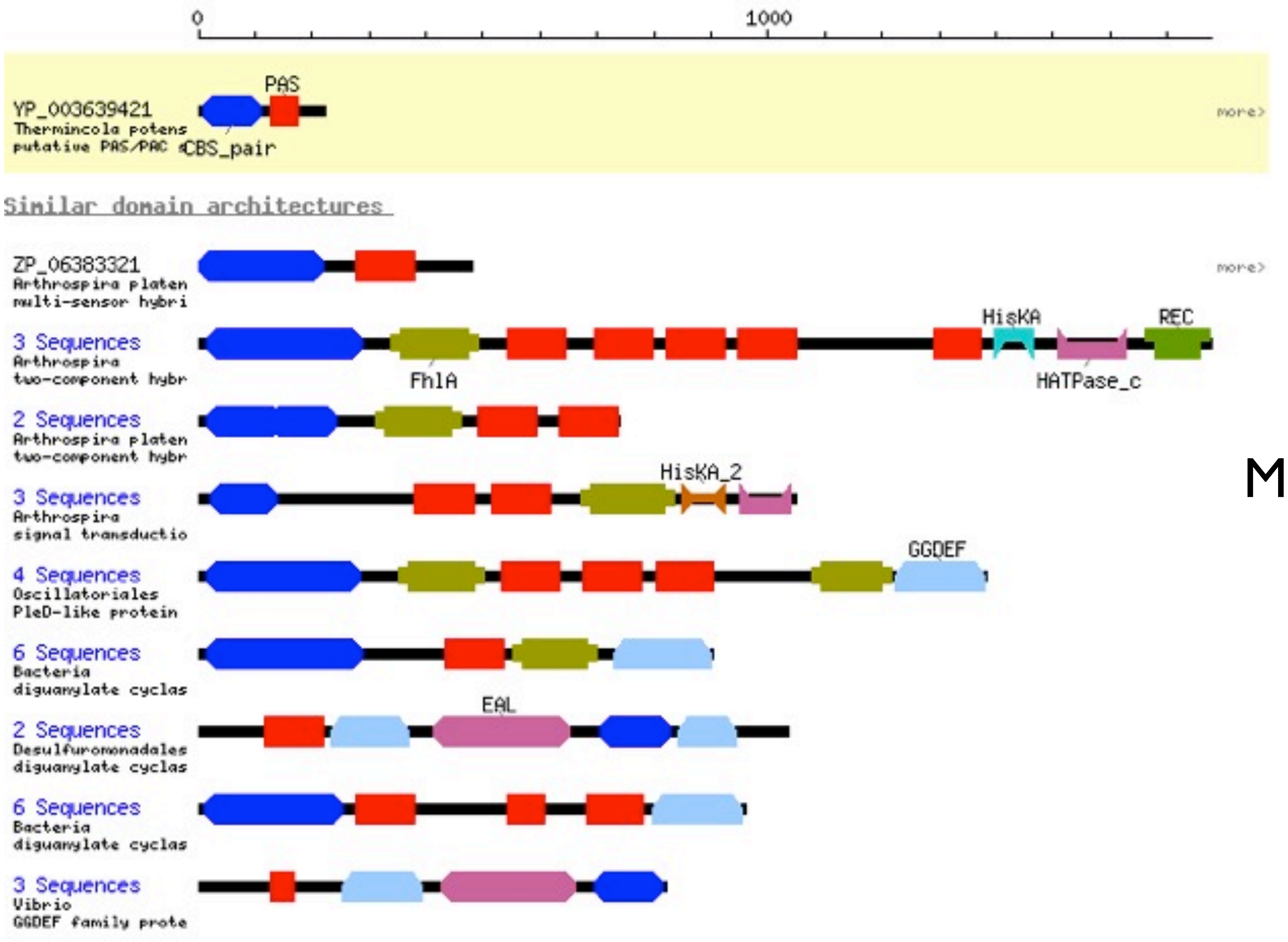
Common amino acids have low weights

Rare amino acids have high weights



# Local Alignment

**Local alignment between s and t:** Best alignment between a subsequence of s and a subsequence of t.



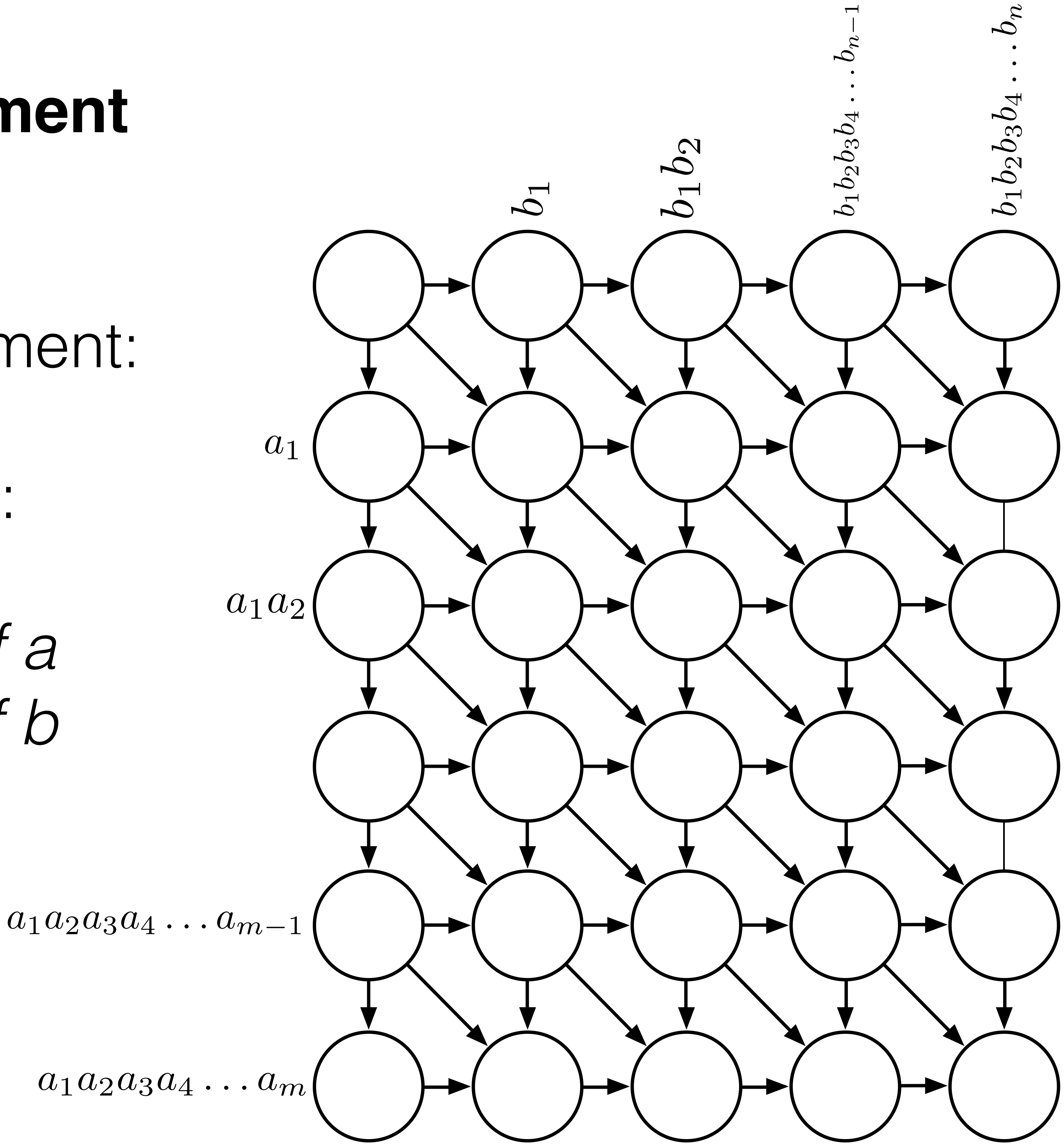
Motivation:

Many genes are composed of *domains*, which are subsequences that perform a particular function.

# Local Alignment

Recall in **global** alignment:
$s_{i,j}$ is the score of
optimally aligning:

***prefix*** *of length i of a*
***prefix*** *of length j of b*


$b_1$
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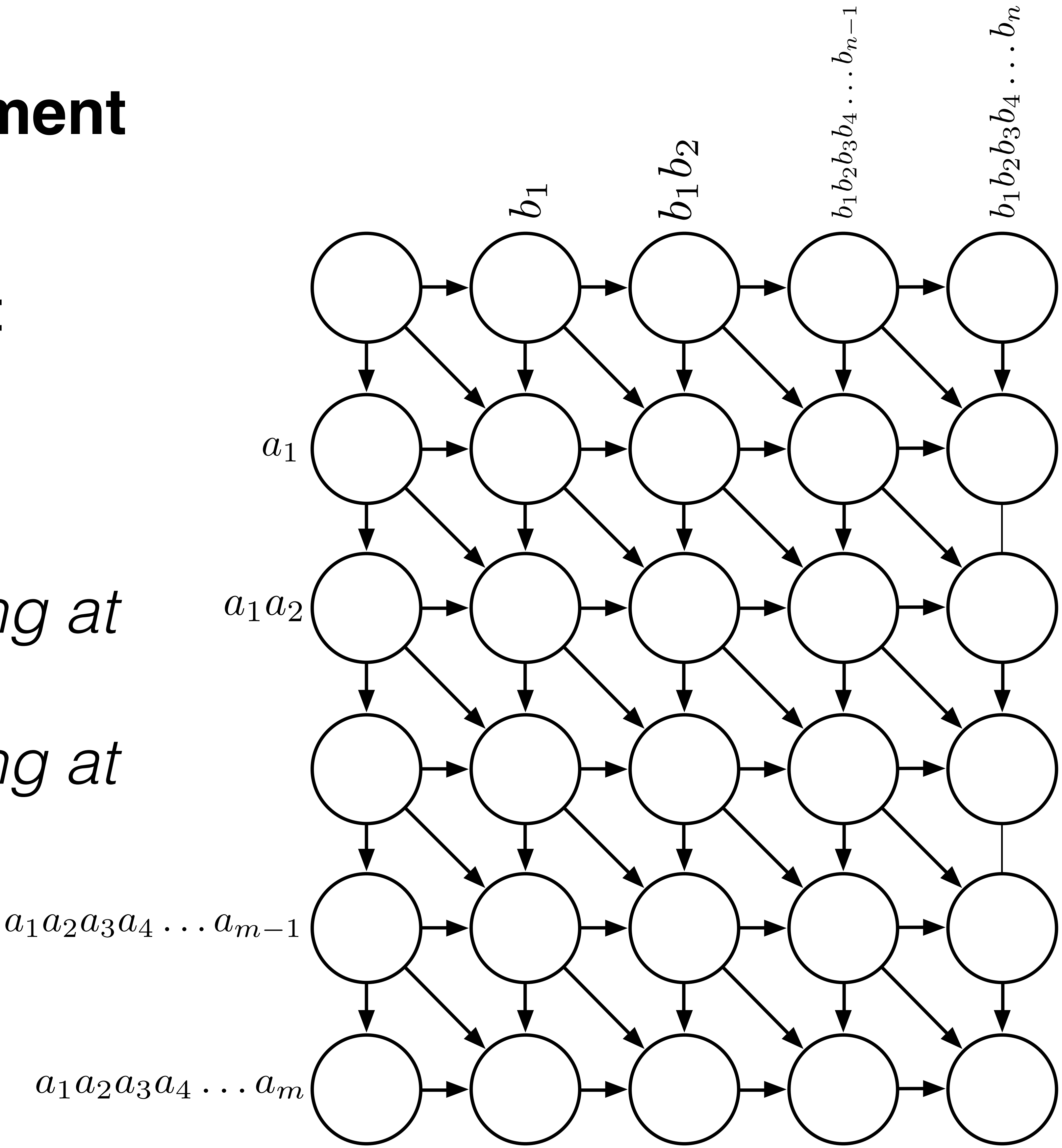
# Local Alignment

In **local** alignment:
$s_{i,j}$ is the score of
optimally aligning:

*some **substring** ending at position i of a*
*some **substring** ending at position j of b*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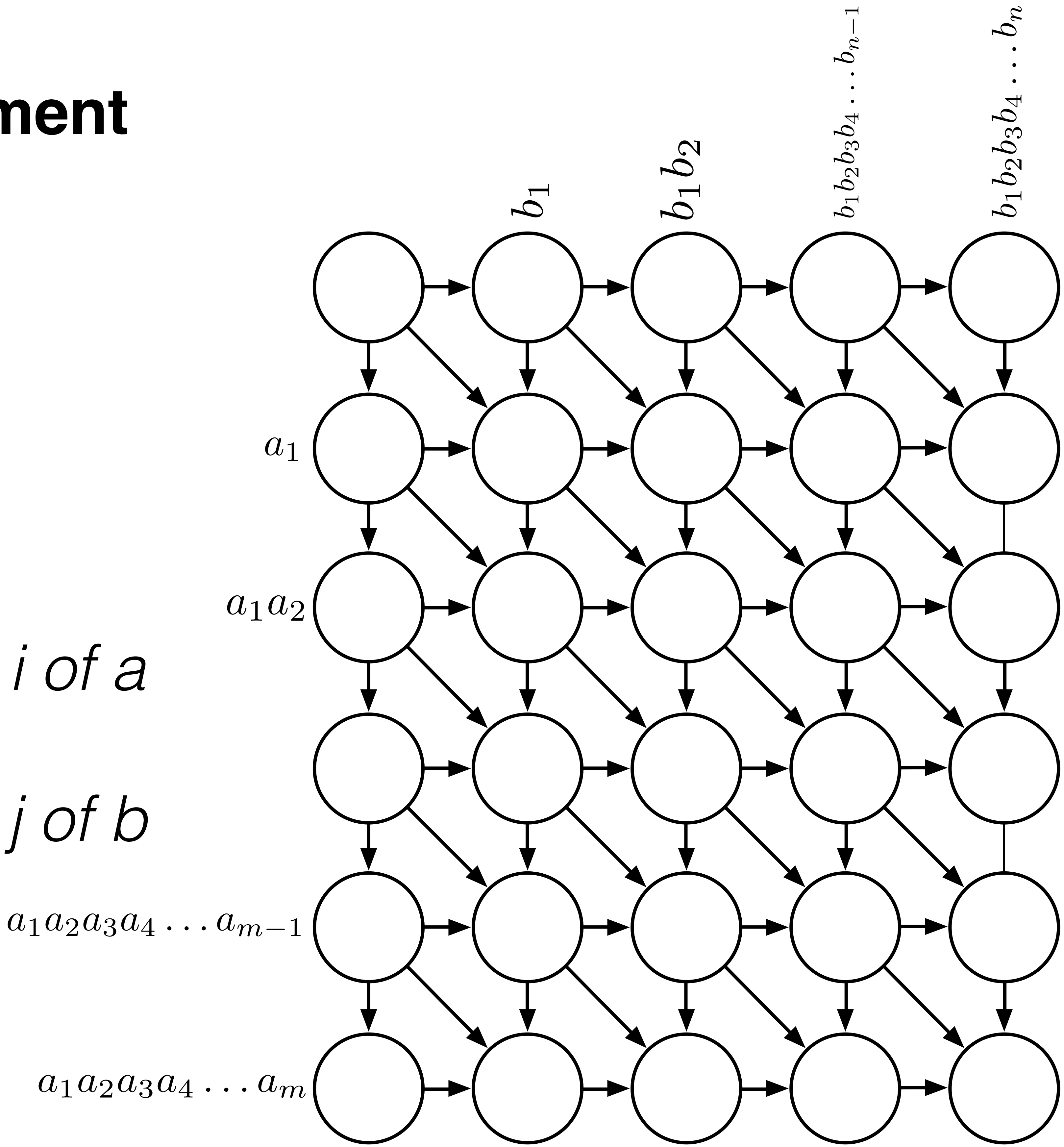
$a_1a_2a_3a_4 \ldots a_m$

# Local Alignment

In **local** alignment:
$s_{i,j}$ is the score of
optimally aligning:

*some **suffix** of the
**prefix** of length i of a*
*some **suffix** of the
**prefix** of length j of b*

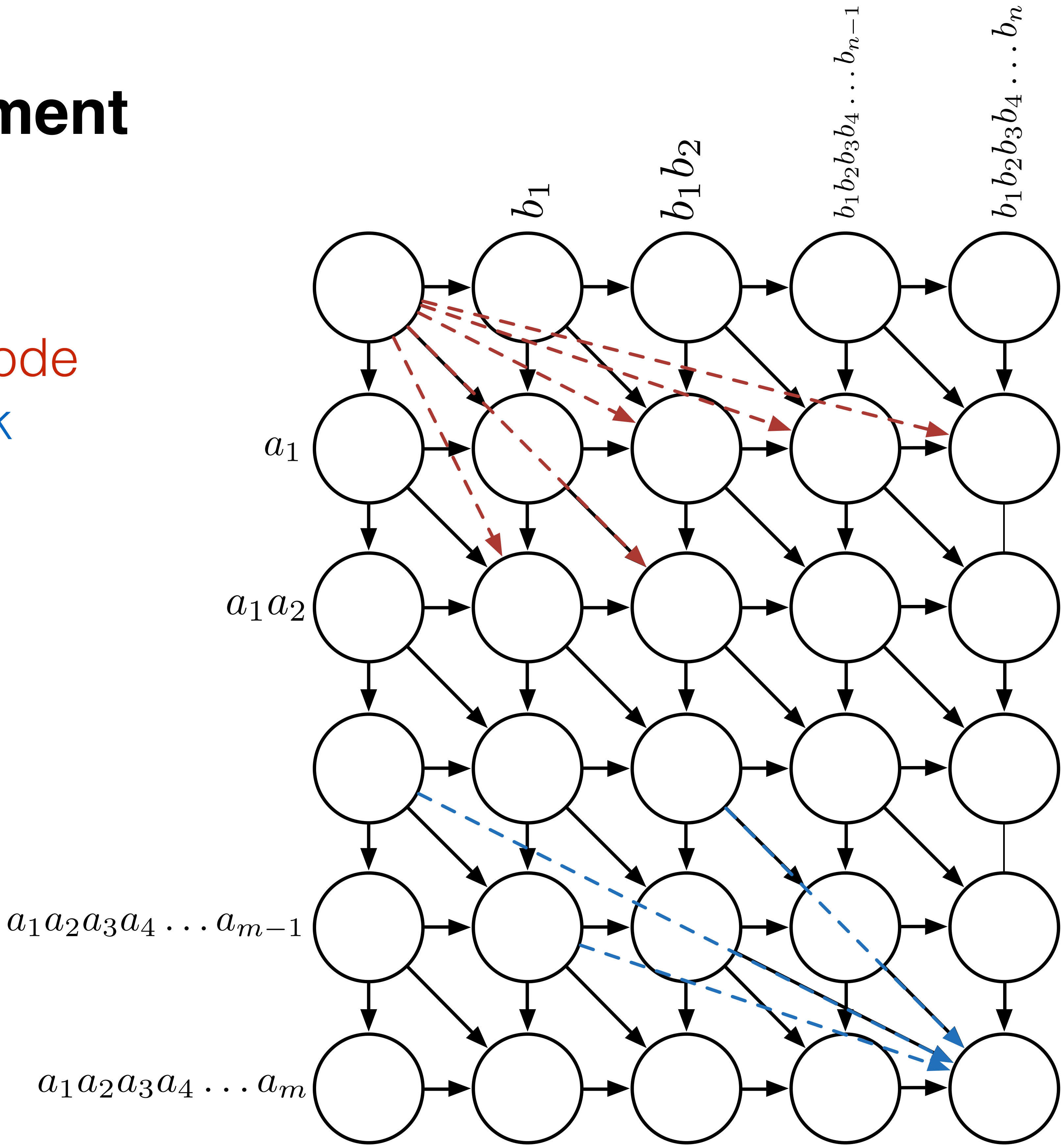


# Local Alignment

Conceptually:

connect source to every node

connect every node to sink



# Local Alignment

Conceptually:

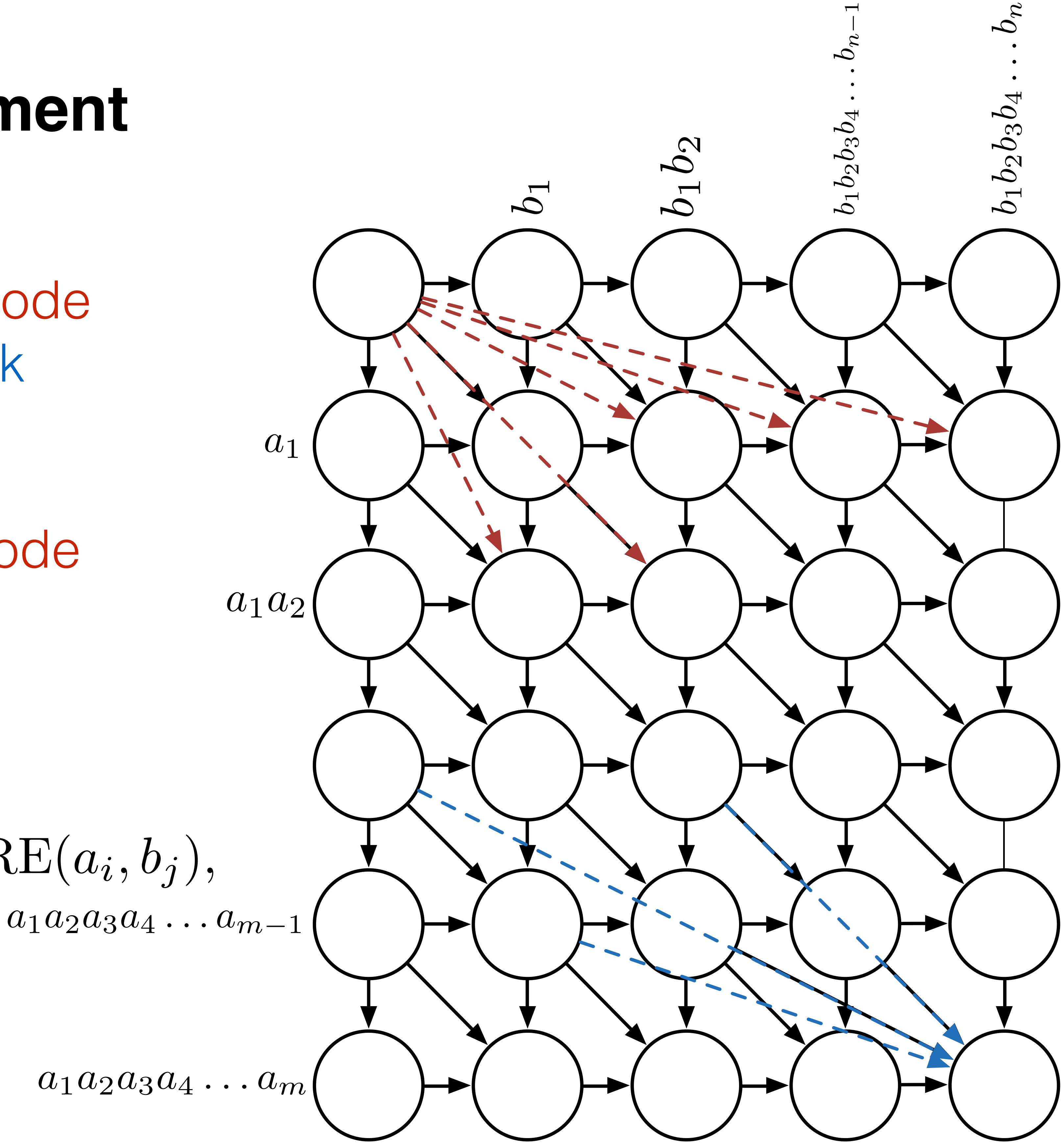
connect source to every node

connect every node to sink

Implementation:

connect source to every node

$$s_{i,j} = \max \begin{cases} 0 \\ s_{i-1,j} - \sigma \\ s_{i,j-1} - \sigma \\ s_{i-1,j-1} + \text{SCORE}(a_i, b_j), \end{cases}$$



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$a_1a_2a_3a_4 \ldots a_m$

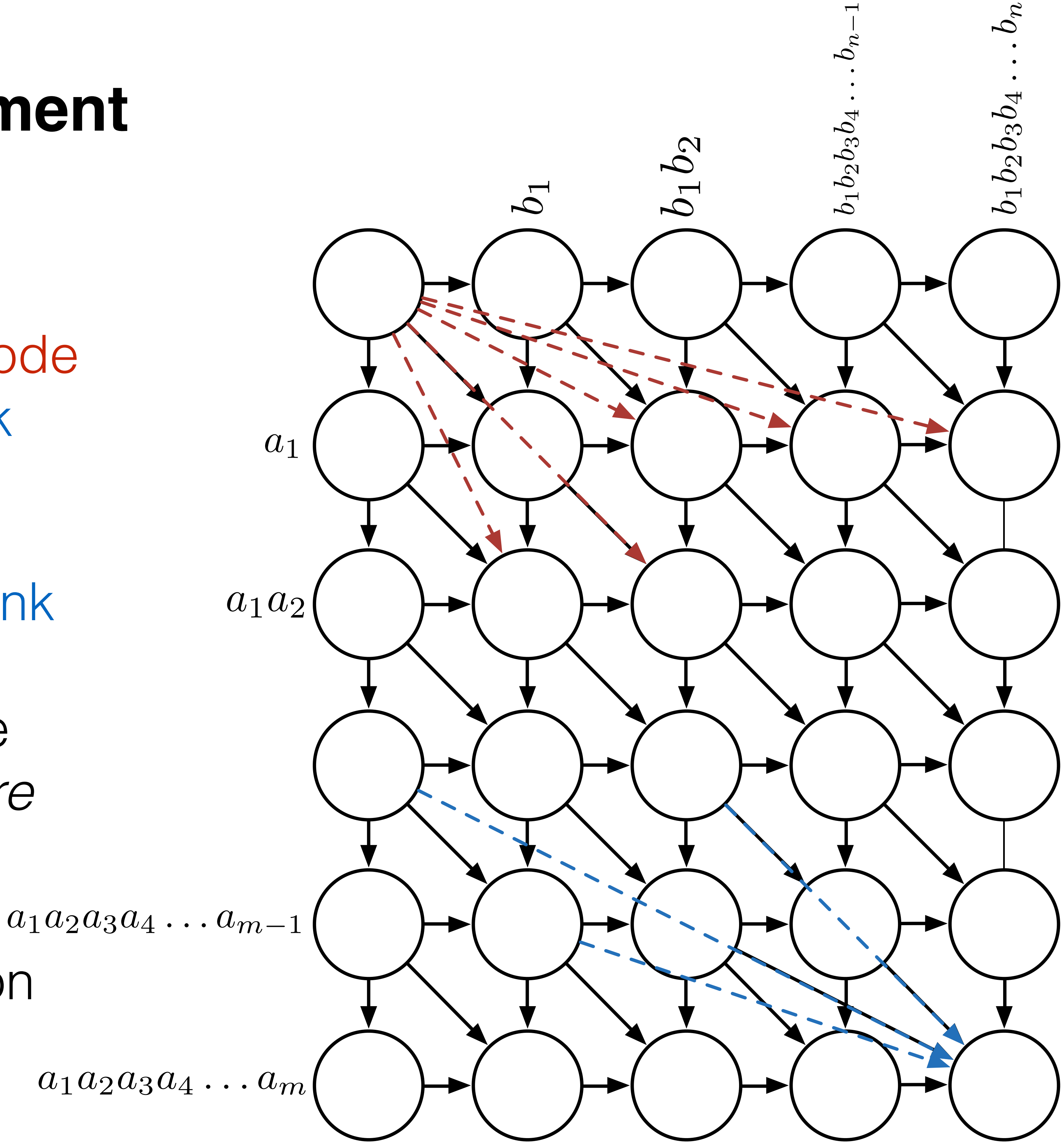
# Local Alignment

Conceptually:
connect source to every node
connect every node to sink

Implementation:
connect every node to sink

start backtrack at node
with max score *anywhere*
in the graph

stop backtrack if *0* option
taken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# Global/Local Alignment Recap

- Scoring matrices: based on probabilistic models of amino acid evolution

- Algorithm for **global** alignment sometimes called “Needleman-Wunsch”

- Algorithm for **local** alignment sometimes called “Smith-Waterman”

- Same basic algorithmic framework